SBIR/STTR at the National Institutes of Health

DETAILS

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SBIR/STTR at the National Institutes of Health

Committee on Capitalizing on Science, Technology, and Innovation: An Assessment of the Small Business Innovation Research Program—Phase II

Board on Science, Technology, and Economic Policy

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Preface

Today's knowledge economy is driven in large part by the nation's capacity to innovate. One of the defining features of the U.S. economy is a high level of entrepreneurial activity. Entrepreneurs in the United States see opportunities and are willing and able to assume risk to bring new welfare-enhancing, wealth-generating technologies to the market. Yet, although discoveries in areas such as genomics, bioinformatics, and nanotechnology present new opportunities, converting these discoveries into innovations for the market involves substantial challenges.[1] The American capacity for innovation can be strengthened by addressing the challenges faced by entrepreneurs. Public-private partnerships are one means to help entrepreneurs bring new ideas to market.

The Small Business Innovation Research (SBIR) program is one of the largest examples of U.S. public-private partnerships. An underlying tenet of the program is that small businesses are a strong source of new ideas, and therefore economic growth, but that it is difficult to find financial support for these ideas in the early stages of their development. The SBIR program was established in 1982 to encourage small businesses to develop new processes and products and to provide quality research in support of the U.S. government's many missions. By involving qualified small businesses in the nation's research and development (R&D) effort, SBIR grants stimulate innovative technologies to help federal agencies meet their specific R&D needs in many areas, including health, the environment, and national defense. The Small Business Technology Transfer (STTR) Program was created in 1992 by the Small Business Research and Development Enhancement Act to

[1]See L. M. Branscomb, K. P. Morse, M. J. Roberts, D. Boville, *Managing Technical Risk: Understanding Private Sector Decision Making on Early Stage Technology Based Projects,* Gaithersburg, MD: National Institute of Standards and Technology, 2000.

expand joint venture opportunities for small businesses and nonprofit research institutions by requiring small business recipients to collaborate formally with a research institution. This report provides an analysis of how well the NIH SBIR and STTR programs are fulfilling their congressionally mandated goals.

In the SBIR Reauthorization Act of 2000, Congress tasked the National Research Council (NRC)[2] with undertaking a "comprehensive study of how the SBIR program has stimulated technological innovation and used small businesses to meet federal research and development needs" and with recommending further improvements to the program.[3] In the first round of this study, an expert committee prepared a series of reports from 2004 to 2009 on the Small Business Innovation Research program at the Department of Defense (DoD), the National Institutes of Health (NIH), the National Aeronautics and Space Administration (NASA), the Department of Energy (DoE), and the National Science Foundation (NSF)—the five agencies responsible for 96 percent of the program's operations.[4] When reauthorizing the SBIR and STTR programs in 2011, Congress expanded the study mandate to include a review of the STTR program.[5]

Building on the outcomes from the first round, this second round examines topics of general policy interest that emerged during the first round as well as topics of specific interest to individual agencies. The results will be published in reports of agency-specific and program-wide findings on the SBIR and STTR programs to be submitted to the contracting agencies and Congress. In partial fulfillment of these objectives, this volume presents the committee's review of the NIH SBIR/STTR program operations.[6]

PROJECT ANTECEDENTS

The current assessment follows directly from an earlier analysis of public-private partnerships by the Board on Science, Technology, and Economic Policy (STEP). From 1990 to 2005, the Committee on Government-Industry Partnerships prepared 11 volumes reviewing the drivers of cooperation among industry, universities, and government; operational assessments of current programs; emerging needs at the intersection of biotechnology and information technology;

[2]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council are used in an historic context identifying programs prior to July 1.

[3]See the SBIR Reauthorization Act of 2000 (H.R. 5667, Section 108).

[4]For a list of publications from the first round review, see Chapter 1, Box 1-1. For an overview of the programs at the five leading SBIR agencies, see National Research Council, *An Assessment of the SBIR Program,* Washington, DC: The National Academies Press, 2008. See also National Research Council, *An Assessment of the SBIR Program at the National Aeronautics and Space Administration,* Washington, DC: The National Academies Press, 2009. The committee also prepared reports on the SBIR program at DoD, DoE, NIH, and NSF.

[5]SBIR/STTR Reauthorization Act of 2011, P.L. 112-81, December 31, 2011.

[6]The formal Statement of Task is presented in Chapter 1 of this report.

the current experience of foreign government partnerships and opportunities for international cooperation; and the changing roles of government laboratories, universities, and other research organizations in the national innovation system.[7]

This analysis of public-private partnerships includes two published studies of the SBIR program. Drawing from a 1998 workshop, the first report, *The Small Business Innovation Research Program: Challenges and Opportunities,* examined the program's origins and identified operational challenges to its future effectiveness.[8] The report also highlighted the relative paucity of research on the SBIR program.

After the release of this initial report, the DoD asked the committee to compare the operations of its Fast Track Initiative with those of its regular SBIR program. The resulting report, *The Small Business Innovation Research Program: An Assessment of the Department of Defense Fast Track Initiative,* relying on case study and survey research, found that the DoD SBIR program was achieving its legislated goals. The report also found that the Fast Track Initiative was achieving its objective of greater commercialization and recommended that it be continued and expanded where appropriate.[9] The report recommended that the SBIR program overall would benefit from further research and analysis, a recommendation subsequently adopted by Congress.

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[7]For a summary of the topics covered and main lessons learned, see National Research Council, *Government-Industry Partnerships for the Development of New Technologies: Summary Report,* Washington, DC: National Academy Press, 2002.

[8]See National Research Council, *The Small Business Innovation Research Program: Challenges and Opportunities,* Washington, DC: National Academy Press, 1999.

[9]See National Research Council, *The Small Business Innovation Research Program: An Assessment of the Department of Defense Fast Track Initiative,* Washington, DC: National Academy Press, 2000.

ACKNOWLEDGMENT OF REVIEWERS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Academies of Sciences, Engineering, and Medicine's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We wish to thank the following individuals for their review of this report: Wendy Baldwin, Population Reference Bureau; Richard Bendis, BioHealth Innovation, Inc.; Georges Benjamin, American Public Health Association; Marjorie Bowman, Wright State University; Erik Fatemi, Cornerstone Government Affairs; Robert Genco, State University of New York at Buffalo; Michael McGeary, Institute of Medicine (retired); Mark McLaughlin, Modulation Therapeutics; John Scott, Dartmouth College; and William Sly, St. Louis University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Edwin Przybylowicz, Eastman Kodak Company (retired), and Irwin Feller, The Pennsylvania State University. Appointed by the Academies, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Jacques S. Gansler Sujai J. Shivakumar

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Summary

Created in 1982 through the Small Business Innovation Development Act, the Small Business Innovation Research (SBIR) program remains the nation's largest innovation program for small businesses. The SBIR program offers competitive awards to support the development and commercialization of innovative technologies by small private-sector businesses. At the same time, the program provides government agencies with technical and scientific solutions that address their different missions.

Seeking to bridge the gap between basic research and commercialization of resulting innovations, the Small Business Technology Transfer (STTR) program, created in 1992 by the Small Business Research and Development Enhancement Act of 1992, seeks to expand joint venture opportunities for small businesses and nonprofit research institutions. Under the STTR program a small business receiving an award must collaborate formally with a research institution.

The SBIR/STTR programs consist of three phases for which standard amounts of funding are specified:[1]

- Phase I provides limited funding (up to $100,000 prior to the 2011 reauthorization and up to $150,000 thereafter) for feasibility studies.
- Phase II provides more substantial funding for further research and development (typically up to $750,000 prior to 2012 and $1 million after the 2011 reauthorization).

[1]NIH and other agencies can and do exercise flexibility in the size of awards to take into account the nature of the technology and to address agency mission priorities.

- Phase III reflects commercialization without providing access to any additional SBIR/STTR funding, although funding from other federal government accounts and other sources is permitted and encouraged.

In FY2014, the Department of Health and Human Services (HHS) awarded $774,065,517 to 1,134 SBIR/STTR projects. Since the beginning of its participation in the program in 1983, HHS has funded 33,797 SBIR/STTR projects totaling $11.1 billion.[2]

CALL FOR ASSESSMENT

Adopting several recommendations from a 2008 National Research Council (NRC) report, Congress reauthorized the SBIR/STTR programs in December 2011 for an additional 6 years. As a part of this reauthorization, Congress called for further studies by the Academies of the SBIR/STTR programs. In turn, the National Institutes of Health (NIH) requested the Academies to provide a subsequent round of analysis, focused on operational questions with a view to identifying further improvements to the program.

The committee's findings and recommendations, summarized below, are based on a complement of quantitative and qualitative tools including a survey, case studies of award recipients, agency data, public workshops, and agency interviews. The methodology is described in Chapter 1 and Appendix A of this report.

The survey, designated the 2014 Survey to distinguish it from an earlier survey conducted in 2005, was sent to 1,652 of a total of 3,375 principal investigators (PI) in companies that received a Phase II award from NIH during fiscal years 2001-2010. The remaining 1,723 PIs could not be contacted at the company listing in the NIH awards database. The 1,652 PIs who were contacted, constitute the effective population for this study. From these, 726 responses were received, for a preliminary population response rate of 21.5 percent and an effective population response rate of 43.9 percent.[3]

This study recognizes that the NIH SBIR/STTR programs are relatively unique in terms of scale, integrity, and mission focus. Therefore, it focuses on the SBIR/STTR programs at NIH and does not purport to benchmark the program with those at other agencies or non-SBIR programs in the United States or abroad. Furthermore, the study does not consider whether or not the NIH SBIR/STTR programs should exist; rather, it assesses the extent to which they

[2]Small Business Administration website: https://www.sbir.gov/analytics-dashboard. Accessed on October 6, 2015. The Department of Health and Human Service (HHS) SBIR and STTR programs operate at each of the 24 participating NIH Institutes and Centers (ICs), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) and the Administration for Children and Families (ACF).

[3]See Appendix A for a description of the survey methodology.

have met the objectives set by Congress, examines the extent to which recent initiatives have improved program outcomes, and provides recommendations for further improvements to meet program objectives.

FOCUS ON LEGISLATIVE OBJECTIVES

This report assesses the performance of the NIH SBIR/STTR programs against the broad congressional objectives for the SBIR and STTR programs.[4]

For SBIR, these objectives were reiterated in the 2011 program reauthorization and elaborated in the subsequent policy directive of the Small Business Administration.[5] Section 1c of the Small Business Administration (SBA) SBIR Directive states program objectives as follows:

> *The statutory purpose of the SBIR Program is to strengthen the role of innovative small business concerns (SBCs) in Federally-funded research or research and development (R/R&D). Specific program purposes are to:*
>
> *(1) stimulate technological innovation;*
> *(2) use small business to meet Federal R/R&D needs;*
> *(3) foster and encourage participation by socially and economically disadvantaged small businesses (SDBs), and by women-owned small businesses (WOSBs), in technological innovation; and*
> *(4) increase private sector commercialization of innovations derived from Federal R/R&D, thereby increasing competition, productivity and economic growth.*[6]

The parallel language from the SBA's STTR Policy Directive is as follows:

> *"(c) The statutory purpose of the STTR Program is to stimulate a partnership of ideas and technologies between innovative small business concerns (SBCs) and Research Institutions through Federally-funded research or research and development (R/R&D). By providing awards to SBCs for cooperative R/R&D efforts with Research Institutions, the STTR Program assists the small business and research communities by commercializing innovative technologies."*[7]

CAVEAT

This study does not seek to provide a comprehensive review of the value of the SBIR/STTR programs, in particular measured against other possible uses of federal funding. Such a review is beyond the study scope. Our work is focused on assessing

[4]See Box 1-2 and the discussion of the Committee's task in Chapter 1 (Introduction).
[5]SBA SBIR/STTR Policy Directive, October 18, 2012.
[6]Ibid., 3.
[7]Small Business Administration, Office of Investment and Innovation, "Small Business Technology Transfer (STTR) Program – Policy Guidance," updated February 24, 2014.

the extent to which the NIH SBIR/STTR programs have met their congressionally mandated objectives, determining in particular whether recent administrative initiatives have improved program outcomes, and providing recommendations for further improvements.

Thus, this study does not consider whether or not the SBIR/STTR programs should exist—Congress has already decided affirmatively on this question, most recently in the 2011 reauthorization of the programs. Rather, the committee is charged with providing assessment-based findings of the benefits and costs of the SBIR and STTR programs in order to improve public understanding of the program and to recommend improvements to the program.

KEY FINDINGS

The NIH SBIR program is having a positive overall impact. It is meeting three of its four legislative objectives, namely, stimulating technological innovation, using small businesses to meet federal R&D needs, and increasing private-sector commercialization of innovations derived from federal R&D. However, more work needs to be done to "foster and encourage participation by socially and economically disadvantaged small businesses (SDBs), and by women-owned small businesses (WOSBs), in technological innovation." The committee also finds that the NIH STTR program is meeting its statutory objectives. Key findings about the SBIR/STTR programs are highlighted and cross referenced below. Chapter 8 of this report lists the committee's findings in full.

Commercialization

- SBIR/STTR projects at NIH commercialize at a substantial rate. Forty-nine percent of SBIR and STTR respondents reported some sales or licensing revenues at the time of the survey, and a further 25 percent expected sales in the future, according to the 2014 Survey. (Finding I-A)
- There is room for improvement: The large number of companies with small-scale revenues suggests that while many companies reach the market, fewer can be described as successful in commercial terms. Despite the high percentage of SBIR/STTR projects with sales, the amount of sales was often small: of those with some sales, 39 percent had sales less than $100,000. Six percent had sales over $10 million.
- For small innovative firms, SBIR/STTR funding makes a substantial difference in determining project initiation, scope, and timing. Seventy-four percent of respondents reported that the project probably or definitely would not have proceeded without SBIR/STTR funding. (Finding I-E)

Fostering the Participation of Women and Underserved Minorities

- Current outcomes data show that the objective of fostering the participation of women and underserved minorities has not been met by the NIH SBIR/STTR programs. (Finding II-A)
- Participation by Black, Hispanic, and Native Americans in the NIH SBIR/STTR programs is low. The 2014 Survey indicates that Black-owned small businesses account for only 0.7 percent of all respondents; Hispanic-owned small businesses, about 1.7 percent.
- Levels of participation by women are also low. NIH data show that 10 percent of SBIR/STTR Phase I awards were to women-owned small businesses (WOSBs) and that these firms receive 12 percent of Phase II awards. However WOSB success rates were persistently lower than those for non-WOSBs for both Phase I and Phase II.

Using Small Business to Meet Federal R/R&D Needs

- The SBIR/STTR programs at NIH support the development and adoption of technological innovations that advance the agency's mission. (Finding III-A)
- The NIH SBIR/STTR programs continue to connect companies to universities and research institutions. (Finding III-B)
- NIH SBIR/STTR projects generate substantial knowledge-based outputs such as patents and peer-reviewed publications. (Finding III-C)

Fostering Innovative Companies

- The NIH SBIR/STTR programs support the foundation of new innovative firms. Many of the survey respondents reported that SBIR/STTR funding was instrumental in the founding of the company. The formation of new innovative companies is a positive outcome for the program. (Finding IV-A)

Program Management

- The NIH SBIR/STTR programs are managed in a flexible way in terms of application topics, dates, and funding. (Finding V-A)
- The NIH application review system can be improved. Case studies, survey responses, and discussions with agency managers all indicate that, although the system is highly regarded and has many positive characteristics, it is not serving the SBIR/STTR community as well as it could. (Finding V-B)

- NIH Institutes and Centers are pioneering new models of program management (e.g., the National Cancer Institute and the National Heart, Lung, and Blood Institute). (Finding V-C)
- A substantial gap remains between the end of Phase I and the beginning of funding for Phase II. (Finding V-F)

STTR

- STTR is meeting the program objectives defined in the Small Business Administration's Policy Guidance for STTR. (Finding VI-A)

KEY RECOMMENDATIONS

Address Underserved Populations

- NIH should immediately examine past and current efforts to address the Congressional mandate to foster the participation of underserved populations in the SBIR/STTR programs, examine and report on best practices, develop an outreach and education program aimed at expanding participation of under-served populations, create benchmarks and metrics to relate the impact of such activities. (Recommendation I)
- Quotas are not recommended. It is not recommended that NIH develop quotas for inclusion of selected populations into the SBIR/STTR programs, because of the potential problems that this might entail, such as raising issues of fairness and lack of transparencies with the selection process. At the same time, it is important that steps be taken to improve the current situation. (Recommendation I-A)

Improve Commercialization Outcomes

- NIH should continue to address the challenges that conducting clinical trials pose for to the commercialization of SBIR/STTR technologies. NIH should provide improved support for awardees in meeting the challenges in funding clinical trials. (Recommendation II-A)
- NIH should continue to operate the Phase II B program and consider expanding its size within the context of a more flexible approach. (Recommendation III-A)

Improving Monitoring, Evaluation, and Assessment

- NIH should improve data collection and organization. NIH should collect outcomes data and improve program evaluation, management, and outcomes. This data collection effort should address the entire range of con-

gressionally mandated outcomes, not only commercialization, and should be extended to other aspects of the program, including demographic data for applicants and awardees. (Recommendation IV-A)
- NIH should take advantage of modern information management and data visualization tools both in its data collection effects, for communication with companies about program activities and operations, and to facilitate networking of program participants. (Recommendation IV-A)
- NIH should improve the utilization of outcomes data. As NIH starts to collect effective outcomes data, it should ensure that these data are systematically employed to guide program management. (Recommendation IV-B)
- NIH should prepare an SBIR/STTR Annual Report to the NIH Director and Congress. (Recommendation (IV-C)

Improving Program Management

- NIH should improve its application review system. In consultation with experts in this process, NIH should convene a high-level task force to improve the consideration of commercial potential in the selection process for SBIR/STTR applications. (Recommendation V-A)
- NIH should address the funding gap between Phase I and II awards. (Recommendation V-B)
- NIH should track and evaluate new program management initiatives. (Recommendation V-C)

1

Introduction

Small businesses are an important driver of innovation and economic growth in the United States.[1] Despite the challenges of changing global environments and the impacts of the 2008 financial crisis and subsequent recession, innovative small businesses continue to develop and commercialize new products for the market, improving the health and welfare of Americans while strengthening the nation's security and competitiveness.[2]

Created in 1982 through the Small Business Innovation Development Act,[3] the Small Business Innovation Research (SBIR) program remains the nation's largest innovation program for small businesses. The SBIR program offers competitive awards to support the development and commercialization of innovative

[1]See Z. Acs and D. Audretsch, "Innovation in Large and Small Firms: An Empirical Analysis," *The American Economic Review*, 78(4):678-690, 1988. See also Z. Acs and D. Audretsch, *Innovation and Small Firms,* Cambridge, MA: The MIT Press, 1991; E. Stam and K. Wennberg, "The Roles of R&D in New Firm Growth," *Small Business Economics,* 33:77-89, 2009; E. Fischer and A.R. Reuber, "Support for Rapid-Growth Firms: A Comparison of the Views of Founders, Government Policymakers, and Private Sector Resource Providers," *Journal of Small Business Management,* 41(4):346-365, 2003; M. Henrekson and D. Johansson, "Competencies and Institutions Fostering High-Growth Firms," *Foundations and Trends in Entrepreneurship,* 5(1):1-80, 2009.

[2]See D. Archibugi, A. Filippetti, and M. Frenz, "Economic Crisis and Innovation: Is Destruction Prevailing over Accumulation?" *Research Policy,* 42(2):303-314, 2013. The authors show that "the 2008 economic crisis severely reduced the short-term willingness of firms to invest in innovation" and also that it "led to a concentration of innovative activities within a small group of fast growing new firms and those firms already highly innovative before the crisis." They conclude that "the companies in pursuit of more explorative strategies towards new product and market developments are those to cope better with the crisis."

[3]Small Business Innovation Development Act of 1982, P.L. 97-219, July 22, 1982.

technologies by small private-sector businesses.[4] At the same time, the program provides government agencies with technical and scientific solutions that address their various missions.

Seeking to bridge the gap between basic science and commercialization of resulting innovations, the Small Business Technology Transfer (STTR) program, created in 1992 by the Small Business Research and Development Enhancement Act of 1992,[5] seeks to expand joint venture opportunities for small businesses and nonprofit research institutions. Under the STTR program, a small business receiving an award must collaborate formally with a research institution.

The SBIR/STTR programs consist of three phases:

- Phase I provides limited funding (up to $100,000 prior to the 2011 reauthorization and up to $150,000 thereafter) for feasibility studies.
- Phase II provides more substantial funding for further research and development (typically up to $750,000 prior to 2012 and $1 million after the 2011 reauthorization).[6]
- Phase III involves commercialization without providing access to any additional SBIR/STTR funding, although funding from other federal government accounts is permitted.

The SBIR program has four congressionally mandated goals: (1) stimulate technological innovation, (2) use small business to meet federal research and development (R&D) needs, (3) foster and encourage participation by minority and disadvantaged persons in technological innovation, and (4) increase private-sector commercialization derived from federal research and development.[7] The goals for the STTR program are to (1) stimulate technological innovation, (2) foster technology transfer through cooperative R&D between small businesses and research institutions, and (3) increase private-sector commercialization of innovations derived from federal R&D.[8] Each of the research agencies has sought to pursue

[4]SBIR awards can be made as grants or as contracts. Grants do not require the awardee to provide an agreed deliverable (for contracts this is often a prototype at the end of Phase II). Contracts are also governed by federal contracting regulations, which are considerably more onerous from the small business perspective. Historically, all Department of Defense (DoD) and National Aeronautics and Space Administration (NASA) awards have been contracts; all National Science Foundation (NSF) and most National Institutes of Health (NIH) awards have been grants, and the Department of Energy (DoE) has used both vehicles.

[5]Small Business Research and Development Enhancement Act, P.L. 102-564, S. 2941, Oct. 28, 1992.

[6]All resource and time constraints imposed by the program are somewhat flexible and are addressed by different agencies in different ways. For example, NIH and to a much lesser degree DoD have provided awards that are much larger than the standard amounts, and NIH has a tradition of offering no-cost extensions to allow for completion of work on an extended timeline.

[7]Small Business Innovation Development Act of 1982, P.L. 97-219, S. 881, July 22, 1982.

[8]Small Business Administration, "About STTR," https://www.sbir.gov/about/about-sttr, accessed July 9, 2015.

these goals in administering its SBIR/STTR programs, utilizing the administrative flexibility built into the SBIR program to address its unique mission needs.[9]

Although the SBIR and STTR programs have similar objectives, they differ, according to the National Institutes of Health (NIH), "in two major ways related to the Program Director (PD)/Principal Investigator (PI) and non-profit research partner. Under SBIR, the PD/PI must be primarily employed with the small business concern at the time of award and for the duration of the project period, unless a waiver is granted by the NIH. Under the STTR Program, primary employment is not stipulated, so the PD/PI may be primarily employed by either the small business concern or the collaborating non-profit research institution at the time of award and for the duration of the project period."[10]

The STTR program also differs from the SBIR program in that it requires that the small business concern formally collaborate with a nonprofit research institution. Research partnerships are permitted under the SBIR program, but the partnering research institution can complete no more than one-third of the Phase I work and no more than one-half of the Phase II work. In contrast, "Under STTR, the small business must perform at least 40 percent of the work and the research institution must perform at least 30 percent. The remaining 30 percent may be . . . [completed by] the small business concern, the collaborating non-profit research institution, or an additional third party."[11]

Over time, through a series of reauthorizations, SBIR/STTR legislation has required federal agencies with extramural R&D budgets in excess of $100 million to set aside a growing share of their budgets for the SBIR program and those with extramural R&D budgets in excess of $1 billion to set aside a growing share of their budgets for the STTR program (see Table 1-2). By FY2012, the 11 federal agencies, listed in Table 1-1, that administer SBIR/STTR programs were disbursing $2.4 billion dollars a year.[12] As shown in Figure 1-1, five agencies administer more than 96 percent of SBIR/STTR funds: Department of Defense (DoD), Department of Health and Human Services (HHS; including particularly NIH), National Aeronautics and Space Administration (NASA), National Science Foundation (NSF), and Department of Energy (DoE). Aggregate award amounts for the five largest agencies for FY2015 are provided in Table 1-2.

In December 2011, Congress reauthorized the SBIR/STTR programs for an additional 6 years,[13] with a number of important modifications. Many of these modifications—for example, changes in standard award size—were consistent

[9]The committee commended this flexibility in its 2008 assessment of the SBIR program. See Finding C, National Research Council, *An Assessment of the SBIR Program,* Washington DC: The National Academies Press, 2008, p. 59.

[10]See https://sbir.nih.gov/about/critical, accessed on July 9, 2015.

[11]Ibid.

[12]Small Business Association (SBA), SBIR/STTR annual report, http://www.sbir.gov/, accessed July 2015. FY2012 is the most recent year for which SBA publishes comparative data across agencies.

[13]Section 5137 of P.L. 112-81.

TABLE 1-1 Agencies Currently Participating in the SBIR and STTR Programs

Agency	SBIR Participant	STTR Participant
Department of Agriculture	X	
Department of Commerce	X	
Department of Defense	X	X
Department of Education	X	
Department of Energy	X	X
Department of Health and Human Services	X	X
Department of Homeland Security	X	
Department of Transportation	X	
Environmental Protection Agency	X	
National Aeronautics and Space Administration	X	X
National Science Foundation	X	X

SOURCE: Small Business Administration (SBA).

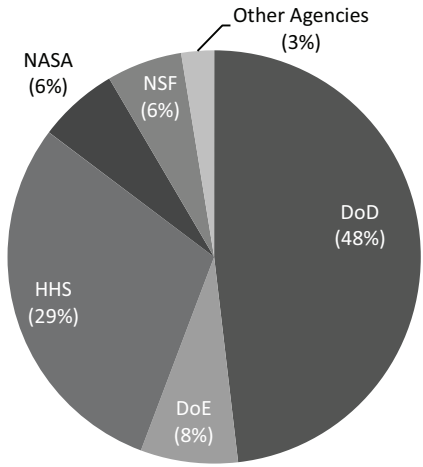

FIGURE 1-1 Percentage of total SBIR/STTR funding by agency, FY2012.
SOURCE: SBA, SBIR/STTR annual report, http://www.sbir.gov, accessed June 4, 2015.

with or followed recommendations made in a 2008 National Research Council (NRC)[14] report on the SBIR program, a study mandated as a part of the program's

[14]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council or NRC are used in an historic context identifying programs prior to July 1.

TABLE 1-2 SBIR/STTR Funding by the Five Principal Funding Agencies, FY 2015

Agency	Sum of Award Amounts (Dollars)
Department of Defense	1,013,041,252
Department of Energy	201,954,290
Department of Health and Human Services	774,065,517
National Aeronautics and Space Administration	159,122,575
National Science Foundation	130,236,977
Total	2,278,420,611

SOURCE: SBA awards database, https://www.sbir.gov/sbirsearch/award/all, accessed July 16, 2015.

2000 reauthorization.[15] The 2011 reauthorization also called for further studies by the Academies.[16]

The first-round assessment resulted in 11 reports including the 2008 report cited above (see Box 1-1 for the list of reports). In a follow-up to the first round, NIH requested from the Academies an assessment focused on operational questions in order to identify further improvements to the program.

This introduction provides general context for the analysis of the program developments and transitions described in the remainder of the report. The first section provides an overview of the history of the SBIR/STTR programs across the federal government. This is followed by a summary of the major changes mandated through the 2011 reauthorization and the subsequent Small Business Administration (SBA) Policy Directive; a review of the programs' advantages and limitations, in particular the challenges faced by entrepreneurs using (and seeking to use) the program and by agency officials running it; and a summary of the technical challenges facing this assessment and recommended solutions to those challenges.

PROGRAM HISTORY AND STRUCTURE[17]

During the 1980s, the perceived decline in U.S. competitiveness due to Japanese industrial growth in sectors traditionally dominated by U.S. firms—autos, steel, and semiconductors—led to concerns about future economic growth in the

[15]National Research Council, *An Assessment of the SBIR Program.* The National Research Council's first-round assessment of the SBIR program was mandated in the SBIR Reauthorization Act of 2000, P.L. 106-554, Appendix I-H.R. 5667, Section 108.

[16]The National Defense Reauthorization Act for Fiscal Year 2012, P.L. 112-81, Section 5137.

[17]Parts of this section are based on the Academies' previous report on the NIH SBIR program, *An Assessment of the SBIR Program at the National Institutes of Health,* Washington, DC: The National Academies Press, 2009.

BOX 1-1
The Academies' First-Round Assessment of the Small Business Innovation Research (SBIR) Program

Mandated by Congress in the 2000 reauthorization of the SBIR program, the National Research Council's first-round SBIR assessment reviewed the SBIR programs at the Department of Defense, National Institutes of Health, National Aeronautics and Space Administration, Department of Energy, and National Science Foundation. In addition to the reports on the SBIR program at each agency and a report on the program methodology, the study resulted in a summary of a symposium on program diversity and assessment challenges, a summary of a symposium on the challenges in commercializing SBIR-funded technologies, two reports on special topics, as well as the committee's summary report, *An Assessment of the SBIR Program*. In all, 11 study reports were published by the National Academies Press:

An Assessment of the Small Business Innovation Research Program: Project Methodology (2004)
SBIR—Program Diversity and Assessment Challenges: Report of a Symposium (2004)
SBIR and the Phase III Challenge of Commercialization: Report of a Symposium (2007)
An Assessment of the SBIR Program at the National Science Foundation (2007)
An Assessment of the SBIR Program at the Department of Defense (2009)
An Assessment of the SBIR Program at the Department of Energy (2008)
An Assessment of the SBIR Program (2008)
An Assessment of the SBIR Program at the National Aeronautics and Space Administration (2009)
An Assessment of the SBIR Program at the National Institutes of Health (2009)
Venture Funding and the NIH SBIR Program (2009)
Revisiting the Department of Defense SBIR Fast Track Initiative (2009)

United States.[18] A key concern was the perceived failure of American industry "to translate its research prowess into commercial advantage."[19] Although the United States enjoyed dominance in basic research—much of which was feder-

[18]See J. Alic, "Evaluating competitiveness at the Office of Technology Assessment," *Technology in Society,* 9(1):1-17, 1987, for a review of how these issues emerged and evolved within the context of a series of analyses at a Congressional agency.

[19]D.C. Mowery, "America's industrial resurgence (?): An overview," in D.C. Mowery, ed., *U.S. Industry in 2000: Studies in Competitive Performance,* Washington, DC: National Academy Press, 1999, p. 1. Other studies highlighting poor economic performance in the 1980s include M.L. Dertouzos et al., *Made in America: The MIT Commission on Industrial Productivity,* Cambridge, MA: The MIT Press, 1989; and O. Eckstein, *DRI Report on U.S. Manufacturing Industries,* New York: McGraw Hill, 1984.

ally funded—applying this research to the development of innovative products and technologies remained a challenge. As the great corporate laboratories of the post-war period were buffeted by change, new models such as the cooperative model utilized by some Japanese keiretsu seemed to offer greater sources of dynamism and more competitive firms.

At the same time, new evidence emerged to indicate that small businesses were an increasingly important source of both innovation and job creation.[20] This evidence reinforced recommendations from federal commissions dating back to the 1960s, that federal R&D funding should provide more support for innovative small businesses (which was opposed by traditional recipients of government R&D funding).[21]

Early-stage financial support to innovative technology-based small businesses for developing high-risk technologies with commercial promise was first advanced by Roland Tibbetts at NSF. In 1976, Mr. Tibbetts advocated shifting some NSF funding for this purpose. NSF adopted this initiative first, and after a period of analysis and discussion, the Reagan administration supported an expansion of this initiative across the federal government. Congress then passed the Small Business Innovation Research Development Act of 1982, which established the SBIR program.

Initially, the SBIR program required agencies with extramural R&D budgets in excess of $100 million[22] to set aside 0.2 percent of their funds for SBIR. Program funding totaled $45 million in the program's first year of operation (1983). Over the next 6 years, the set-aside grew to 1.25 percent.[23]

SBIR Reauthorizations of 1992 and 2000

The SBIR program approached reauthorization in 1992 amidst continued worries about the ability of U.S. firms to commercialize inventions. (See Box 1-2.) Finding that "U.S. technological performance is challenged less in the creation of new technologies than in their commercialization and adoption," the Academies

[20]For an alternate view, see S.J. Davis, J. Haltiwanger, and S. Schuh, *Small Business and Job Creation: Dissecting the Myth and Reassessing the Facts,* Working Paper No. 4492, Cambridge, MA: National Bureau of Economic Research, 1993. Evaluating the empirical basis for conventional claims about the job-creating prowess of small businesses, the authors find inter alia that conventional wisdom about the job-creating prowess of small business rests on misleading interpretations of the data.

According to Per Davidsson, these methodological fallacies, however, "ha[ve] not had a major influence on the empirically based conclusion that small firms are over-represented in job creation." See P. Davidsson, "Methodological concerns in the estimation of job creation in different firm size classes," Working Paper, Jönköping International Business School, 1996.

[21]For an overview of the origins and history of the SBIR program, see G. Brown and J. Turner, "The federal role in small business research," *Issues in Science and Technology,* Summer 1999, pp. 51-58.

[22]That is, those agencies spending more than $100 million on research conducted outside agency labs.

[23]Additional information regarding SBIR's legislative history can be accessed from the Library of Congress. See http://thomas.loc.gov/cgi-bin/bdquery/z?d097:SN00881:@@@L.

BOX 1-2
Commercialization Language from 1992 SBIR Reauthorization

Phase II "awards shall be made based on the scientific and technical merit and feasibility of the proposals, as evidenced by the first phase, considering, among other things, the proposal's commercial potential, as evidenced by—

(i) the small business concern's record of successfully commercializing SBIR or other research;
(ii) the existence of second phase funding commitments from private sector or non-SBIR funding sources;
(iii) the existence of third phase, follow-on commitments for the subject of the research; and
(iv) the presence of other indicators of the commercial potential of the idea."

SOURCE: P.L. 102-564-OCT. 28, 1992.

recommended an increase in SBIR funding as a means to improve the economy's ability to adopt and commercialize new technologies.[24]

The Small Business Research and Development Enhancement Act (P.L. 102-564) reauthorized the SBIR program until September 30, 2000, and doubled the set-aside rate to 2.5 percent. The legislation also more strongly emphasized the need for commercialization of SBIR-funded technologies.[25] Legislative language explicitly highlighted commercial potential as a criterion for awarding SBIR contracts and grants.

At the same time, Congress expanded the SBIR program's purposes to "emphasize the program's goal of increasing private sector commercialization developed through federal research and development and to improve the federal government's dissemination of information concerning the small business innovation, particularly with regard to woman-owned business concerns and by socially and economically disadvantaged small business concerns."[26]

The Small Business Reauthorization Act of 2000 (P.L. 106-554) extended the SBIR program until September 30, 2008. It also called for an NRC assessment of

[24]See National Research Council, *The Government Role in Civilian Technology: Building a New Alliance,* Washington, DC: National Academy Press, 1992, p. 29.

[25]Small Business Research and Development Enhancement Act, P.L. 102-564, S. 2941, October 28, 1992. See also R. Archibald and D. Finifter, "Evaluation of the Department of Defense Small Business Innovation Research program and the Fast Track Initiative: A balanced approach," in National Research Council, *The Small Business Innovation Research Program: An Assessment of the Department of Defense Fast Track Initiative,* Washington, DC: National Academy Press, 2000, pp. 211-250.

[26]Small Business Research and Development Enhancement Act, P.L. 102-564, S. 2941, October 28, 1992.

the program's broader impacts, including those on employment, health, national security, and national competitiveness.[27]

STTR Reauthorizations

Established by the Small Business Technology Transfer Act of 1992 (P.L. 102-564, Title II), the STTR program was reauthorized until the year 2001 by the Small Business Reauthorization Act of 1997 (P.L. 105-135) and reauthorized again until September 30, 2009, by the Small Business Technology Transfer Program Reauthorization Act of 2001 (P.L. 107-50).

As explained below, the SBIR/STTR Reauthorization Act of 2011 included a number of changes to the SBIR/STTR programs, including increases in the set-asides over the next 6 years and expanded eligibility for STTR awardees to take part in technical assistance programs.

The 2011 SBIR/STTR Reauthorization

The anticipated 2008 reauthorization was delayed in large part by a disagreement between long-time program participants and their advocates in the small business community and proponents of expanded access for venture-backed firms, particularly in biotechnology where proponents argued that the standard path to commercial success includes venture funding at some point.[28] Other issues were also difficult to resolve, but the conflict over participation of venture-backed companies dominated the process[29] following an administrative decision to exclude these firms more systematically.[30]

After a much extended discussion, passage of the National Defense Act of December 2011 reauthorized the SBIR/STTR programs through FY2017.[31] The new law maintained much of the core structure of both programs but made some

[27]The current assessment is congruent with the Government Performance and Results Act (GPRA) of 1993: http://govinfo.library.unt.edu/npr/library/misc/s20.html. As characterized by the Government Accountability Office (GAO), GPRA seeks to shift the focus of government decision making and accountability away from a preoccupation with the activities that are undertaken—such as grants dispensed or inspections made—to the results of those activities. See http://www.gao.gov/new.items/gpra/gpra.htm.

[28]For a review of the issues, see National Research Council, *Venture Funding and the NIH SBIR Program,* Washington DC: National Academies Press, 2009. See also D.C. Specht, "Recent SBIR extension debate reveals venture capital influence," *Procurement Law,* 45:1, 2009.

[29]W.H. Schacht, "The Small Business Innovation Research (SBIR) program: Reauthorization efforts," Congressional Research Service, Library of Congress, 2008.

[30]A. Bouchie, "Increasing number of companies found ineligible for SBIR funding," *Nature Biotechnology,* 21(10):1121-1122, 2003.

[31]SBIR/STTR Reauthorization Act of 2011, P.L. 112-81, December 31, 2011.

important changes, which were to be implemented via the SBA's subsequent Policy Guidance.[32]

The eventual compromise on the venture funding issue allowed (but did not require) agencies to award up to 25 percent of their SBIR grants or contracts (at NIH, DoE, and NSF) or 15 percent (at the other awarding agencies) to firms that benefit from private, venture capital investment. It is too early in the implementation process to gauge the impact of this change.

The reauthorization made changes to the SBIR program that were recommended in prior Academies reports.[33] These included the following:

- Increased award size limits
- Expanded program size
- Enhanced agency flexibility—for example, for Phase I awardees from other agencies to be eligible for Phase II awards or to provide an additional Phase II award
- Improved incentives for the utilization of SBIR technologies in agency acquisition programs
- Explicit requirements for better connecting prime contractors with SBIR awardees[34]
- Substantial emphasis on developing a more data-driven culture, which has led to several major reforms, including the following:
  - adding numerous areas of expanded reporting
  - extending the Academies' evaluation
  - adding further evaluation, such as by the Government Accountability Office and Comptroller General
  - tasking the SBA with creating a unified platform for the collection of data from agencies with SBIR/STTR agencies
- Expanded management resources (through provisions permitting use of up to 3 percent of program funds for [defined] management purposes)
- Expanded commercialization support (through provisions providing companies with direct access to commercialization support funding and through approval of the approaches piloted in Commercialization Pilot Programs)
- Options for agencies to add flexibility by developing other pilot programs—for example, to allow awardees to skip Phase I and apply for a Phase II award directly or for NIH to support a new Phase 0 pilot program

[32]See SBA post, S. Greene, "Implementing the SBIR and STTR Reauthorizations: Our Plan of Attack," 02/21/2012. http://www.sbir.gov/news/implementing-sbir-and-sttr-reauthorization-our-plan-attack, February 21, 2012.

[33]See Appendix B for a list of the major changes to the SBIR program resulting from the 2011 Reauthorization Act.

[34]Prime Contractors, who have primary contracts for a project, are often interested in subcontracting with small businesses.

The reauthorization also made changes that were not mentioned in previous reports of the Academies. These included the following:

- Expansion of the STTR program
- Limitations on agency flexibility—particularly in the provision of larger awards
- Introduction of commercialization benchmarks for companies, which must be met if companies are to remain in the program. These benchmarks are to be established by each agency.

Other clauses of the legislation affect operational issues, such as the definition of specific terms (such as "Phase III"), continued and expanded evaluation by the Academies, mandated reports from the Comptroller General on combating fraud and abuse within the SBIR program, and protection of small firms' intellectual property within the program.

PREVIOUS RESEARCH ON SBIR

Studies pre-dating the Academies' first-round assessment in 2002–2009, most notably by the Government Accountability Office and the SBA, focused only on specific aspects or components of the SBIR/STTR programs.[35] In addition, prior to the first-round assessment, there had been few internal assessments of agency SBIR/STTR programs. The academic literature on SBIR was also limited,[36] except for an assessment in the 1990s by Joshua Lerner of the Harvard Business School who found "that SBIR awardees grew significantly faster than a matched set of firms over a ten-year period."[37]

To help fill this assessment gap, the NRC's Committee for Government-Industry Partnerships for the Development of New Technologies (GIP, which preceded the NRC's first-round congressionally mandated study of the SBIR program) convened a workshop in 1998 to discuss the SBIR program's history

[35]An important step in the evaluation of the program has been to identify existing evaluations of the program. These include U.S. Government Accounting Office, *Federal Research: Small Business Innovation Research Shows Success But Can Be Strengthened,* Washington, DC: U.S. General Accounting Office, 1992; and U.S. Government Accounting Office, *Evaluation of Small Business Innovation Can Be Strengthened,* Washington, DC: U.S. General Accounting Office, 1999. There is also a 1999 unpublished SBA study on the commercialization of SBIR Phase II awards from 1983 to 1993 among non-DoD agencies.

[36]Early examples of evaluations of the SBIR program include S. Myers, R. L. Stern, and M. L. Rorke, *A Study of the Small Business Innovation Research Program,* Lake Forest, IL: Mohawk Research Corporation, 1983; and Price Waterhouse, *Survey of Small High-tech Businesses Shows Federal SBIR Awards Spurring Job Growth, Commercial Sales,* Washington, DC: Small Business High Technology Institute, 1985.

[37]See J. Lerner, "The government as venture capitalist: The long-run effects of the SBIR program," *Journal of Business,* 72(3), 1999.

and rationale, review existing research, and identify areas for further research and program improvements.[38] In addition, in its report on the SBIR Fast Track Initiative at the Department of Defense, the GIP committee found that the SBIR program contributed to mission goals by funding "valuable innovative projects."[39] It concluded that a significant number of these projects would not have been undertaken absent SBIR funding[40] and that DoD's Fast Track Initiative encouraged the commercialization of new technologies[41] and the entry of new firms into the program.[42] The GIP committee also found that the SBIR program improved both the development and utilization of human capital and the diffusion of technological knowledge.[43] Case studies provided some evidence that the knowledge and human capital generated by the SBIR program have positive economic value, which spills over into other firms through the movement of people and ideas.[44] Furthermore, by validating promising new technologies, SBIR awards encourage further private-sector investment in an award-winning firm's technology.[45]

ROUND ONE ASSESSMENT OF THE SBIR PROGRAM

The 2000 SBIR reauthorization mandated that the NRC complete a comprehensive assessment of the SBIR program.[46] The assessment of the SBIR programs at DoD, NIH, NASA, NSF, and DoE began in 2002 and was conducted in three steps. As a first step, the committee authoring this study developed a research methodology[47] and gathered information about the program by convening workshops where officials at the relevant federal agencies described their program operations, challenges, and accomplishments. These meetings highlighted the important differences in agency goals, practices, and evaluations. They also served to describe the evaluation challenges that arise from the diversity in program objectives and practices.[48]

The committee implemented the research methodology during the second step. As set out in the methodology, multiple data collection modalities were deployed. This included the first large-scale survey of SBIR award recipients. Case

[38]See National Research Council, *The Small Business Innovation Research Program: Challenges and Opportunities,* Washington, DC: National Academy Press, 1999.

[39]National Research Council, *An Assessment of the DoD SBIR Fast Track Initiative*, 32.

[40]Ibid., 32.

[41]Ibid., 33.

[42]Ibid., 34.

[43]Ibid., 33.

[44]Ibid., 33.

[45]Ibid., 33.

[46]SBIR Reauthorization Act of 2000, P.L. 106-554, Appendix I-H.R. 5667, Section 108.

[47]National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology,* Washington, DC: The National Academies Press, 2004.

[48]Adapted from National Research Council, *SBIR: Program Diversity and Assessment Challenges,* op. cit.

studies were also developed on a wide variety of SBIR firms. The committee then evaluated the results and developed the findings and recommendations presented for improving the effectiveness of the SBIR program.

During the third step, the committee reported on the program through a series of publications in 2008-2010: five individual volumes on the major funding agencies and an additional overview volume titled *An Assessment of the SBIR Program*.[49] Together, these reports provided the first detailed and comprehensive review of the SBIR program and, as noted above, served as an important input into SBIR reauthorization prior to December 2011 (see Box 1-1).

CURRENT, ROUND TWO STUDY: CHALLENGES AND OPPORTUNITIES

The first-round study of the SBIR program found that the program was, overall, "sound in concept and effective in practice."[50] Furthermore, in its review of the NIH SBIR program, the committee concluded: "**The NIH SBIR program is making significant progress in achieving the congressional goals for the program**"[51] [emphasis in original]. The current study, described in the Statement of Task in Box 1-3, provides a second snapshot to measure the program's progress against its legislative goals.

This volume partially addresses this Statement of Task. It is supplemented by a number of workshops and other publications from the Committee on Capitalizing on Science, Technology, and Innovation: An Assessment of the Small Business Innovation Research Program—Phase II. For example, workshops were convened on the participation of women and minorities in the SBIR/STTR programs (February 2013), the evolving role of university participation in the programs (February 2014), the relationship between state innovation programs and the SBIR program (October 2014), the STTR program (May 2015), and the economics of entrepreneurship in relation to the SBIR program (June 2015). The committee published a report on *Innovation, Diversity, and Success in the SBIR/STTR Programs* (2015), based on the 2013 workshop.

The current volume updates the Academies' 2009 assessment of the NIH SBIR program, by refreshing the data, providing new descriptions of recent programs and developments, and providing fresh company case studies. Guided by this Statement of Task, the committee has sought answers to questions such as the following:

[49]National Research Council, *An Assessment of the SBIR Program.*

[50]Ibid., 54.

[51]National Research Council, *An Assessment of the Small Business Innovation Research Program at the National Institutes of Health,* 19.

- Are there initiatives and programs within NIH that have made a significant difference to outcomes and in particular to agency take-up of SBIR-funded technologies?
- Can they be replicated and expanded?
- What are the main barriers to meeting Congressional objectives more fully?
- What program adjustments would better support commercialization?

BOX 1-3
Statement of Task

In accordance with H.R. 5667, Sec. 108, enacted in Public Law 106-554, as amended by H.R. 1540, Sec. 5137, enacted in Public Law 112-81, the National Research Council is to review the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) programs at the Department of Defense, the National Institutes of Health, the National Aeronautics and Space Administration, the Department of Energy, and the National Science Foundation. Building on the outcomes from the Phase I study, this second study is to examine both topics of general policy interest that emerged during the first-phase study and topics of specific interest to individual agencies.

Drawing on the methodology developed in the previous study, an ad hoc committee will issue a revised survey, revisit case studies, and develop additional cases, thereby providing a second snapshot to measure the program's progress against its legislative goals. The committee will prepare one consensus report on the SBIR program at each of the five agencies, providing a second review of the operation of the program, analyzing new topics, and identifying accomplishments, emerging challenges, and possible policy solutions. The committee will prepare an additional consensus report focused on the STTR Program at all five agencies. The agency reports will include agency-specific and program-wide findings on the SBIR and STTR programs to submit to the contracting agencies and Congress.

Although each agency report will be tailored to the needs of that agency, all reports will, where appropriate:

1. Review institutional initiatives and structural elements contributing to programmatic success, including gap funding mechanisms such as applying Phase II-plus awards more broadly to address agency needs and operations and streamlining the application process.
2. Explore methods to encourage the participation of minorities and women in SBIR and STTR.
3. Identify best practice in university-industry partnering and synergies with the two programs.
4. Document the role of complementary state and federal programs.
5. Assess the efficacy of post-award commercialization programs.

In partial fulfillment of this Statement of Task, this volume presents the committee's review of the operation of the SBIR/STTR program at NIH.

- Are there tools that would expand utilization by woman- and minority-owned firms and participation by female and minority principal investigators?
- Can links with universities be improved?
- Are there aspects of the program that make it less attractive to small firms? Could they be addressed?
- What can be done to expand access in underserved states while maintaining the competitive character of the program?
- Can the program generate better data on both process and outcomes and use those data to fine-tune program management?

STUDY METHODOLOGY

The SBIR/STTR programs are unique in terms of scale and mission focus. In addition, the evidence suggests that there are no truly comparable programs in the United States, and those in other countries operate in such different ways that their relevance is limited.[52] Thus, it is difficult to identify programs comparable to SBIR/STTR against which to benchmark their results.

Assessing the SBIR/STTR programs at NIH is challenging for other reasons as well. Unlike DoD and NASA, SBIR/STTR awards at NIH are not primarily designed to generate tools and capabilities for agency use. They are instead explicitly designed to generate technologies that will be adopted outside the agency, primarily in the private sector. Thus success cannot be measured internally by commercialization of projects sold to the agency.

The NIH SBIR/STTR programs are also highly decentralized. Although the SBIR/STTR program office within the Office of Extramural Programs sets policy and provides critical cross-agency communication flows, as well as links the program to outside stakeholders, award funding is determined by each Institute or Center (IC) separately. ICs take different views of the program and use different approaches to program management. Therefore, generalizations about the NIH SBIR/STTR programs must be made with care. Indeed, approximately 24 separate programs are run by the various NIH ICs.

Focus on Legislative Objectives

This volume—and this study—do not seek to provide a comprehensive review of the value of the SBIR/STTR programs, in particular measured against other possible uses of federal funding. Such a review is beyond the study's scope. Rather, the work is focused on assessing the extent to which the NIH SBIR/STTR programs have met their congressionally mandated objectives, determining in

[52]See National Academies of Sciences, Engineering, and Medicine, Workshop on "Learning from Each Other: U.S. European Perspectives on Small Business Innovation Programs," Washington, DC, March 19, 2015.

particular whether recent initiatives have improved program outcomes, and providing recommendations for further program improvements.[53]

Thus, as in the first-round study, this second-round study will "*not* consider whether or not SBIR should exist"—Congress and the President have already decided affirmatively on this question, most recently in the 2011 reauthorization of the program.[54] Rather, this study is charged with "providing assessment-based findings of the benefits and costs of SBIR . . . to improve public understanding of the program, as well as recommendations to improve the program's effectiveness." Also as in the first-round study, this study will "*not* seek to compare the value of one area with other areas; this task is the prerogative of the Congress and the Administration acting through the agencies. Instead, the study is concerned with the effective review of each area."[55]

Defining Commercialization

Commercialization offers practical and definitional challenges. As described in Chapter 5, several different definitions of commercialization can be used when discussing the SBIR/STTR programs. In fact, it is important to use more than one simple definition. For example, the percentage of funded projects that reach the marketplace is not the only measure of commercial success.

In the private sector, commercial success over the long term requires profitability. However, in the short term, the path to successful commercialization can involve many different aspects of commercial activity, from product rollout to licensing to patenting to acquisition. Even during new product rollout, companies often do not generate immediate profits. This report uses multiple metrics to address the question of commercialization (see Chapter 5).

Quantitative Assessment Methods

More practically, several issues relate to the application of quantitative assessment methods, including decisions about which kinds of program participants should be targeted for survey deployment, the number of responses that are appropriate, selection bias, nonresponse bias, the design and implementation of survey questionnaires, and the level of statistical evidence required for drawing conclusions in this case. These and other issues were discussed at a workshop

[53]These limited objectives are consistent with the methodology developed by the committee. See National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology.*

[54]National Defense Authorization Act of 2012 (NDAA), HR.1540, Title LI.

[55]National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology.*

and summarized in a 2004 report.[56] Also, as noted above, a peer-reviewed report on the study methodology completed by the first-round committee provided the baseline for the initial study and for follow-on studies—including this one.[57]

Survey Development

For the current study, a survey of SBIR and STTR award recipients was developed and deployed, a necessity given the absence of quantitative outcomes data at NIH. The survey was based closely on previous surveys, particularly the 2005 Survey that focused exclusively on SBIR, but nonetheless included significant improvements.[58] The description of the survey and improvements in methodology, including a discussion of the survey outreach and response, are documented in Appendix A. Most notably, the survey development made an ambitious but ultimately unsuccessful effort to develop a comparison group to provide context and a benchmark for analyzing the results (this effort is also discussed in Appendix A).

The survey delved more deeply into the demographics of the program. It also included questions about the role of agency liaisons who deal with contract operations and thereby provide a link between individual projects and NIH. Furthermore, it provided unique opportunities to collect qualitative opinions on the program and recommendations for improvement from award recipients.

It was the intention of the 2014 Survey to send a questionnaire to every principal investigator (PI) who received a Phase II award from NIH during fiscal years 2001-2010. The preliminary population prior to contact was 3,375. Of these, 1,723 were determined to be not contactable at the SBIR/STTR company listed in the NIH awards database.[59] The remaining 1,652 awards constitute the effective population for this study. From this group, 726 responses were received, for a preliminary population response rate of 21.5 percent and an effective population response rate of 43.9 percent. PIs of more than one awarded project were asked to complete a maximum of two questionnaires.

Appendix A provides a detailed discussion of the issues related to quantitative methodologies, as well as a review of potential biases. As a result of the relatively small response rate, there are significant limitations on the conclusions that can be drawn from this quantitative assessment, which is reflected in the wording of findings and recommendations (Chapter 8). At the same time, drawing on

[56]National Research Council, *The Small Business Innovation Research Program: Program Diversity and Assessment Challenges,* National Academies Press, Washington DC, 2004.

[57]National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology.*

[58]The survey carried out as part of this study was administered in 2014, and the survey completed as part of the Academies' first-round assessment of the SBIR program was administered in 2005. In this volume all survey references are to the 2014 survey unless noted otherwise.

[59]See Appendix A for a description of the survey effort.

quantitative analysis is a crucial component of the overall study, reflective of the need to identify and assess outcomes that are found only by querying individual projects and participating companies.

A Complement of Approaches

Partly because of these limitations, the 2004 methodology report stressed the importance of utilizing a complement of research modalities, an approach that has been adopted here.[60] Although quantitative assessment represents the bedrock of our research and provides insights and evidence that could not be generated through any other modality, it is, in and of itself, insufficient to address the multiple questions posed in this analysis. Consequently, we undertook a series of additional activities:

- **Case studies.** We conducted in-depth case studies of 20 NIH SBIR recipients. These companies were geographically and demographically diverse (by sex and race), funded by different NIH ICs, focused on different kinds of technologies, and at different stages of the company lifecycle. Lessons from the case studies are described in Chapter 7, and the case studies themselves are included as Appendix E.
- **Workshops.** We conducted workshops, including workshops to discuss the participation of women and minorities and the role of universities in the SBIR/STTR programs,[61] to allow stakeholders, agency staff, and academic experts to provide insights into program operations, as well as to identify issues that need to be addressed.
- **Analysis of agency data.** As appropriate, we analyzed and included data from NIH that cover various aspects of SBIR/STTR activities.
- **Open-ended responses from SBIR/STTR recipients.** For the first time, we collected textual responses in the survey. More than 450 recipients provided narrative comments. These comments are addressed in Chapter 7.
- **Agency consultations.** We engaged in discussions with agency staff at several of the Centers about the operation of their programs and the challenges they face.

[60]National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology.*

[61]Workshops convened by the committee as part of the overall analysis include *NASA Small Business Innovation Research Program Assessment: Second Phase Analysis,* January 28, 2010; *Early-Stage Capital in the United States: Moving Research Across the Valley of Death and the Role of SBIR,* April 16, 2010; *Early-Stage Capital for Innovation—SBIR: Beyond Phase II,* January 27, 2011; *NASA's SBIR Community: Opportunities and Challenges,* June 21, 2011; *Innovation, Diversity, and Success in the SBIR/STTR Programs,* February 7, 2013; *Commercializing University Research: The Role of SBIR and STTR,* February 5, 2014; *SBIR/STTR & the Role of State Programs,* October 7, 2014; *The Small Business Technology Transfer Program,* May 1, 2015, and the *Economics of Entrepreneurship*, June 29, 2015. Each of these workshops was held in Washington, DC.

- **Literature review.** Since the start of our research in this area, a number of academic and policy papers have been published that address various aspects of the SBIR/STTR programs, many drawing from the survey and other data made available by our reviews. In addition, other organizations—such as the Government Accountability Office—have reviewed specific parts of the SBIR/STTR programs. The committee has incorporated references to this work, where useful, into its analysis.

Data Sources and Limitations

Multiple research modalities are especially important because limitations still exist in the data collected for the SBIR/STTR programs. As described in Chapter 5, the survey deployed in the past by NIH to identify SBIR outcomes is no longer current. Furthermore, NIH thus does not maintain a comprehensive dataset on award outcomes and cannot provide data about the take-up of technologies funded by the SBIR/STTR programs. NIH is however making efforts to address this issue (see Chapter 5).

The lack of current outcomes data from NIH means that the current survey provides the only available quantitative data on SBIR/STTR outcomes and processes at NIH.

Cooperation with NIH

In general, we received substantial cooperation from NIH and its ICs. Agency staff and researchers deployed by the committee engaged in numerous discussions, and NIH provided data, papers, and presentations.

In short, within the limitations described, the study utilizes a complement of tools to ensure that a wide spectrum of perspectives and expertise is reflected in the findings and recommendations. Appendix A provides an overview of the methodological approaches, data sources, and survey tools used in this study.

ORGANIZATION OF THE REPORT

The analysis and conclusions are organized as follows. Chapter 2 provides a review of program operations, describing the program in some detail and addressing a range of issues related to program management. Chapter 3 describes and analyzes agency initiatives that have been developed and implemented over the past 8 to 10 years, including the role of awards larger than SBA guidelines (approved with an SBA waiver). Chapter 4 reviews NIH data concerning applications and awards, drawing out demographic and geographic differences as well as previous experience with the program. Chapter 5 provides a quantitative assessment of the program, based primarily on the 2014 Survey in the absence of data from NIH or other sources. Chapter 6 addresses the congressional man-

date to foster the participation of women and minorities, utilizing data from NIH and from the 2014 Survey. Chapter 7 draws on company case studies and on the textual responses from survey respondents to provide a qualitative picture of program operations, issues, and possible solutions. Chapter 8 provides the findings and recommendations from the study.

The report's appendixes provide additional information. Appendix A sets out an overview of the methodological approaches, data sources, and survey tools used in this assessment. Appendix B describes key changes to the SBIR program from the 2011 reauthorization. Appendix C reproduces the 2014 Survey instrument. Appendix D lists the research institutions involved in NIH SBIR/STTR awards. Appendix E presents the case studies of selected firms with NIH awards. Appendix F provides a glossary of acronyms used, and Appendix G provides a list of references.

2

NIH Program Management

The National Institutes of Health (NIH) is a large and complex organization, with 24 different Institutes and Centers (ICs), each with a different mission and different needs. Although SBIR/STTR is managed by the NIH SBIR/STTR Program Office, all awards are made by individual ICs, using procedures that they themselves largely determine.

This chapter describes a number of aspects of SBIR/STTR program management. It addresses the processes through which awards are solicited and funding decisions are made. It also focuses on some of the initiatives developed by NIH to support these processes, such as the commercialization training and support program and efforts to attract new applicants. The focus on the selection process reflects the fact that it was the subject of concern for case study companies and many survey respondents. The funding gap between Phase I and Phase II receives attention, because it can have a seriously negative effect on small companies. The chapter also describes some of the challenges facing award recipients, notably in relation to the clinical trials through which almost one-half must work before they can sell their products commercially. Finally, the chapter considers data collection and analysis, which is a core element in an effective and data-driven program.

A COMPLEX PROGRAM

The assessment of the NIH SBIR/STTR programs is made more challenging by the growing complexity of funding mechanisms at NIH in recent years. Expanding beyond the original Phase I/Phase II grants, the programs now include Phase I/Phase II grants, Phase I/Phase II contracts, Fast Track awards that include both Phase I and Phase II, Phase IIB awards, Bridge awards, Direct to Phase II,

and supplementary awards. These different awards are discussed in this chapter. Table 2-1 shows the number of awards and amount of funding provided through Phase I, Phase II, and Fast Track for SBIR/STTR in fiscal year (FY) 2014. Overall, the SBIR/STTR programs at NIH provided $805.5 million in FY2014, of which $94.4 million was disbursed by the STTR program.

The NIH SBIR/STTR programs support research in a range of areas. A chart from the National Cancer Institute (NCI) illustrates the breadth of the program at that Institute alone, which ranges from short cycle work in health care software and information technology (IT) to the very long cycle of research and development for therapeutic drugs (Figure 2-1).

TABLE 2-1 NIH SBIR/STTR Funding by Program, Phase, and Funding Mechanism, FY2014

	Funding (Millions of Dollars)				
	Phase I	Phase II	Fast Track (Phases I and II combined)	Total	Percentage of Total Funding
SBIR grants					
competing (new)	146.1	170.4		316.5	39.3
non-competing (renewals)	26.0	212.5		238.5	29.6
Fast Track (new)			17.1	17.1	2.1
Fast Track (renewals)			29.9	29.9	3.7
SBIR grants total	172.1	382.9	47.0	602.0	74.7
STTR grants					
competing (new)	35.8	21.7		57.5	7.1
non-competing (renewals)	5.6	23.9		29.5	3.7
Fast Track (new)			1.1	1.1	0.1
Fast Track (renewals)			6.3	6.3	0.8
STTR total	41.4	45.6	7.4	94.4	11.7
SBIR contracts	33.2	75.9		109.1	13.5
Total	246.7	504.4	54.4	805.5	100.0
SBIR total	205.3	458.8	47	711.1	88.3
STTR total	41.4	45.6	7.4	94.4	11.7

SOURCE: NIH Reporter database, Table 126.

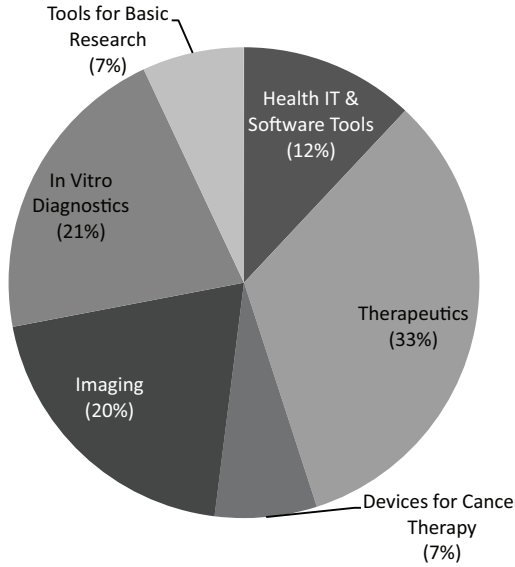

FIGURE 2-1 Funding areas for NCI SBIR/STTR program.
SOURCE: Patti Weber and Andy Kurtz (NCI), "Leveraging NCI SBIR/STTR Opportunities," webinar presentation, March 6, 2014.

MAJOR FUNDING MECHANISMS

Pathways to Funding

A number of pathways to funding exist within the NIH SBIR/STTR programs. All fall under the general heading of funding opportunity announcements (FOAs). FOAs of all kinds are published weekly in the NIH Guide for Grants and Contracts, which is delivered to subscribers in electronic form.

- **Parent announcement.** The primary mechanism is the parent announcement from each IC, which is a broad description of IC interests, defined by the agency as an "NIH-wide funding opportunity announcement enabling applicants to submit an electronic investigator-initiated grant application for a specific activity code, e.g., Research Project Grant (Parent R01). Some NIH Institutes or Centers may not participate in all parent announcements."[1]
- **Omnibus Solicitation.** Parent announcements from ICs are aggregated into the Omnibus Solicitation, which includes areas of interest to many of

[1]NIH Grants Glossary, http://grants.nih.gov/grants/glossary.htm#P, accessed February 14, 2014.

the 24 ICs. The NIH SBIR program publishes one Omnibus Solicitation annually, with three deadline dates for proposal receipt.

- **Contract solicitation.** NIH publishes one contract solicitation annually, where applicants can seek to meet NIH needs through the contract mechanism, rather than through the more usual grants. (Contracts are discussed separately below.)
- **Direct to Phase II solicitation.** Topics that will be funded under the direct to Phase II authority are published in a separate direct to Phase II solicitation, which applies to SBIR only.
- **Special funding opportunity announcements** are periodically issued by one or more ICs and focus on specific areas of science that are priorities of the issuing ICs. Special requirements (e.g., amount of funds that may be requested) may be imposed under these announcements.[2] Proposals may also be reviewed directly by the IC rather than through the agency-wide Center for Scientific Review (discussed below).

According to NIH staff, although these various publications provide guidance about NIH priorities, applicants are welcome to apply for funding for projects that are not covered by the various FOAs. This practice lies in contrast with those of the contract research agencies—Department of Defense (DoD) and National Aeronautics and Space Administration (NASA)—and also with the Department of Energy (DoE) and to a lesser extent the National Science Foundation (NSF), where the topic descriptions in the solicitation are more binding.

These different pathways can utilize different funding mechanisms. Along with the standard SBIR and STTR Phase I, NIH offers the following mechanisms:

- **Fast Track.** This program allows companies to apply for Phase I and Phase II simultaneously, by providing what is effectively a Phase II application that shows the milestones that would be necessary for both Phase I and Phase II funding. Some of the companies studied for this report applied for and received Fast Track funding but found it to be a difficult pathway suitable only for a small number of proposals. In FY2014, Fast Track accounted for 5.8 percent of total Phase I/Phase II SBIR funding.
- **Direct to Phase II.** Under the 2011 reauthorization, agencies are permitted to offer companies the opportunity to skip Phase I and apply directly for Phase II funding. This policy innovation emerged in large part in response to requests by NIH, the only agency actively using this mechanism. Data on take-up is discussed in Chapter 3. Direct to Phase II applications must show the equivalent of Phase I results prior to award.

[2]NIH Description of the NIH Guide for Grants and Contracts, http://grants.nih.gov/grants/guide/description.htm#foa, accessed February 14, 2014.

- **Contracts.** Although a large majority of its SBIR and STTR awards are grants, NIH does provide some contracts as well for SBIR. Contracts are for "direct benefit of the government," but this benefit is in the form of achieving SBIR goals, not for developing use of technologies at NIH. NIH may be one customer but not the only customer—these are not fee for service contracts. The contracting mechanism is somewhat different from the standard grants mechanism and is discussed in more detail below. NCI has been particularly active in using contracts and provided 35 percent of its SBIR funding through this mechanism in FY2013 (see Figure 2-4).
- **Phase IIB.** For a number of years, NIH has used the Phase IIB mechanism to address the gap between the end of Phase II funding and the point at which technologies become attractive to private investors by offering additional funding as companies traverse the difficult and expensive regulatory process. These additional awards were originally known as Competing Continuation Awards and are now known as Phase IIB awards. Distinct from NSF's Phase IIB awards, they offer up to $1 million annually for a period of 3 years and are awarded in addition to Phase II funding.[3] Some ICs, notably NCI, offer a separate program that is a variation on Phase IIB that acts similar to Bridge awards to support commercialization at the end of Phase II.
- **Bridge awards.** Bridge awards also provide awards of up to $1 million annually for up to 3 years. In this case, however, NCI focuses on projects that are particularly ripe for commercialization that address high-priority topic areas for NCI. More importantly, for an application to be "competitive," NCI expects it to bring in matching funds. As of March 2014, NCI had made 16 Bridge awards totaling more than $35 million, which had attracted matching funds of more than $94 million (Figure 2-2).[4]

Bridge awards provide milestone-driven funding (see Figure 2-3). Matching funds are not legally mandatory, but NCI has determined that such funding will be required in practice.

The considerable variety of funding mechanisms and pathways at NIH generates a flexible and complex funding landscape, which is further characterized by the varying extent to which the different ICs participate. Not all ICs participate in all of these mechanisms, and those that do, do so to varying and changeable degrees.

[3]This is not consistent across ICs. The National Heart, Lung, and Blood Institute offers $3 million over 3 years, but doesn't stipulate the annual amount.

[4]Patti Weber and Andy Kurtz (NCI), "Leveraging NCI SBIR/STTR Opportunities," webinar presentation, March 6, 2014.

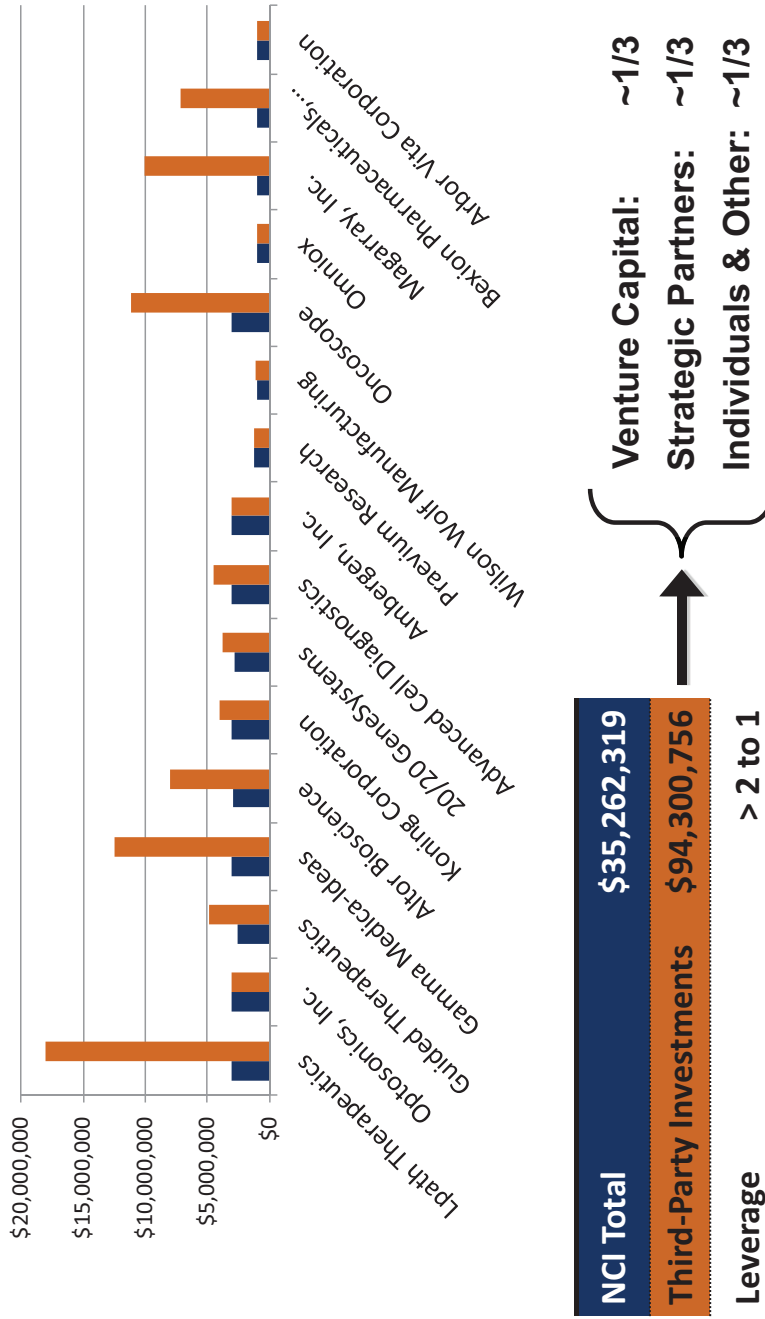

FIGURE 2-2 Bridge awards at NCI.
SOURCE: Patti Weber and Andy Kurtz (NCI), "Leveraging NCI SBIR/STTR Opportunities," webinar presentation, March 6, 2014.

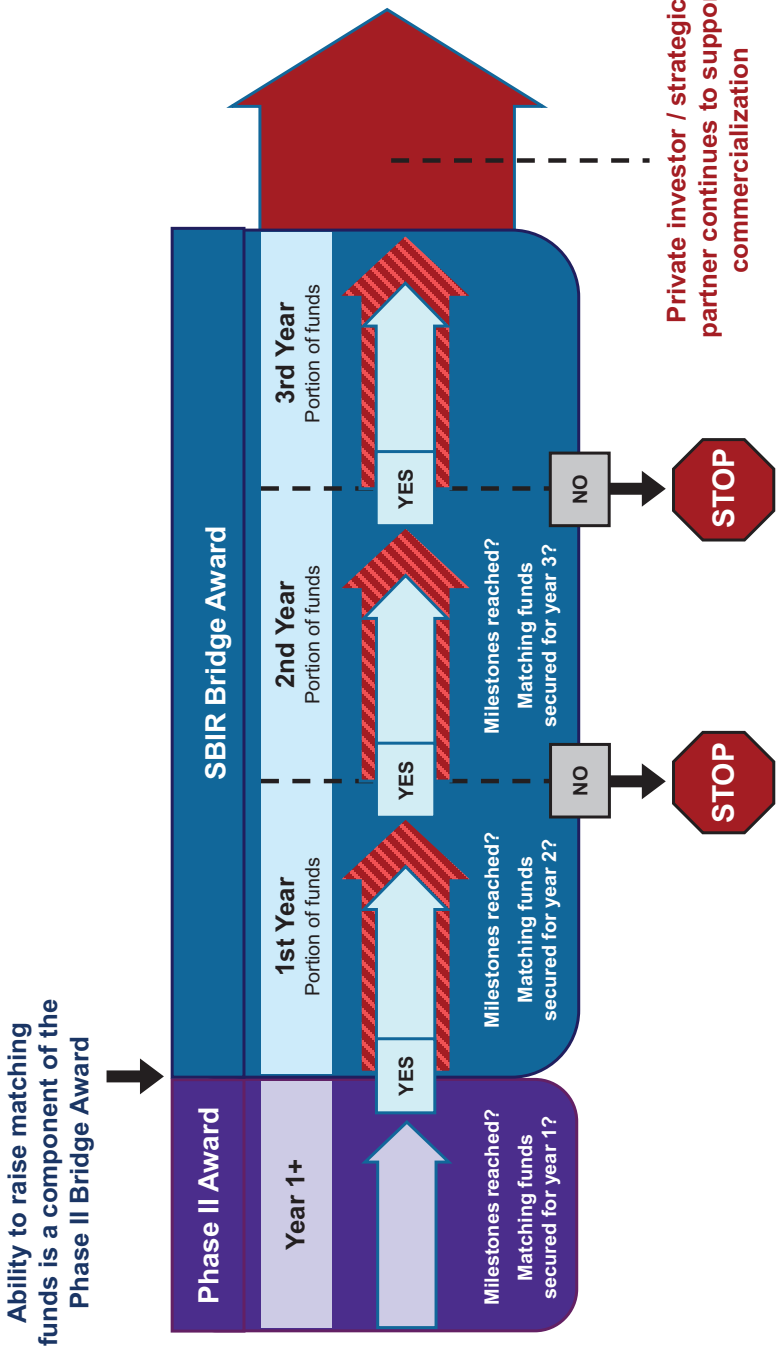

FIGURE 2-3 Milestone-driven funding through Bridge awards.
SOURCE: Patti Weber and Andy Kurtz (NCI), "Leveraging NCI SBIR/STTR Opportunities," webinar presentation, March 6, 2014.

Contract Funding

The contract solicitation for NIH and the Centers for Disease Control and Prevention (CDC) is published once annually. It is governed by Federal Acquisition Regulations (FAR) and is designed to address targeted milestone-driven topics. For the FY2014 solicitation, for which proposals were due November 5, questions about the solicitation had to be formally submitted by September 19. The period between these dates constitutes a quiet period during which the agency is limited in how it may respond to questions posed by potential applicants.

Contract funding continues to expand at NIH, particularly at some ICs. At the forefront of this expansion, NCI utilizes contracts for more than one-third of its NCI SBIR funding (see Figure 2-4). Discussions with NCI staff indicate that NCI appears focused on contracts because this mechanism leaves control of selection entirely with the IC (the Center for Scientific Review is not involved in study sections) and because it offers tighter control of the project itself, where payments are linked to milestones not just time and materials.

There are a number of key differences between grants and contracts at NIH. Contract opportunities are more narrowly defined and are usually not open to investigator-initiated ideas. Potential applicants are required to discuss their proposals with the contracting officers. Contracts can be funded through specific amounts set aside by the IC for particular topic areas, unlike grants, which in principle are funded from the same pot. Reporting requirements also differ; in general, contracts require more extensive program staff involvement.

The selection process and criteria are also different for grants and contracts. Contract applications are reviewed directly at the IC, at the separate Center for Scientific Review (CSR) which governs most grant applications. The review process is also more focused as special review panels are formed for each topic rather than the more general panels at CSR which consider clusters of related topics. The basis for a contract includes additional criteria: the specific negotiated deliverables and the proposed budget. These differences are summarized in Table 2-2.

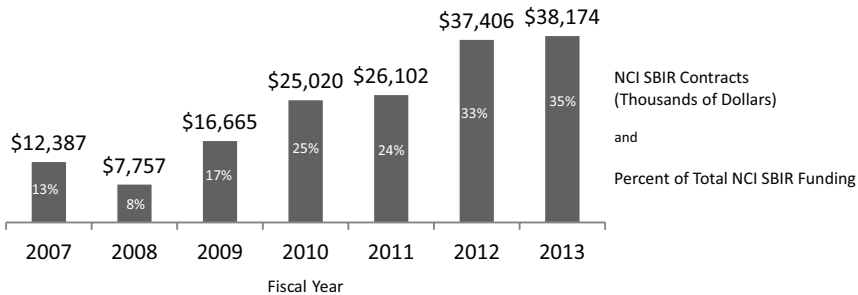

FIGURE 2-4 Contracts funding at NCI.
SOURCE: NCI Contracts webinar, September 14, 2014, http://sbir.cancer.gov/objects/pdfs/2014-09-18_nih-sbir-contracts-webinar.pdf, accessed February 16, 2015.

TABLE 2-2 Differences Between Contracts and Grants

	SBIR Grants	SBIR Contracts
Scope of the proposal	Investigator-defined within the mission of NIH	Defined (narrowly) by the NIH
Questions during solicitation period?	May speak with any Program Officer	MUST contact the contracting officer (see solicitation)
Receipt dates	3 times/year for Omnibus	Only once per year
Reporting	One final report (Phase I); Annual reports (Phase II)	Kickoff presentation, quarterly progress reports, final report, commercialization plan
Set-aside funds for particular areas?	No	Yes
Program staff involvement	Low	High
Peer review locus	NIH Center for Scientific Review (CSR)	At each IC
Review sections	Sections review applications for different programs in similar topic areas	Specific sections for each single topic
Basis for award	Peer review score Program assessment	Peer review score Program relevance and balance Negotiation of technical deliverables Budget

SOURCE: NCI Contracts webinar, September 14, 2014, http://sbir.cancer.gov/objects/pdfs/2014-09-18_nih-sbir-contracts-webinar.pdf, accessed February 16, 2015.

NCI in particular uses contracts to focus funding on specific areas where it sees considerable commercial potential (see Figure 2-5). Contracts allow NCI to control the flow of funding more directly by topic.

The timeline for contracts is also quite tight. For example, companies whose proposals are rejected can receive a formal debrief if requested within 3 business days of the announcement.

It could be said that this use of contracts is an effort to turn the NCI SBIR program from a traditional science-based research program into a portfolio-oriented investment program analogous to, though in many ways different from, those run by venture capital investors. This approach is discussed in more detail in Chapter 3 (Program Initiatives at NIH).

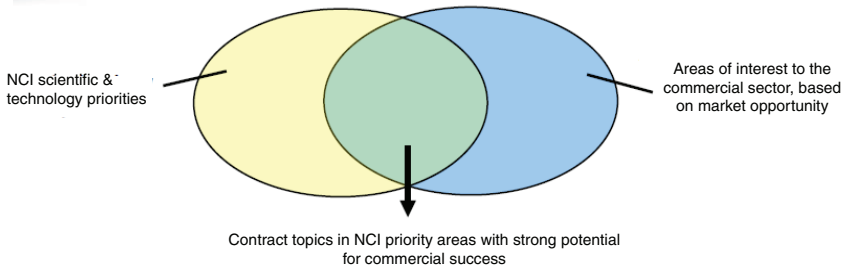

FIGURE 2-5 NCI strategy for contracts.
SOURCE: "NCI Presentation to 16th Annual NIH SBIR/STTR Conference," October 21-23, 2014, Albuquerque, New Mexico.

TOPIC DEVELOPMENT

The topics published in the Omnibus Solicitation and in the more specialized Program Announcements are developed within each of the ICs, and that process can vary by IC. In general, topics are suggested by program managers who are specialists in specific research areas within the IC, and are then vetted, edited, and eventually approved for publication via internal review mechanisms that differ by IC. The IC Director eventually signs off on the IC's SBIR/STTR topics, although most often as a formality. Because NIH does not limit applications to topics identified in solicitations (except for contracts), the topic selection process itself is not the gating procedure it is for other agencies. Therefore, topic selection is important, but not nearly as important as at DoD or NASA.

Program Flexibility

The NIH SBIR/STTR programs are uniquely flexible and can adapt to meet the needs of applicants in ways that more rigid programs cannot. On most dimensions, they are the most flexible of all the SBIR/STTR programs.

- Focus on investigator-initiated research. NIH makes clear that topics listed in the Omnibus Solicitation are guides, not boundaries, for applicants: "SBIR grant applications will also be accepted and considered in any area within the mission of the Components of Participating Organizations listed for this FOA."[5] Although targeted solicitations have become more common and contracts a more important mechanism (contracts are more tightly specified), research conducted under SBIR/STTR at NIH is still largely investigator driven.

[5]PHS 2014-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]).

- Multiple funding opportunities and announcements. Although NIH publishes its Omnibus Solicitation only once annually, numerous other funding opportunities emerge over the course of the year. A solicitation for NIH contracts is published annually, and ICs and clusters of ICs publish targeted funding announcements throughout the year.
- Multiple applications dates. Although there is only one solicitation, NIH offers three submission dates annually, which provides investigators with a reduced timeline to funding compared to an annual deadline. This is especially helpful for small companies.
- Provision of funding flexibility. NIH funding for SBIR/STTR provides several flexible elements.

    - Funding amounts. Amounts are not pre-set, and selection panels do not compare funding requests between applications. NIH has consistently provided funding in response to applications that goes beyond Small Business Administration (SBA) guidelines (with appropriate SBA waivers). See more on extra-large awards in Chapter 3.
    - Supplementary funding. NIH provides small amounts of supplementary funding in cases where the research plans can be completed with a minor increase in support.
    - No-cost extensions. NIH will normally extend the timeline for an award, sometimes substantially. A single, 12-month, no-cost extension is automatically approved for grants and can be managed directly by the awardee through the NIH electronic grants management system.[6]
    - Multiple support mechanisms. The introduction of Phase IIB and Direct to Phase II indicates that NIH continues to seek ways to match available funding with the needs of companies and investigators.

- Resubmission of applications. The ability to resubmit applications after addressing flaws identified by selection panels is a unique feature of the NIH SBIR/STTR programs and is highly commendable.[7]

Overall, the flexibility of the NIH SBIR/STTR programs is a strongly positive characteristic, and other agencies should examine how they might—within their own organizations and cultures—adapt some of the mechanisms developed by NIH.

[6]NIH, Electronic Records Administration, https://era.nih.gov/services_for_applicants/reports_and_closeout/no-cost_extension.cfm, accessed July 16, 2015.

[7]NIH, NIH Policy on Resubmission of Grant Applications, http://grants.nih.gov/grants/policy/amendedapps.htm, accessed July 16, 2015.

AWARD SELECTION

Award selection procedures are different for grants and contracts and are discussed separately below. Grants continue to predominate, although the numbers of and funding for contracts have expanded sharply in recent years.

Grant selection at NIH is a five-step process:

- Administrative review
- Peer review
- Program officer prioritization
- Advisory Council review
- Director approval

Administrative Review and Assignment to Study Section

All incoming grant applications are reviewed by the CSR to ensure that all of the necessary material is provided and all of the requirements described in the solicitation are met. According to CSR staff, CSR reviews 70-80 percent of SBIR/STTR applications, with the remainder reviewed by the IC.

Applications that pass administrative review are then assigned to a Scientific Review Group (SRG) served by a scientific review officer (SRO). The SRO manages the peer-review process for a particular technical area and usually handles two to three selection panels per funding round.

A primary SRO responsibility is to recruit academic and other experts to participate on review panels (in an unpaid capacity). Each panel is expected to handle approximately 100 applications for each funding round, during the course of one or two (sometimes three) meetings. Given the number of panels in operation at any given time, recruiting panelists remains a challenging assignment for SROs. Panelists are expected to work on 8-10 applications per round. Over time, the CSR has developed specialized panels to handle SBIR/STTR applications, with a goal that each will include one or more representatives with commercial experience.

Panel organization and expertise vary by review group. Of the five broad divisions, two have a single Integrated Review Group (IRG[8]) that handles all SBIR/STTR applications for that area. Each of the remaining three divisions has an SBIR/STTR panel. Panels tend to be supported by the same SRO for a number of years.

[8]For details on IRGs, see NIH Integrated Review Groups, http://public.csr.nih.gov/StudySections/IntegratedReviewGroups/Pages/default.aspx, accessed August 9, 2015.

Ease of Application

The 2014 Survey sought to probe more deeply into the process of application and award management. One question concerned the degree of difficulty involved in applying for a Phase II award compared with applications to other federal programs.

Overall, about 20 percent of respondents reported that the Phase II application process was easier or much easier than the application process for other sources of federal funding, while 13 percent of respondents indicated that it was more difficult or much more difficult (see Table 2-3).

The Peer Review Process[9]

Peer review is a primary cornerstone of NIH grant disbursement. Through this process, applications are reviewed by a group of technical experts from outside NIH, who provide numerical scores for each application. NIH peer-review criteria are mandated by federal regulations and can be summarized as follows:[10]

- **Project Significance,** focused on new knowledge and techniques, and new applications.
- **Principal Investigator qualifications and expertise.**
- **Innovation,** defined as "novel theoretical concepts, approaches or methodologies, instrumentation, or interventions."
- **Effectiveness of the approach,** showing that researchers understand and have addressed key problems and risks.
- **Research environment,** including access to adequate institutional support, equipment, and other physical resources.

Notably, commercial potential or even proposed distribution or dissemination of new technologies does not appear explicitly on this list or on the supplementary list of additional criteria that may be applied, though it may be seen as being subsumed under "project significance."

Overall, the peer reviewers' responsibilities constitute an extensive remit, covering activity before, during, and after the study panel meeting.[11] SROs do not

[9]The general information in this section is drawn from the NIH Peer Review Process webpage, http://grants2.nih.gov/grants/peer_review_process.htm#Initial. More specialized information about SBIR/STTR review is drawn from discussion with agency staff. The NIH peer-review system itself is mandated by statute under section 492 of the Public Health Service Act and Federal regulations governing "Scientific Peer Review of Research Grant Applications and Research and Development Contract Projects" (42 CFR Part 52h).

[10]National Institutes of Health, "Peer Review Process," http://grants2.nih.gov/grants/peer_review_process.htm#Initial, accessed May 13, 2014.

[11]See NIH Role of the SRO—A Quick Guide for a more extensive overview, http://public.csr.nih.gov/ReviewerResources/MeetingOverview/Pages/ROLE-OF-THE-SRO----A-QUICK-OVERVIEW.aspx, accessed March 31, 2015.

TABLE 2-3 Ease of Application for SBIR/STTR Phase II Awards at NIH

	Percentage of Respondents			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Much easier than applying for other federal awards	2.8	2.9	2.2	
Easier	17.8	17.2	21.1	22.2
Easier or much easier	20.6	20.1	23.3	22.2
About the same	42.9	41.2	52.2	37
More difficult	9.1	9.1	8.9	7.4
Much more difficult	3.5	3.5	3.3	
More or much more difficult	12.6	12.6	12.2	7.4
Not sure, not applicable, or not familiar with other federal awards or funding	23.9	26.1	12.2	33.3
BASE: TOTAL RESPONDENTS ANSWERING QUESTION[a]	573	483	90	27

[a] Due to a high percentage of the population that could not be reached, and a low response rate from those who were reached, the number of respondents is relatively small.
SOURCE: 2014 Survey, Question 53.

have any direct input into selection: their role is to manage the peer-review process. The program officer may or may not be present during the review panel meeting.

Traditionally, application reviews have been led by a primary reviewer and include a secondary reviewer and a third or monitoring reviewer. Although NIH has not provided data on the composition of study sections (as review panels are known at NIH), discussions for case studies and numerous comments from survey respondents indicate that these panels are largely dominated by academic scientists. More recently, in an effort to improve commercialization review, the CSR has issued guidelines asking SROs to ensure a larger percentage of panelists with commercialization expertise.

Peer-Review Outcomes

Selection Criteria

NIH publishes selection criteria for SBIR/STTR awards. They are listed below and described in more detailed in Box 2-1:

- Significance of the project
- Principal investigator (PI) qualifications

BOX 2-1
NIH SBIR/STTR Selection Criteria

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventive interventions that drive this field? Does the proposed project have commercial potential to lead to a marketable product, process, or service? (In the case of Phase II, Fast-Track, and Phase II Competing Renewals, does the Commercialization Plan demonstrate a high probability of commercialization?)

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance, and organizational structure appropriate for the project?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and

continued

BOX 2-1 Continued

ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment, and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangement?

SOURCE: NIH Grants Guide Section V, http://grants.nih.gov/grants/guide/pa-files/PAR-14-088.html#_Section_V._Application, accessed September 29, 2015.

- Innovation
- Approach (does the technical approach seem appropriate)
- Environment (focused on the facilities in which the work will be done)

Study sections divide up review responsibilities. As noted above, most applications will have a primary reviewer, secondary reviewer, and third or monitoring reviewer. Discussions with agency staff and researchers with experience on study sections indicate that the primary reviewer's views carry considerable weight in most cases. The reviewers provide a written review that scores each application against each of the criteria on a 1-9 scale with 1 being the best and 9 the worst. The reviewers also provide a preliminary single impact score for the application. These scores are used to determine which applications will be discussed at the meeting (not all applications are discussed). Significantly different scores among assigned reviewers will likely be discussed in the study section.

At the meeting, after discussion, each committee member provides an overall impact score for the application. The average of all committee scores, including those from assigned reviewers, is then averaged and multiplied by 10 to provide a score ranging from 10 (maximum) to 90 (minimum).

Commercialization potential and capabilities are not among the formal criteria for selection. They are therefore not reflected in the criterion scores, although they can be (and, in the case of SBIR/STTR, should be) a factor in the overall impact score for a proposal.

An appeals process is outlined on the NIH website, but company executives indicated during case study discussions that they consider appeals to be of little use and prefer to resubmit an application for subsequent review (see below).

Conflicts of Interest

Scientific review offices are assigned responsibility for managing conflicts of interest. Panel members are required to disclose any known conflicts and to recuse themselves from consideration of related proposals. In general, discussions with company participants and responses from the 2014 Survey did not indicate that conflict of interest is a widespread problem.

Nonetheless, academics working in technical areas that are very close to those of an applicant can have an intellectual conflict of interest. Even if no direct financial interest is at stake, researchers may still be concerned that the company's work overlaps and hence competes with their own. Instructions to panelists do not describe this kind of conflict of interest and the need for academic reviewers to recuse themselves as necessary.

There is also a tension between ensuring that panels contain members with experience in the commercialization of technology—which often means experience in private-sector companies that are working in closely aligned technical areas—and ensuring that there are no commercial conflicts of interest. Several case study respondents noted that they paid careful attention to the composition of study sections; some tried to ensure that their proposals were assigned to the "right" study section, and others sought the recusal of specific panel members when needed.

Study sections must therefore tread a narrow line: they must ensure that appropriate scientific expertise and commercial understanding are available for an effective review, and at the same time, they must try to ensure that conflicts of interest are eliminated for a fair review. In general, this assessment did not reveal systematic problems in this area, but it did reveal the existence of concerns among small business.

Lack of Sufficient Commercial Expertise

Several of the company executives who took part in case study discussions indicated that selection panels lacked commercialization experts and that most were heavily weighted toward research scientists. Many survey respondents expressed similar views (see Box 2-2). A CSR staff member working on SBIR/STTR said that no rules exist about including panelists with commercial expertise, although 20-50 percent representation by commercialization experts is recommended. However, company executives who had served on selection panels suggested that it was not uncommon for panels to include only one or two such reviewers.

Company executives also observed that what counted as commercialization expertise was often unclear; scientists from the private sector are assumed to have commercialization expertise, even though most industry scientists' work is heavily focused on science rather than commercialization.

CSR staff confirmed that CSR does not track the extent to which SROs follow the guidelines noted above. There are no data on the availability of commer-

BOX 2-2
2014 Survey Respondent Recommendations for Improved Review (Representative Comments)

Need more company reviewers on SBIR panels. Need less academic reviewers.

Enhance expertise of review panels in order to better align review with objectives of SBIR/STTR program.

Often review panels do not understand the FDA [U.S. Food and Drug Administration] process and difficulties getting clearance or approval from the FDA . . . review panel members should be educated on the purpose of Phase IIBs before the review panel and proposal reviews take place.

CSR and program need to step up hugely, as they have even less of a clue about the FDA regulatory process than the entrepreneur. Yet, they make funding decisions with little or no knowledge of what needs to be done.

[We recommend] an easier way to assess the appropriateness of each review group to your application to get the best match, and improved education of peer reviewers in academia who review R43s and R44s like R01s.

Give proposal reviewer fewer proposals to review so they can do a better job. Insist that reviewers who do not understand what is proposed recuse themselves from being one of the three primary reviewers.

Instruct reviewers to act professionally, and not to be biased in favor of typical academic biases (number of "good" publications). I have sat in review panels where participants exclaim their pride that none of their research will ever be marketable. Additionally, there is built-in bias against collaboration with foreigners, even when all the research occurs in the USA.

Integrate greater support for products with real market potential into the peer review process. For educational products, review panels tend to focus on products that will have low market potential.

Offering additional funding opportunities that are reviewed by non-academic based reviewers. It would great to have reviewers with experience in getting a biotech device to market.

Make sure all review panels know the specific requirements from the FDA that are needed and provide a clear path to ensure communication.

Provide funding for FDA related consultants independent of the SBIR funds through a mechanism that does not involve the study section. Most SBIR study sections are made up of academic investigators with little to no understanding [of] the FDA or the commercialization process. SBIR grants are handled as if they were R01 or R21 proposals.

Provide review process that allows for best assessment of the product for commercialization. Reviewers with appropriate backgrounds would be helpful.

. . . [The] majority of the reviewers for SBIR/STTR are professors, who have no commercialization backgrounds or experiences . . . reviewer committee should add some reviewers with more marketing and product development background.

Stop demanding a randomized control trial in Phase I. Allow for a more commercially viable development process in Phase I so a minimum viable product is evaluated for market acceptance not just effectiveness of intervention.

continued

BOX 2-2 Continued

The NIH review process for SBIR/STTR has become more and more frustrating to all device companies. The funding repeatedly rewards proposals including complex biochemical research devoted to a new test or therapy that will be of little direct benefit to patients.

The reviewers of our Phase IIB were TOTALLY unaware that the company proposing had written the Phase IIB following FDA guidelines as to what we had to complete for clearance.

SOURCE: 2014 Survey.

cialization expertise to selection panels, and a review of commercial potential can be provided by any panelist, either in the scoring or in the course of discussion.

At a minimum, NIH does not track or manage panels to ensure that sufficient commercial expertise is available to help guide deliberations.

Resubmission

As a unique feature of the NIH SBIR/STTR programs, applicants are permitted to resubmit their applications during the 37 months following the initial rejection.[12] This gives applicants the opportunity to address weaknesses identified during the first review and to strengthen their proposals. In recent years, about one-third of all funded Phase I grants have utilized the resubmission process, according to the NIH SBIR/STTR Program Office. According to NIH, "Resubmissions normally are not permitted for applications received in response to a Request for Applications (RFA) unless it is specified in the FOA, in which case only one resubmission will be permitted."[13]

Meetings with applicants (see case studies) indicate that while considerable unhappiness with the peer-review process in general remains, the existence of the resubmission mechanism acts as an important safety valve for the programs. Resubmission is seen as a very valuable aspect of the programs.

Although resubmission offers an important route for improved applications, the process itself does not work as well as possible from the company's perspective. Most notably, the applicant receives the debrief from the NIH review process too late to resubmit by the next deadline. As a result, resubmission currently

[12]NIH Policy on Resubmission, http://grants.nih.gov/grants/policy/amendedapps.htm, accessed June 16, 2015.

[13]Ibid.

imposes an 8-month delay, which is challenging for smaller companies without other revenue sources. Aware of this issue, the NIH SBIR/STTR Program Office is considering changes to the review process so that debriefs can be provided to companies in time for them to resubmit by the next deadline.

An Agency Perspective

The difficulties facing small business concerns in the NIH review process have been acknowledged by some NIH staff: namely, that the NIH review process is not well designed to ensure that commercial plans submitted as part of the application process—especially for Phase II—are reviewed by panelists with expertise in the commercialization of biomedical technologies in general and the specific technologies at hand in particular.

Program Officer Prioritization

Upon receipt of the scores from the review panel, the IC program officer creates a priority list based on the scores, ranking each proposal within the officer's technical area relative to others. The program officer then runs these scores against the available budget to create the draft pay line (proposals scoring below this line are to be funded—given that lower scores are better in the NIH system).

The draft pay line is subject to review and adjustment by the program officer, who accounts for issues such as budgets and agency priorities. For example, it may be that the IC is already funding a similar technology, in which case the program officer may decide that the funds would be better spent elsewhere. The program officer may also determine that, although of high quality, the proposal will cost too much to be worth the IC's investment. (It is only at this point that the relative budgets for proposals are compared and become a factor. Study sections do not compare budgets.) The program officer may also decide that a proposal scoring below the pay line is nonetheless of strategic importance to the IC and should be funded anyway. In addition, the program officer may decide that the review of a proposal was in some way done incorrectly and that a different (and perhaps fundable) score should have been given.

Different ICs have different cultures and different rules. Some give their program officers a considerable degree of freedom to make funding decisions that conflict with the initial ranking from the study sections. Others see this as an exception and expect most rankings to be respected. NIH does not retain aggregate data about the extent to which program officers change funding decisions. However, discussions with agency staff suggest that such changes occur in no more than 10 percent of proposals, and for most ICs, no more than 5 percent.

Advisory Council Review and IC Director Approval

NIH provides an additional layer of review, focused on what program officers see as special cases.

The Advisory Council deals with all of the funding provided by the IC, in which SBIR is only a small fraction. The Advisory Council discusses much larger funding decisions, and therefore can feasibly address only a small number of SBIR cases. According to agency staff, these cases tend to fall into two areas: (1) the program officer is overriding the original ranking list and seeks confirmation that his or her judgment is appropriate and (2) the amount of funding is especially large. Thus discussion in the Advisory Council is unusual for an award the size of an SBIR/STTR award.

The final step in the approval process is approval by the IC director. Once again, different ICs have different procedures for this last step, but the small size of SBIR awards makes it unlikely that any single proposal will attract substantial senior management time and concern. In most cases director approval is a formality.

Checks and Balances Within the Review Process

A common concern raised by case study and 2014 Survey respondents centered on the reviewers. Companies reported cases in which reviewers did not understand the technology, the business, the market, or NIH interest in a technology despite its publication as a topic.

Given the number of applications and the difficulties in finding competent and experienced reviewers to sit on panels, it is not surprising that applicants complain about unwarranted or illegitimate criticism from reviewers. This is not a problem unique to NIH, but the nature of the review process at NIH seems to generate more cases.

NIH is well aware of these issues, not only for SBIR/STTR grants but also for all NIH grants. However, the problem may be exacerbated within the SBIR/STTR programs because of the need for commercial review, which most academic scientists are not competent to provide. NIH has taken a number of steps to provide checks and balances.

- **Three lead reviewers.** The assignment of three lead reviewers to a proposal is in and of itself an effort to provide checks and balances. Still, in most cases there will be a primary reviewer who carries the most weight.
- **The role of the scientific review officer (SRO).** Although SROs do not participate in the discussion and have no hand in the final recommendation and feedback to the company, they are responsible for ensuring that potential conflicts of interest are addressed and also in a larger sense that the process is fair. However, it is not clear whether SROs usually take

action in cases where they believe the proposal may not have received an appropriate review.

- **The role of the program officer.** Although driving the funding decision, the reviewer scoring is not determinative. Program officers can reach beyond the pay line to fund a project that they consider to be of special merit and equally can decide not to fund a project that is within the pay line but that they believe does not meet the IC priorities. In general, this process works more to align scores with IC priorities than to deal with problematic reviewer scoring.
- **Resubmission.** Unique among SBIR funding agencies, NIH permits resubmission and reconsideration of unfunded proposals against subsequent deadlines. If a company believes that its proposal did not receive a fair review, then it can make adjustments and resubmit. This is an important mechanism for improving the overall quality of both proposals and the overall process, and it is recognized as such by applicants and NIH staff. However, this process involves significant costs: there is no guarantee that the proposal will be funded; it may go to a different study section or study section with different personnel who have different concerns; and it imposes significant costs on the small business. Moreover, prior to 2015, feedback arrived too late for companies to submit during the next cycle, so resubmission in effect imposed an 8-month wait. For small businesses, such a delay can be very challenging. NIH is now working to provide companies with feedback from selection panels in time for them to resubmit at the next SBIR deadline, but this issue has not yet been fully addressed.

Almost all of the company executives who engaged in case study discussions have served on selection panels and thus fully understand their operations as well as their strengths and weaknesses. Few of them thought that the current system should be replaced by systems similar to those of other agencies, where small groups of agency staff drive the selection process. However, many were interested in finding better ways to address weaknesses in the system. In particular, many suggested that NIH allow companies to rebut or address criticism in the course of review, rather than through the resubmission process. NIH staff hold that rebuttal would impose significant delays and costs on the review process and that improving and streamlining resubmission was perhaps a more effective approach.

Excluding Poor-Quality Proposals

Most proposals to the NIH SBIR/STTR programs fail. Success rates for Phase I are usually well below 20 percent, depending on the number of applications submitted and the amount of funding available. NIH undertakes a triage within the study section, providing a score only for the top 50 percent of proposals.

It is apparent that reducing the number of poor-quality proposals would be of immediate benefit to NIH, because reviewers could focus on better proposals and because conceivably there could be fewer study sections. Fewer failing proposals would also benefit the applicants.

However, NIH does not use some of the methods employed at other agencies to reduce the number of poor-quality proposals. For example,

- NSF limits the number of applications to two annually per firm, ensuring that firms focus on their most promising projects.
- DoE requires a white paper before application and provides applicants with rapid feedback to help inform decisions as to whether or not to apply. NSF also uses a white paper process, although its approach is somewhat less rigorous. Neither process prevents a company from applying even if advised that its application is unlikely to succeed.

Perhaps in part because the number of applications to NIH has been falling for some time (see Chapter 4, SBIR and STTR Awards at NIH), the NIH SBIR program has historically had little interest in limiting applications to make the application process more efficient.

FUNDING GAPS AND AWARD TIMELINES

The 2014 Survey asked respondents about funding gaps. Case studies as well as prior reports by the Academies[14] have noted that funding gaps are particularly difficult for small businesses that have few other resources. Projects can be badly damaged by funding gaps that may require staff to be reassigned or even let go, and delays can be crippling in areas where technology is advancing rapidly.

The 2014 Survey provides some insights into the impact and effects of funding gaps between Phase I and Phase II. Sixty-eight percent of respondents indicated that they had experienced a gap between the end of Phase I and the start of Phase II for the surveyed award.[15] This is down since the 2005 Survey, which reported 80 percent of respondents for SBIR only, compared with 69 percent (for SBIR only) for the 2014 survey.[16]

This gap can have a range of consequences for the company. Table 2-4 indicates the kinds of impact on respondents who had experienced a funding gap. Thirty-one percent of respondents reported that they stopped work altogether

[14]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council or NRC are used in an historic context identifying programs prior to July 1.

[15]2014 Survey, Question 22.

[16]National Research Council 2009 op. cit. p. 258. STTR recipients were not included in the 2005 Survey.

TABLE 2-4 Effects of Funding Gaps Between Phase I and Phase II

	Percentage of Respondents			
	NIH Total	SBIR Awardees	STTR Awardees	PHASE IIB Awardees
Stopped work on this project during funding gap	31.2	34.1	14.8	5.3
Continued work at reduced pace during funding gap	57.1	54.4	72.1	68.4
Continued work at pace equal to or greater than Phase I pace during funding gap	9.3	9.2	9.8	26.3
Company ceased all operations during funding gap	0.5	0.6		
Other (specify)	2.2	2.3	1.6	
Received gap funding between Phase I and Phase II	6.1	5.7	8.2	5.3
BASE: EXPERIENCED A FUNDING GAP BETWEEN PHASE I AND II[a]	410	349	61	19

[a]Due to a high percentage of the population that could not be reached, and a low response rate from those who were reached, the number of respondents is relatively small.
NOTE: Numbers do not sum to 100 percent because multiple responses were permitted.
SOURCE: 2014 Survey, Question 23.

during this period, while 57 percent worked at a reduced level of effort. About 1 percent ceased operations.

Aside from the direct impact of delayed projects, funding gaps can have long-term consequences, especially for smaller companies, where in some cases there is insufficient work to retain key project staff during the gap period. Many of the comments received from the 2014 Survey reflected the negative impact of funding gaps (see Box 2-3). Suggestions from survey and case study respondents fall into three main categories:

- Create or expand a gap funding mechanism between Phase I and II. Currently NIH relies on "work at your own risk" as the sole mechanism. In this case, a company can continue to work at its own risk. If the project eventually receives a Phase II award, then the company can be repaid for the resources expended during this period.
- Reduce the time between Phases, in part by making decisions more quickly, creating conditions that allow immediate resubmission in the next cycle.

BOX 2-3
2014 Survey Responses
Related to Funding Gaps Between Phase I and Phase II
(Representative Comments)

Bridge funding between Phase I and II SBIR should be much easier.

Reduce gap in funding between Phase I and Phase II. Recent "direct to Phase II" awards are a good step forward.

The SBIR program rocks—[but] the gap between phase 1 to 2 is terrible—it kills projects in startup companies.

Improved access to gap funding and/or ways to reduce the gap between Phases 1 and 2. Since the odds of winning a fast-track NIH grant are close to zero.

One of the biggest problems we face is the gap between phase 1 and phase II.

The funding gap between Phase I and II is difficult. Some thought needs to be given to gap funding.

Address the gap between Phase I and Phase II. Create review cycles that allow for earlier re-submit of un-funded grant applications.

Opportunities for gap funding (with suitable milestones met) would help to retain valuable/trained staff used on the Phase I and would help to assure a smooth transition to Phase II

Reducing the gap time between Phase I and Phase II would be most helpful, or providing some Phase I to Phase II interim funding

Shorter time between phase I and phase II would be helpful. Perhaps a program review of quantifiable phase I milestones would allow phase II funding to start without going to traditional study section. This would expedite the commercialization process.

SOURCE: 2014 Survey.

- Enhance access to Fast Track and/or direct to Phase II. Some survey respondents noted that Fast Track is difficult to access, which could be improved with better guidance to study sections.

NIH has tried to address potential funding gaps between Phase I and Phase II in three ways. Most notably, NIH offers a "work at own risk" approach. This approach cannot be used for contracts because of FAR, but it provides grant recipients with an important way to continue work on projects during the gap before Phase II funding. Of course, companies that do not eventually receive Phase II funding will incur costs but receive no repayment.

NIH has also tried to reduce the actual time between the end of Phase I and the beginning of Phase II. The gap is reported to SBA in the agency's annual report. However, because NIH offers three funding opportunities per year and in particular because the agency allows resubmission, the gap data are not especially useful and are not comparable to those of other agencies. Agency staff are work-

ing to accelerate delivery of debriefs, an initiative which would allow companies to resubmit more rapidly.

The gap can also be eliminated through either Fast Track—which provides for smooth transition to Phase II without recourse to a study section review—and direct to Phase II—a new program permitted under reauthorization. In FY2014, Fast Track accounted for 71 of the 730 Phase I + Fast Track awards; the success rate for Fast Track applications was 19 percent, compared to 16 percent for Phase I SBIR applications.[17]

More generally, survey and case study respondents expressed concerns about the length of time between initial application and eventual Phase II funding. Box 2-4 presents some of their concerns.

Both the NIH Program Office and SBA are working to monitor the pace of awards and to reduce unnecessary delays. However, SBA focuses only on aggregated data, which are of little use in pin-pointing problems. In addition, because awards are made by individual ICs it is not clear whether the Program Office has either access to data or sufficient influence to lead change in this area. NIH has not provided information that reflects an understanding of best practices among the ICs in this regard.

CLINICAL TRIALS AND SBIR/STTR

Unlike at most other SBIR/STTR agencies, many NIH awardees must comply with a potentially expensive and time-consuming regulatory process before they can market new products. This section addresses that process.

The Changing Role of Large Pharmaceutical Companies and Venture Capital Firms

Starting around 2004, venture capital firms supplied a considerable amount of the financial fuel for biomedical startups and early-stage companies, while large pharmaceutical companies have waited to see the results of early clinical trials before considering investments. However, that support declined sharply after the financial crash of 2008, and the retreat of venture capital (VC) funding from seed stage in investments is by now quite well known. Figure 2-6 shows data for the biotechnology and medical device sectors for seed-stage funding from the PwC/NVCA Moneytree™ Report based on data from Thomson Reuters.

The retreat of venture capital firms means that small innovative companies must find other sources of funding for clinical trials. There is conflicting evidence about the role of large pharmaceutical companies, which use the work of smaller companies as a pipeline for their own later development of new drugs and therapies. On the one hand, companies report that partnering with large pharmaceutical

[17]NIH Annual Funding Report, SBIR grants, Table 127.

BOX 2-4
2014 Survey Respondent Concerns About the Lengthy Timeline for NIH SBIR/STTR Awards (Representative Comments)

Reduce delay between application and award decision and actual award (can stretch to 12 months or longer). Reduce administrative delays for non-competitive renewals (delays of several months are often encountered).[a] Reduced delays in F&A negotiation. We experienced 12+ month delays in processing proposals.

Reduce time between application and award decision. This has taken more than 12 months in our case. Reduce administrative delays in funding release each year during phase II. This has taken greater than 4 months in our case. That is we have at times experienced a four month delay between years of Phase II.

Overall, the process of submission, review, & funding was fair, but agonizingly slow. One must start the Phase 2 proposal process almost as soon as Phase-1 funding is received in order to avoid funding gaps and reduced progress.

Shortening the time between Phase I and Phase II. Balancing awards and an award process where most of the Phase I's awardees receive Phase II funding.

Faster grant reviews and quicker funding decisions.

Faster review cycles. Currently it takes approximately 1 year between conception of a research project and funding. Waiting on reviews or any feedback is sometimes detrimental to our company as the funding or non-funding of a project alters our strategic direction. Review feedback within a month or two after submission would be very helpful even if the actual funding comes later.

Faster turn-around time from grant deadline to notification to start date if successful.

Turn around the application reviews more quickly so there's time for careful thought before resubmitting.

[a]In some cases, Phase I grants are renewed for a second year of Phase I without having to compete against other SBIR applications for money. In NIH jargon, this is called a non-competing renewal.

SOURCE: 2014 Survey

companies has become more difficult.[18] On the other hand, these companies are setting up new incubator-type arrangements in a number of places. Johnson & Johnson recently announced four research centers—two in the United States, one in Massachusetts and one in California, one in China, and the one in the United Kingdom. Merck has established the California Institute for Biomedical Research (CB3) in San Diego to fund early-stage drug research. Bayer has partnered with the University of California, San Francisco, to support translational research.

[18]See Chapter 5 (Quantitative Outcomes) and Appendix E (Case Studies).

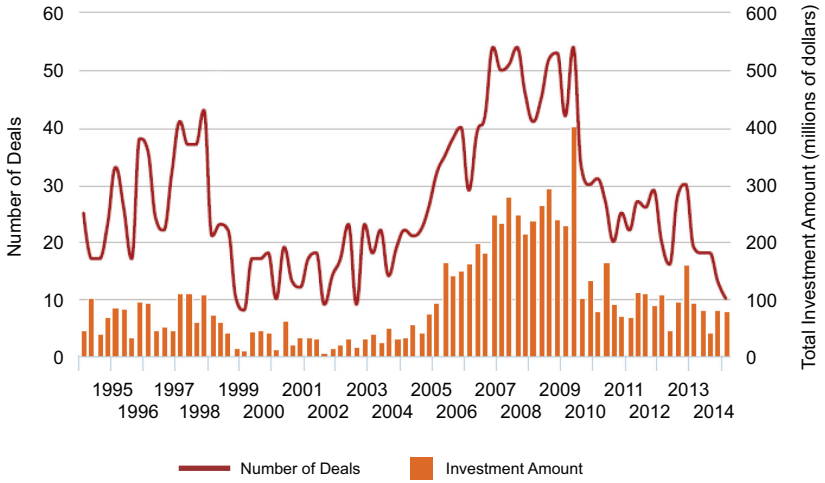

FIGURE 2-6 Seed-stage funding and deals for biotechnology and medical devices, 1995-2015.
SOURCE: PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report, Data: Thomson Reuters.
NOTE: Accessed July 14, 2015. Customized for stage and industry sector.

Pfizer has also announced several academic relationships, aimed at providing early access to cutting-edge technology and relationships with academic leaders in their fields.[19]

Foundations have also started to provide funding for translational research. The Bill & Melinda Gates Foundation has a $1 billion fund for venture philanthropy investing. It provided a $10 million investment round in Liquidia Technologies in 2010.[20] It also invested $29.3 million in Sanaria (see Appendix E: Sanaria case study).

The extent to which these larger companies and other actors fill the gaps left by the retreating VCs is unclear, however. Only 15 percent of SBIR respondent companies had received funding from other companies.

Survey Data About Food and Drug Administration Approvals

Forty-six percent of respondents to the 2014 Survey reported that their projects required U.S. Food and Drug Administration (FDA) approval for drugs,

[19]Ed Mathers, "Life Science Startups Looking for New Sources of Funding," Scale Finance, July 14, 2015.

[20]Bill & Melinda Gates Foundation, "Liquida Technologies Receives Investment to Bolster Development of Vaccines," March 4 2011.

TABLE 2-5 Current Status of Project in Relation to Clinical Trials

	Percentage of Respondents			
	NIH Total	SBIR Awardees	STTR Awardees	PHASE IIB Awardees
Process abandoned	35.5	35.9	33.3	5.3
Preparation under way for clinical trials	34.4	35.5	28.2	47.4
IND granted	4.7	4.1	7.7	10.5
In Phase I clinical trials	4.7	5.1	2.6	
In Phase II clinical trials	9.4	7.4	20.5	15.8
In Phase III clinical trials	2.3	1.8	5.1	
Completed clinical trials	9.0	10.1	2.6	21.1
BASE: NIH PROJECTS REQUIRING FDA APPROVAL[a]	256	217	39	19

[a] Due to a high percentage of the population that could not be reached, and a low response rate from those who were reached, the number of respondents is relatively small. Moreover, it is possible that companies that had abandoned the clinical process were disproportionately represented in the companies who could not be reached.
SOURCE: 2014 Survey, Question 41.

devices, and products. This sizable percentage underlines the importance of the FDA approval process for the eventual success of the program.[21] Respondents that reported the need for FDA approval were asked about the current status of the project in relation to FDA approval (see Table 2-5). This is an important milestone; only 9 percent of projects requiring the need for FDA approval had completed clinical trials, with a further 2 percent in Phase III trials.

In contrast, more than twice as many Phase IIB respondents reported completion of clinical trials. Given that the funding is explicitly designed to support clinical trials, this is not surprising (see Chapter 3). Among all respondent companies, 35 percent had abandoned the clinical trials process for the surveyed project. A further one-third was in the preparatory stage as of 2014, and a further one-third was in the clinical trials process. A further 2 percent were engaged in Phase III trials. These figures illustrate the enormous challenges for small companies working in life sciences. The raw numbers for Phase IIB are very small (19 respondents), and Phase IIB only began in FY2005, so results should be interpreted with caution. Still, only 5 percent of Phase IIB respondent companies have abandoned the process, and 21 percent have completed clinical trials.

[21] 2014 Survey, Question 40.

From another perspective, Phase IIB funding forms an important but not dominant element in the patchwork of funding that supports the efforts of SBIR/STTR projects to complete clinical trials (see Figure 2-7).

The 2014 Survey also asked about the *completion* of different clinical trials. Figure 2-8 shows that about a one-third of the 21 respondents indicated that the Phase IIB funding was not sufficient to complete Phase I clinical trials, while 4 percent (1 respondent) indicated that it had been sufficient for all three phases. The results (given the small number of respondents) are far from conclusive, but they suggest that Phase IIB can be seen as supporting most projects into Phase II trials.

Support Needed for FDA-related Activities

The need for FDA approval presents a financial challenge—for reasons discussed elsewhere—as well as a technical challenge: the requirements for acquiring FDA approval or even for entering the FDA approval process are not easy to satisfy, particularly for small businesses without expertise in this area.

Most of the case study companies have long since passed this point in the process and are quite knowledgeable about FDA requirements, but many of the survey respondents indicated that these challenges were formidable. Box 2-5 captures the range of concerns reported by these respondents.

Recommendations from survey respondents for improving NIH support for regulatory compliance included:

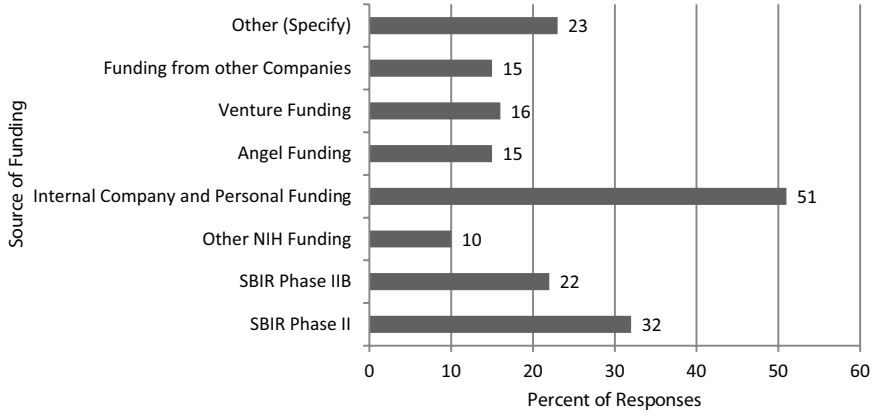

FIGURE 2-7 Sources of funding for clinical trials (percentage of respondents mentioning each source).
NOTE: Numbers do not sum to 100 percent because multiple answers were permitted.
SOURCE: 2014 Survey, Question 42.

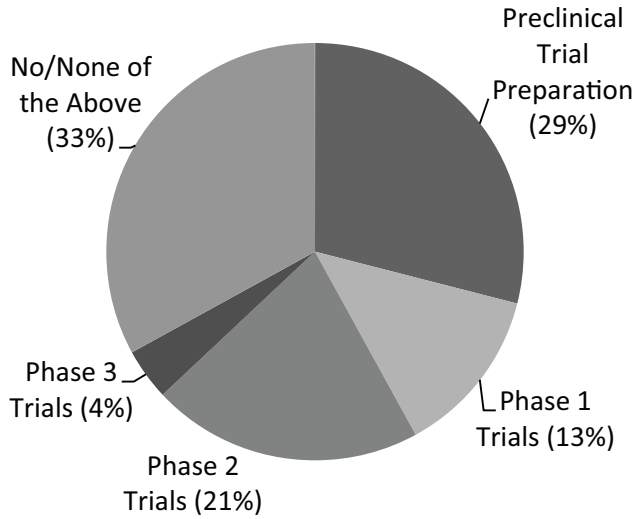

FIGURE 2-8 Clinical trial phase completed as a result of Phase IIB funding (percentage of respondents).
SOURCE: 2014 Survey, Question 47.

- Access to an FDA consultant permanently attached to the SBIR/STTR programs.
- Provision of more or better educational materials and training at the start of the SBIR/STTR award cycle, to allow companies to better align their efforts with FDA requirements.
- Creation of a better and more durable connection between NIH and FDA, through which companies could be guided.
- Direct NIH support for FDA regulatory filings and paperwork.
- Preliminary FDA review of clinical plans approved by NIH for SBIR/STTR.

Responsibility for these recommended activities is shared between the NIH SBIR/STTR Program Office and the ICs. At the National Heart, Lung, and Blood Institute (NHLBI), an FDA expert is currently part of the advisory service portfolio provided by its SBIR/STTR programs.[22] However, it appears that for the programs as a whole and for many of the ICs, regulatory assistance is limited to a link to the FDA website.

[22]See OTAC Resources at NHLBI, http://www.nhlbi.nih.gov/about/org/dera/otac/resources, accessed July 10, 2015.

BOX 2-5
2014 Survey Responses Related to FDA Approvals
(Representative Comments)

Small businesses are often inadequately informed about the requirements and process for obtaining FDA approval for products they envision. Efforts by the NIH to (1) educate and encourage small businesses to appropriately approach the FDA for regulatory approval and (2) encourage the FDA to work with and facilitate the regulatory process for medical devices arising from NIH-funded small business and academic grants would be enormously helpful.

NIH really needs to provide some FDA trained regulatory people and a course that details what needs to be done to get an IND and beyond in clinical trials. There are a million consultants in this space, and without any knowledge beforehand, it is pretty daunting to pick a good one.

There is a huge disconnect between NIH and FDA. FDA is looking for more simple solutions to problems (i.e. one drug delivery) and NIH reviewers are typically looking at extremely innovative solutions, which FDA does not look favorably upon.

Direction regarding the preparation of documents and assembly of protocols to meet FDA requirements.

FDA guidance and some funding that are directed by awardee to work with an external regulatory expert.

. . . helping small business to receive from the FDA more clear guidance with respect to the Agency's expectations regarding the supporting clinical data needed would be of a huge significance.

Some kind of review by FDA of the clinical research plan that is approved by NIH would be very helpful.

IND development training would have been helpful at the time of receiving the funds. The company took 3 drugs through IND into clinical trials so gained experience on its own but would have benefited from having regulatory training.

It would be great if the NIH hosted a web site, webinar, handouts, etc. explaining more clearly how to approach and work with the FDA; these materials should be oriented to small firms with no prior FDA experience.

It would be helpful if NIH had a program to help with FDA filings and document preparation. Companies at our stage have a tough time spending a large amount of resources on CROs for these services.

NIH should have an advocacy desk at the FDA. The FDA is the worst agency in the US to work with.

Small businesses are uneducated and intimidated by the requirements for obtaining FDA approval. NIH could assist by (1) facilitating appropriate timely communication between the small business and the FDA and (2) encouraging the FDA to reach out in a user-friendly way to small businesses.

SOURCE: 2014 Survey.

PHASE IIB

Phase IIB began in earnest in FY2005 after a short pilot program. Since then, NIH has awarded approximately 20 Phase IIB awards annually (see Chapter 4). Our research suggests that this funding is of great significance to awardees. More comments were received from the 2014 Survey about the need to bridge the funding gap around clinical trials than any other topic. Several case study companies had received Phase IIB awards, and in general they believed them to be helpful.

Awardees are concerned about the massive challenge of funding clinical trials. Dr. Tseng (TissueTech) said that bridge funding was his main concern while the company moved a product through the FDA regulatory pathway. This concern has been of declining importance for TissueTech, which has other resources available for this purpose, but Dr. Tseng believes it could be a critical problem for other companies. He noted that currently, SBIR funding is available for Phase I clinical trials, and it was barely possible—if resources were used very carefully—to complete Phase II clinical trials using SBIR Phase II awards. However, in most cases that was not possible—and many companies faced huge challenges in finding that funding.

Dr. Hogan (GMS) said that the Phase IIB program is an excellent idea. Because the valley of death is large and growing, such a program is critical in the absence of other NIH funding and declining interest in early-stage investments from venture capital firms and large pharmaceutical companies. In the current environment, he believes it is extremely difficult to attract outside funding if the company does not have a product ready to sell: it is not necessary to have substantial sales, but some sales should be imminent.[23]

Aside from numerous calls for more or larger Phase IIB awards, survey respondents also provided more detailed comments about the Phase IIB program (see Box 2-6).

INTELLECTUAL PROPERTY

Intellectual property under the SBIR/STTR programs is governed by two sets of regulations, which are not always in complete alignment.

In general, ownership of intellectual property generated from research grants made by the federal government is governed by the Bayh-Dole Act (1980). The Act provides that small businesses and nonprofit organizations (including universities) can elect to take title of inventions developed using federal funding. Before this, all inventions were automatically the property of the government.[24]

[23]The Valley of Death refers to the early stages of a startup, before a new product or service brings in revenue from real customers.

[24]David C. Mowery, et al. "The Growth of Patenting and Licensing by US Universities: An Assessment of the Effects of the Bayh–Dole Act of 1980." *Research Policy,* 30(1): 99-119, 2001.

BOX 2-6
2014 Survey Respondent Comments on Phase IIB and the Need for Post-Phase II Funding (Representative Comments)

A mechanism should be established to financially assist companies to advance candidate products to clinical trials development (beyond phase I and Phase II programs).

All NIH institutes need to support Phase III commercialization grants. The Pharmaceutical Industry in the current environment will only partner with companies whose products have undergone Phase I or Phase II clinical trials.

Consider additional funding to help move the project through the FDA process, and if necessary perform an initial clinical trial.

Have ability to have Bridge grant re-award after completion of first Bridge grant.

Increase the number of "bridging funds or grants" so that we can complete the planned FDA IND approval process.

Increased access to P2B funding to bridge from P2 to commercialization.

Increased availability of post Phase II funding to complete pre-clinical demonstration (typically on animals) and pursue FDA approvals.

More opportunities for RAID, or TRND or BRIDGE to assist in preclinical development.

Phase III to proceed with Product Development, Validation and Toxicity testing and to hire Consultants to help us interact/navigate the needs of the Federal Regulating/Licensing Agency. It was quite difficult to get it all together (2 years) to be able to fund raise from Venture Capitalists.

PIIB funding is challenging and given the current venture capital landscape is critical to companies.

Small companies need funding to offset the late stage clinical studies required for FDA approval of products. Current SBIR/STTR funding helps with early stage in vitro proof of concept work and early stage clinical trials (Phase 1 and possibly Phase 2). NIH funding is not available after this point. Depending on commercial opportunity and industrial partner comfort with the science, additional funding can be found. However really innovative science cannot always find additional funding.

The current system is quite adequate to validate an idea, build a prototype, and collect relevant biological data. That leaves a large financial barrier to cross in turning a prototype into a manufacturable product and bringing it to market. Whether NIH could or should address this issue is problematic. It is currently left to the private sector. Sadly, the private sector evaluates a technology solely on its financial potential rather than on whether the science is good and will predictably be beneficial. NIH has historically taken a broader view of the problem, a perspective that would lead to a number of important products being available to people who need them if such an involvement were possible.

To summarize, respondents indicated the following:

- Phase IIB is an important and welcome initiative
- In the current environment, Phase IIB often makes the difference at a key point in the commercialization process.

continued

BOX 2-6 Continued

- The $3 million in funding would not be sufficient to complete Phase III clinical trials and in many cases would not be enough to complete Phase II.
- The matching fund restrictions imposed by NCI are onerous.
- The timeline for disbursement does not necessarily meet company needs, which might be clustered toward the start of the process.

SOURCE: 2014 Survey, Question 53.

Inventions (as defined by federal law) that are made under SBIR/STTR awards are subject to the invention reporting requirements based on Bayh-Dole. For contractor organizations (which would generally include grantees), the agreement to disclose inventions to the government is included in the original grant or contract. Under these provisions, an invention report must be filed within 2 months of senior management becoming aware of the invention (at NIH using the electronic iEdison portal). The company then has 2 more years to claim title to the invention. Once the title has been claimed, the company then has 1 more year to file a patent application, although the company can apply for an extension of this time period.[25]

March-in rights are potentially granted to the government to take ownership of intellectual property in cases where the invention is not sufficiently commercialized. However, although this has been a concern in some cases at DoD and NASA, where prime contractors have been able to utilize technology developed under the SBIR program, march-in rights have been exercised infrequently at NIH. Four applications for march-in rights have been brought at NIH as of 2013, and all have been denied.[26]

Although inventions developed under the SBIR/STTR programs must follow the invention reporting mechanisms described in Bayh-Dole, the data rights described in the SBIR/STTR authorizing legislation are otherwise operative.[27] These rights implicitly refer to intellectual property that is not patentable or has not been patented. Bayh-Dole refers only to patentable inventions and provides for a clear path through which companies can patent inventions funded by federal agencies.

[25]iEdison Invention Timeline, http://era.nih.gov/iedison/invention_timeline.cfm, accessed February 14, 2014.

[26]William O'Brien, O'Brien, "March-in Rights Under the Bayh-Dole Act: The NIH's Paper Tiger?," *Seton Hall Law Review*, 30: 1403, 2013.

[27]Ronald S. Cooper, "Purpose and Performance of the Small Business Innovation Research (SBIR) Program," *Small Business Economics* 20(2): 137-151, 2003.

Regarding data rights provided under the reauthorization legislation (see Chapter 1), small companies own all rights to data produced under SBIR/STTR awards for a period of 4 years after the end of any SBIR/STTR award that is related to the technology. It remains to be seen whether Phase III contracts count toward an extension of these data rights. These rights explicitly cannot be negotiated away by agency contracting or grants officers; they are not subject to negotiation; and the company is not required to file any registration papers on an invention, file a patent application, or otherwise take steps to protect its intellectual property. SBIR/STTR data rights accrue to the company regardless of its other actions.

There are therefore clear differences between the regimes imposed via Bayh-Dole and that described in the reauthorization legislation and subsequent policy guidance from SBA.

2014 Survey respondents did not raise the issue described above. However, some respondents indicated that the costs of protecting intellectual property through patents were onerous for small companies and that the recent shift to "first to file" system has added pressure to protect intellectual property at a time when small companies have least financial ability to do so. Several recommended that intellectual property costs be permitted as allowable expenses under the SBIR/STTR awards.

COMMERCIALIZATION SUPPORT

NIH operates two commercialization support programs: the Commercialization Assistance Program (CAP) and the NICHE program.

The Commercialization Assistance Program (CAP)

For 10 years, NIH has funded a third-party organization, the Larta Institute, to provide commercialization support for selected NIH SBIR and STTR Phase II award winners. The Commercialization Assistance Program (CAP) is voluntary, and award winners from the five most recent years are eligible to participate. Since 2009, the program has offered two tracks, the Commercialization Training Track (CTT) and the Advanced Commercialization Training Track (ACT). The program lasts 10 months, and Larta notes that the program provides personalized 1-on-1 business mentoring.[28]

As of the most recent NIH report on the program,[29] 758 Phase II companies had participated in Larta training (see Figure 2-9).

[28]Larta program description, https://portal.larta.org/nih/home, accessed August 8, 2015.

[29]NIH Office of Extramural Research, NIH SBIR/STTR Commercialization Assistance Program (NIH-CAP): Impact Overview 2004-2013, June 2014. This section is based on this report and on meetings with NIH and LARTA staff.

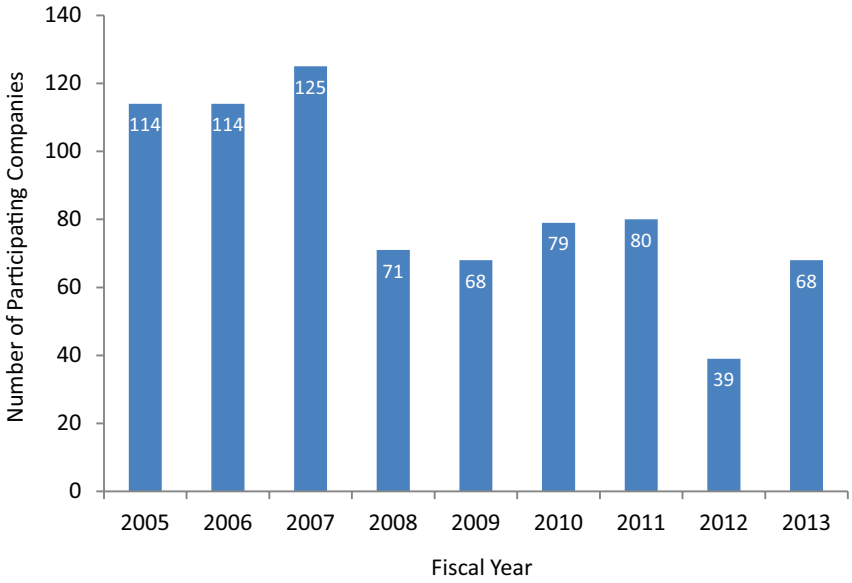

FIGURE 2-9 Participation in NIH Commercialization Assistance Program (CAP). SOURCE: NIH Office of Extramural Research, NIH SBIR/STTR Commercialization Assistance Program (NIH-CAP): Impact Overview 2004-2013, June 2014.

The data in Figure 2-9 show that participation levels dropped in 2007-2008 and have remained approximately constant since then (except for 2011-2012).[30] On average, 250 new Phase II grants were made every year during this period, and since 2007-2008 Larta has served between 68 and 80 companies each year (except for 2011-2012). Figure 2-10 shows the distribution of companies by sector. The training covers a range of business-related areas, some specialized to life sciences companies. These include the following:

- Business and strategic planning
- Investor and partnership pitch
- Technology valuation
- FDA regulatory requirements
- Intellectual property and licensing Issues
- Go-to-market strategies

Larta claims to have provided substantial positive outcomes for participating companies. The data below are generated from Larta's tracking of participat-

[30]NIH did not provide an explanation for this drop in participation.

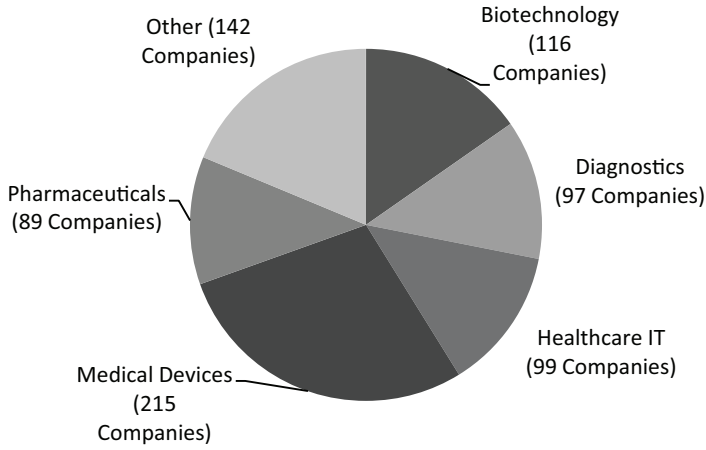

FIGURE 2-10 Commercialization Assistance Program: Distribution of participating companies, by sector.
NOTE: Other category includes clinical research, instrumentation, and research tools.
SOURCE: NIH Office of Extramural Research, NIH SBIR/STTR Commercialization Assistance Program (NIH-CAP): Impact Overview 2004-2013, June 2014.

ing companies during the 10-month CAP period and for a further 18 months thereafter. Commercialization of new technologies and processes especially in the life sciences, typically takes much longer.[31]

Larta tracking covers all of the most important indicators of commercial activity:

- Financial indicators
- Grant/loans received
- Investment funds raised
- New jobs created
- New products
- Partnerships
- Product sales
- Qualitative assessment

Overall, about 70 percent of participants reported that the CAP has had a "valuable and major impact" on their commercialization progress. About 30 percent reported little or no impact.[32]

[31]NIH Office of Extramural Research, NIH SBIR/STTR Commercialization Assistance Program (NIH-CAP): Impact Overview 2004-2013, June 2014.
[32]Ibid.

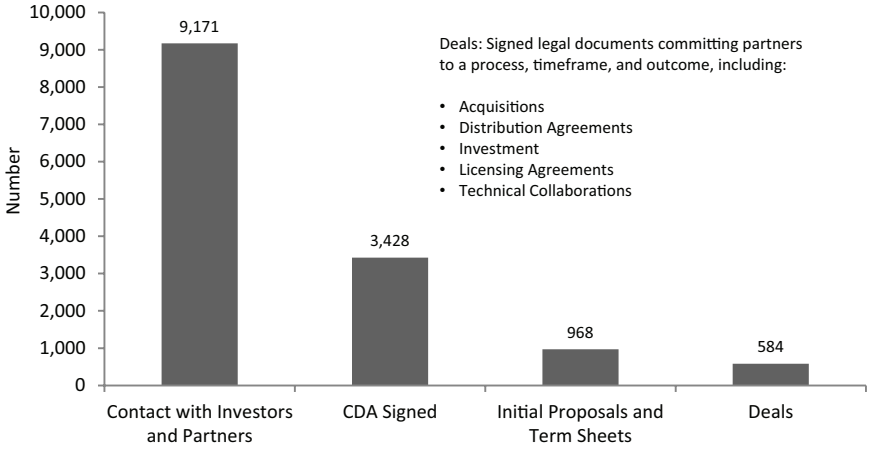

FIGURE 2-11 Number of commercialization milestones for CAP participants, FY2004-2012.
SOURCE: NIH Office of Extramural Research, NIH SBIR/STTR Commercialization Assistance Program (NIH-CAP): Impact Overview 2004-2013, June 2014.
NOTE: CDA refers to Confidential Disclosure Agreements

Commercialization progress requires the company to work through a series of milestones, which are depicted in Figure 2-11. The LARTA data show that participants made more than 9,000 contacts with investors or potential partners, which translated into 584 signed deals.[33]

Although the number of deals in relation to other milestones varies somewhat across years, no clear patterns emerge. However, the amounts of additional funding secured by companies participating in the CAP do vary widely, which is expected in an environment where a few large deals have a disproportionate impact. Figure 2-12 shows the distribution of nongovernment funding raised by CAP participants by year. The 2005 and 2006 fiscal years were in particular affected by the completion of large individual deals. Overall, the data report about $585 million in financing, through 223 deals.

The NIH CAP impact report also covers job creation as a result of the program, as well as mergers and acquisitions.

Analysis of NIH's CAP Impact Report

The existence of the report in and of itself is important evidence that the NIH program is concerned about outcomes (as described in Chapter 5, the SBIR Program Office is now working to develop better output indicators and data).

[33]Ibid.

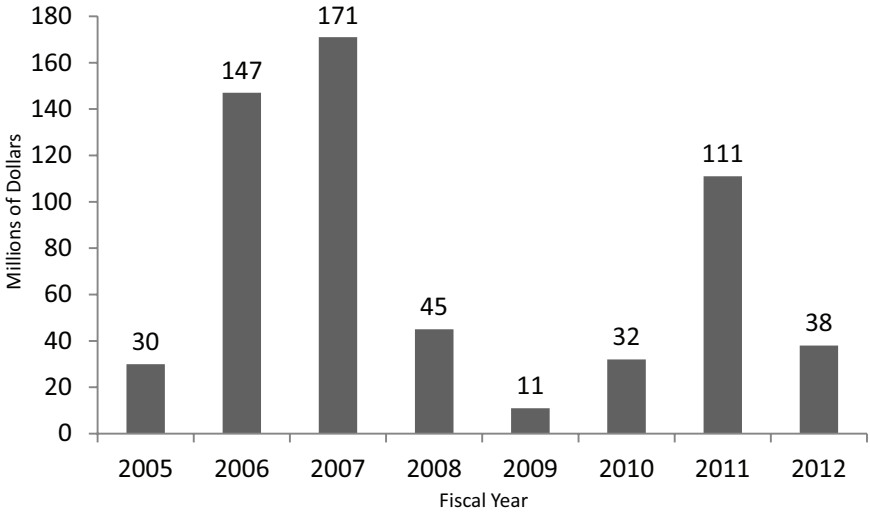

FIGURE 2-12 CAP participant nongovernment funding raised, FY2004-2012.
SOURCE: NIH Office of Extramural Research, NIH SBIR/STTR Commercialization Assistance Program (NIH-CAP): Impact Overview 2004-2013, June 2014.

However, the publicly available report[34] is insufficiently detailed to permit the development of robust conclusions. The activity indicators are reported at an aggregated level that makes it difficult to determine how much impact the program generates:

- Deals are reported by year and by dollars. Given the likely impact of outliers, it would be helpful to see the distribution of outcomes across all companies with deals.
- Data tend to be provided in categories that are overly broad. For example, the mergers and acquisitions activity does not disaggregate purchase and sales of participating companies. There is little detail about partnering activities, which are important and span from shared R&D to downstream marketing agreements.
- There is no geographical breakout. Larta is located in Los Angeles, close to West Coast sources of venture capital. There is no information about the connections between these sources and companies located in other regions of the country.
- Recently, the NIH Program Office has assumed management of data collection and metrics. This is a positive step toward providing a more neutral

[34]Ibid.

data source, but it would be appropriate to consider at least one round of third-party analysis.

Respondents to the 2014 Survey were generally positive about the CAP's utility and impact. No respondents recommended ending the CAP or NICHE Program. Some of their responses are provided in Box 2-7.

Overall, NIH has consistently provided commercialization support. The data reported by LARTA suggest that a deeper look at the metrics might lead to further program improvements.

NICHE Program for Phase I Participants

In addition to the CAP, NIH operates a commercialization support program for Phase I participants. This program is unique among SBIR agencies. It is open on a voluntary basis to all Phase I participants (grants and contracts), on a first-come, first-served basis.

BOX 2-7
2014 Survey Responses Related to Commercialization Support Programs (Representative Comments)

The Commercialization Assistance Program is a great idea. In addition to providing assistance to prepare a "pitch" and participation in a venture show; it would be helpful to go through the methods to get the FDA approval processes, such as IDE or 501 etc.

The offered support, including business counseling, was very good.

CAP and NICHE programs were very helpful.

Continue SBIR program, NIH CAP program and Administrative Supplements.

NIH-CAP was very helpful, overall NIH does a great job fostering SBIR research.

Some training was offered for commercialization—market study was conducted by a NIH partner company. All great help to the project.

The Commercialization Assistance Program is very good.

The NIH CAP program is beneficial. But the final meeting is in front of "advisors," rather than true investors. We've had so many meetings with "advisors" and many fewer with true potential investors.

We are now participating in the CAP which is a help.

We participated in NIH-CAP, which was helpful.

We've participated in the CAP program and that was very helpful and exposed us to commercialization thinking and resources.

SOURCE: 2014 Survey.

The number of participants is capped at 136 annually. The program reviews the company's technology portfolio and then for one selected technology provides a more detailed market assessment. Each participant receives an in-depth report of Foresight's findings.

The NICHE Program aims to help small businesses strategically position their technology in the marketplace, by helping them to generate higher quality commercialization plans for their Phase II application and to seek out potential partners. The NICHE services are provided by Foresight Science & Technology of Providence, Rhode Island.[35]

In FY2014, the NICHE program filled its annual quota of participants on February 15, 2015. This suggests that the program is successfully attracting participants and that NIH should consider expanding the number of seats available.

There are no available data on outcomes related to the NICHE program.

OUTREACH

Until recently, outreach for the SBIR/STTR program was tightly constrained by the limited funding available. Reauthorization changed that by providing up to 3 percent of program funding for program administration, in line with recommendations by the National Research Council in its 2008 report.[36]

The NIH Program Office has used these funds for a variety of activities, including efforts to improve outcomes tracking (see Chapter 5). In part, funding has been spent to improve outreach. The NIH SBIR/STTR website is now expanded and much improved, with a considerable amount of useful information for potential applicants, including introductory webinars, sample applications, contact information for the Program office and for individual ICs, a detailed description of the electronic application process, and deadline information. NIH also maintains an active electronic mailing list of more than 22,000 companies and other organizations for its SBIR/STTR programs.[37]

The 2014 Department of Health and Human Services (HHS) annual outreach report for the program indicates a considerable amount of activity. Activities in FY2014 were "directed at increasing name-recognition and awareness of the SBIR/STTR programs, and identifying new SBIR/STTR applicants, with a special emphasis on woman-owned businesses (WOSB), socially and economically disadvantaged businesses (SDB) and under-represented states, known as Institutional Development Award (IDeA) states."[38] Outreach efforts related to women and minorities are discussed in Chapter 6 (Participation of Women and Minorities).

[35]See https://sbir.nih.gov/nap.

[36]Recommendation J.3 in National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, Washington, DC: The National Academies Press, 2008.

[37]HHS SBIR/STTR Outreach Overview, FY 2014, n.d., p.1.

[38]Ibid.

NIH uses its annual conference as an important outreach tool. As with past conferences, the 2015 conference in Seattle, Washington, provides existing award winners with an opportunity to connect to Phase III funders and to network with agency staff, as well as initial training of potential applicants. The conference has been running for 17 years. Past conferences have been targeted at underserved states, such as the 2013 meeting in South Dakota and the 2014 meeting in New Mexico.

NIH is active on social media. It has a Twitter account and is working to develop content for other platforms, including YouTube videos. Its electronic mailing list has 22,000 names.

It is fair to say that the need for outreach has changed. The advent of numerous Phase 0 programs funded by individual states (designed to help and encourage new firms to apply to the SBIR/STTR programs), the wider interest in SBIR among universities, and the shift among state economic development agencies from job attraction to innovation-oriented job creation have all helped to bring knowledge of SBIR/STTR to a wider range of potential applicants.[39]

Finally, NIH has worked to generate data about its outreach activities. A summary is provided in Box 2-8, drawing from the FY2014 outreach report.[40]

One measure of outreach effectiveness is new entrants into the program. These data are presented in detail in Chapter 4 (Awards), but it is worth noting here that from FY2005 to FY2013 inclusive, an average of 35 percent of applying companies were first-time applicants.[41]

Coordination with the NIH Institutional Development Award (IDeA) Program[42]

The NIH IDeA program seeks to "broaden the geographic distribution of NIH funding for competitive biomedical research. It builds research capacities in states that have not traditionally received significant levels of NIH research dollars. It supports basic, clinical and translational research, faculty development, and infrastructure improvements in 23 states and Puerto Rico. IDeA states include AK, AR, DE, HI, ID, KS, KY, LA, ME, MS, MT, ND, NE, NH, NM, NV, OK, PR, RI, SC, SD, VT, WV, and WY."[43] As a result of this mandate, NIH has developed a list of activities (summarized in Table 2-6).

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[39]National Academies of Sciences, Engineering, and Medicine, Workshop on "SBIR/STTR and the Role of State Programs," Washington, DC, October 7, 2014.

[40]HHS SBIR/STTR Outreach Overview, FY 2014, n.d., p. 1.

[41]See Chapter 4 section on new entrants.

[42]Material in this section unless otherwise noted is drawn from NIH Office of Extramural Research, Coordination of the NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs and the NIH Institutional Development Award (IDeA) Program, December 2014, and from discussions with agency staff.

[43]HHS SBIR/STTR Outreach Overview, FY 2014, n.d., p. 1.

BOX 2-8
Outreach Outcomes for FY2014

83 total events (in-person and virtual) hosted in 24 states plus the District of Columbia and Puerto Rico that reached more than 7,197 attendees.

79 of these events were in-person conferences, exhibitions, or workshops that reached 5,790 attendees; 4 were virtual webinars that reached 1,407 attendees.

223 socially and economically disadvantaged businesses reached through 30 events.

360 woman-owned small businesses reached through 36 events.

Collaborated with the IDeA program to reach all 23 IDeA states and Puerto Rico through outreach events.

601 attendees participated in an HHS SBIR/STTR outreach event in an IDeA state.

7 of the 23 IDeA states plus Puerto Rico hosted 10 HHS SBIR/STTR outreach events, including AR, KY, LA, NE, NV, PR, SD, and WY.

The 15th Annual NIH SBIR/STTR conference hosted in Sioux Falls, South Dakota, an IDeA state, on October 28-30, 2013, reached 366 people in 37 states plus Puerto Rico and the District of Columbia. Thirteen of the states plus Puerto Rico were IDeA states; 39 percent of total attendees were from IDeA states including Puerto Rico.

Planning began for the 16th Annual NIH SBIR/STTR conference to be held in Albuquerque, New Mexico, an IDeA state, on October 21-23, 2014 (FY2015).

SOURCE: NIH SBIR/STTR Program Office.

With the 2011 SBIR/STTR reauthorization, Congress sought to increase coordination between the SBIR/STTR programs and the IDeA program, with a view to increasing the number of SBIR/STTR applications from IDeA states.[44] From the perspective of the SBIR/STTR programs, four key initiatives emerge:

- Hiring a dedicated outreach coordinator (FY2013)
- Targeting at least 25 percent of outreach activities to IDeA states
- Holding National and Regional NIH SBIR/STTR Conferences in IDeA states
- Cross-promoting NIH SBIR/STTR and NIH IDeA activities

NIH has also undertaken an initial analysis and comparison of SBIR application success rates from IDeA and non-IDeA states (see Tables 2-7 and 2-8) from FY2011 to FY 2014. The data on SBIR applications and success rates show little difference between IDeA and non-IDeA states: applications declined from both, success rates changed approximately in tandem.

[44]P. L. 112-81, Section 5168, December 2011.

TABLE 2-6 NIH SBIR/STTR Coordination with IDeA

Time Frame	Activity	Status of Activity as of November 1, 2014
August-November 2012	Brainstorm meetings with personnel from NIH IDeA and SBIR/STTR programs.	Completed
January 2013	Use the IDeA listserv to introduce the IDeA community to the NIH SBIR/STTR program.	Completed
January 2013	Cross-promote the SBIR/STTR and IDeA programs on their respective websites.	Completed
April-September 2013	Hire a dedicated NIH SBIR/STTR Outreach Coordinator who will, in part, coordinate IDeA/SBIR/STTR outreach.	Completed
Regional IDeA Conferences: May 20-22, 2013 (Central); August 14-16, 2013 (Northeast); October 7-8, 2013 (Western); November 15-17, 2013 (Southeastern); National IDeA Symposium: June 16-18, 2014	Conduct SBIR/STTR outreach to IDeA states via their annual national and regional conferences (approximately five conferences every 2 years). Hold four Regional IDeA Conferences scheduled for 2015: June 1-3 (Central); September 24-26 (Northeast); October 12-14 (Western); and November 11-13 (Southeastern).	Completed and Ongoing
Ongoing	Conduct targeted outreach to IDeA states via coordination with state economic development offices.	Completed and Ongoing
Ongoing	Monitor SBIR/STTR applications from IDeA states.	Completed and Ongoing
Ongoing	Identify institutions in IDeA states doing applied clinical research and match them with small business concerns in their state for collaborations.	Completed and Ongoing
July/August 2013 and future years	Hold the annual NIH SBIR Conference in an IDeA state as feasible and coordinate the conference program/agenda with IDeA institutions in that state.	Completed and Ongoing

SOURCE: HHS SBIR/STTR Outreach Overview, FY 2014, n.d., pp. 1, 3.

TABLE 2-7 SBIR Applications, Awards, and Success Rates for IDeA and Non-IDeA States, FY2011-2014

	Number of SBIR Applications		Number of SBIR Awards		Success Rate (Percent)	
Fiscal Year	IDeA	Non-IDeA	IDeA	Non-IDeA	IDeA	Non-IDeA
2011	507	5,255	68	713	13.4	13.6
2012	420	4,782	76	870	18.1	18.2
2013	416	4,177	57	665	13.7	15.9
2014	385	4,074	71	867	18.4	21.3

SOURCE: HHS SBIR/STTR Outreach Overview, FY2014, n.d., p. 7.

TABLE 2-8 STTR Applications, Awards, and Success Rates for IDeA and Non-IDeA States, FY2011-2014

	Number of STTR Applications		Number of STTR Awards		Success Rate (Percent)	
Fiscal Year	IDeA	Non-IDeA	IDeA	Non-IDeA	IDeA	Non-IDeA
2011	69	584	12	109	17.4	18.7
2012	80	565	11	138	13.8	24.4
2013	88	609	18	122	20.5	20.0
2014	111	824	23	179	20.7	21.7

SOURCE: HHS SBIR/STTR Outreach Overview, FY2014, n.d., p. 7.

The picture for STTR is slightly different. Applications rates increased for both IDeA and non-IDeA states, but more rapidly for the former than the latter. As a result, there was a sharp increase in the number of STTR awards to IDeA states—approximately double over the time period (Table 2-8).

NIH staff expect all the core elements of this program to continue into the future, including the data monitoring described above.

DATA COLLECTION, TRACKING, AND ANALYSIS[45]

NIH has an extensive and generally excellent approach to online access to awards through the NIH RePORTER grants search program.[46] It permits seamless navigation through the awards database, although it provides data as though each

[45]Information in this section is based on discussions with NIH Program Office staff and material provided by the staff.

[46]See http://projectreporter.nih.gov/reporter.cfm, accessed July 15, 2015.

year of an award is a separate award, which complicates analysis. NIH staff were able to generate award-level data and were generally able to provide clear and consistent data on applications and awards. This is important especially given the proliferating number of mechanisms and programs involved.

In the 2009 NRC report, the committee recommended that data collection and analysis be substantially improved. Specifically, recommendations included:

- A.2.I Significant improvement in data collection and assessment is needed.
- A.2.II Efforts to identify outcomes across a variety of metrics should be improved.[47]

Since the 2009 report, NIH has initiated changes to address these limitations. As part of its revised mandate under reauthorization, SBA is developing a central commercialization database for tracking SBIR/STTR outcomes. This database is designed to be used by SBIR/STTR awardees from all 11 agencies to update their commercialization outcomes (e.g., sales, licensing, patents, partnering, Phase III). NIH has included an update to this database as a part of its terms of award for all grants and contracts.

NIH is also proceeding with its own data collection tools and strategy. This work involves an update to its existing internal SBIR/STTR Performance Outcomes Data Systems (PODS) database to be able to hold all of the outcomes data required by the reauthorization and additional outcomes data unique to NIH/HHS and life sciences technology development (e.g., clinical trials status, FDA filing status, Centers for Medicare & Medicaid Services [CMS] reimbursement status).

The PODS database historically only held outcomes for CAP participants, but will now hold outcomes for the entire portfolio of NIH awards. NIH is also working directly with SBA and particularly its commercialization database staff to connect the SBA database and PODS via Web Services. This will allow PODS to pull in company commercialization data so that companies do not have to enter this information twice. Companies will only have to enter data into PODS that SBA does not collect (e.g., in relation to FDA, CMS, etc.).

USE OF ADMINISTRATIVE FUNDS

In the 2011 reauthorization, Congress permitted agencies to use up to 3 percent of SBIR/STTR funds to support program administration for a range of approved purposes. This is a pilot program, and proposed activities must be submitted to SBA for approval. As SBA noted, "The funds should be used to provide added support rather than replace the non-SBIR funds formerly used, and

[47]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 32.

the work should focus on material improvements in performance of the program on critical issues (e.g., streamlining the award process)."[48]

At NIH, that 3 percent is divided between the SBIR/STTR Program Office, which uses 1 percent, and the ICs, which *may* use the remaining 2 percent. Table 2-9 shows the amounts spent on administrative funding for FY2014 by the individual ICs: the percentage of potentially available funding varies widely. ICs can use 2% plus any 1% that comes back from Office of the NIH Director. The table shows that many ICs spent zero, preferring to use their funding for SBIR/STTR awards instead. It also shows that NHLBI spent the additional funds from the Office of the NIH Director.

Spending by the Program Office has been focused primarily on information technology expenditures that are designed to improve data collection and tracking of projects at NIH, and on the congressionally mandated Academies assessment of the SBIR/STTR programs.

SBIR AND STTR[49]

As noted at the beginning of this chapter, the SBIR/STTR programs are closely aligned at NIH but are, of course, not identical. The SBIR program is much larger, and it permits but does not require partnering with or outsourcing (within limits) to research institutions (RIs). The SBIR program also requires that the principal investigator (PI) be at least 51 percent employed by the small business; the STTR program allows the PI to be employed either by the small business or the research institution partner (see Table 2-10). The different employment rules are potentially very important in the context of the NIH program, where a large number of PIs come out of the academic environment. The STTR rules allow the PI to retain an academic position while working on the project; the SBIR rules conflict with employment rules at many RIs.

Discussions with agency officials and with companies indicated that these differences between SBIR and STTR in some cases matter a great deal to some companies and to individual PIs. However, they do not reflect any systematic differences from the agency's perspective: for NIH, SBIR and STTR are equivalent mechanisms with identical objectives. Discussions with SBIR/STTR Program Office and IC contacts supported this view.

A new component of the 2014 Survey focused on the STTR process and the impact of these awards. A total of 88 responses were received from NIH Phase II STTR awardees, so caution should be employed in the analysis given the relatively small sample size.

Table 2-11 shows that for most STTR respondents the award enhanced or substantially enhanced the relationship between the company and participating

[48]SBA Key Changes in the SBIR and STTR Policy Directives, https://www.sba.gov/content/key-changes-sbir-and-sttr-policy-directives, accessed June 16, 2015.

[49]STTR awards and applications are discussed in Chapter 4 (SBIR and STTR Awards at NIH).

TABLE 2-9 Administrative Fund Spending by HHS/NIH Institutes and Centers, FY2014

Institute/ Center	Amount of Administrative Funding Available (Thousands of Dollars)	Amount of Administrative Funding Spent (Thousands of Dollars)	Percentage of Administrative Funding Expended
NCI	2,095	126	6.0
NIAID	2,042	397	19.4
NHLBI	1,485	1,980	133.4
NIGMS	1,154	22	1.9
NIDDK	912	20	2.2
NINDS	772	220	28.5
NIMH	658	11	1.7
NICHD	576	392	68.1
NIA	568	0	0.0
NIDA	486	286	58.9
NEI	327	0	0.0
NCATS	308	218	70.7
NIEHS	296	91	30.8
CDC	257	100	39.9
NIAMS	243	0	0.0
NHGRI	209	0	0.0
NIAAA	204	0	0.0
NIDCD	193	0	0.0
NIDCR	171	8	4.6
NIBIB	165	12	7.3
NIMHD	142	0	0.0
NINR	63	0	0.0
NCCAM	56	0	0.0
FDA 3%	39	0	0.0
NLM	14	0	0.0
ACF 3%	0	0	n/a
FIC	0	0	n/a
OD-ORIP	123	67	54.5
OD-OEP 1%	6,631	2,019	
TOTAL	20,189	5,969	

SOURCE: NIH, Technology Transfer Programs: Consolidated and Continuing Appropriations FY2014.
NOTE: With regards their administrative funds allocation, NHLBI staff clarified that the additional amounts were allocated in accordance with procedures defined by the Office of the NIH Director.

TABLE 2-10 Comparison of SBIR and STTR at NIH

	SBIR	STTR
Program Size	2.8% set aside	0.4% set aside
Partnering Requirement	**Permits** partnering	**Requires** a nonprofit research institution partner
Principal Investigator	Primary employment (>50%) **must** be with the small business	PI may be employed **by either** the research institution partner or small business
Work Requirement	**Guidelines:** May outsource up to 33% (Phase I), 50% Phase II	Minimum Work **Requirements**: 40% Small Business 30% Research Institution Partner

SOURCE: NCI Contracts webinar, September 14, 2014, http://sbir.cancer.gov/objects/pdfs/2014-09-18_nih-sbir-contracts-webinar.pdf, accessed February 16, 2015.

TABLE 2-11 Impact of Company-Research Institute Relationships for STTR Winners

	Percent of Respondents
Enhanced	68.1
Substantially enhanced	42.0
Somewhat enhanced	26.1
Made no real difference	23.9
Made worse	7.9
Made somewhat worse	6.8
Made substantially worse	1.1
BASE: STTR AWARD RECIPIENTS	88

SOURCE 2014 Survey, Question 74.

RI. Eight percent reported that it made the relationship worse. For 85 percent of respondents,[50] the relationship between the company and RI was not new, and about one-third of PIs[51] reported that they had also received an SBIR award at some point. Together, these data suggest that, although there are cases where STTR acts as a bridge between academia and business, in many cases it is not a unique pathway.

[50]2014 Survey, Question 75, N=89.
[51]2014 Survey, Question 76, N=90.

TABLE 2-12 Ease of Managing STTR Awards

	Percentage of Respondents
STTR is easier to manage than SBIR	5.4
They are about the same	62.5
STTR is harder to manage than SBIR	32.1
BASE: HAVE RECEIVED BOTH SBIR AND STTR AWARDS	56

SOURCE: 2014 Survey, Question 80.

TABLE 2-13 Should the Share of Funding to Research Institution be Increased?

	Percentage of Respondents
Agree	39.3
Strongly agree	21.3
Somewhat agree	18.0
Neither agree nor disagree	30.3
Disagree	30.4
Somewhat disagree	13.5
Strongly disagree	16.9
BASE: STTR AWARD RECIPIENTS	89

SOURCE: 2014 Survey, Question 81.

Exactly one-half of respondents who had received both SBIR and STTR awards said there was a substantial difference between them.[52] Of these respondents, about one-third said that the STTR award was more difficult to manage, and 5 percent said that it was easier (see Table 2-12). Opinions were mixed about the possibility of increasing the share of funding available to the research institution (Table 2-13). Finally, about 20 percent of respondents had tried to switch an award between SBIR and STTR.[53]

CONCLUSION

Program management at NIH is highly diffuse. It is spread across 24 ICs and the Program Office. Moreover, SBIR/STTR awards are managed in different ways within the different divisions. To understand how this varied and diverse

[52]2014 Survey, Question 78. N=56.
[53]2014 Survey, Question 82. N=87.

constellation of activities affects the companies themselves, we turn to the following chapters. Chapter 5 provides a more quantitative analysis, drawing again from the survey in the absence of outcomes data from NIH. Chapter 7 provides qualitative insights based on case study meetings and textual responses to the 2014 Survey.

3

Program Initiatives at NIH

In the 30 years since SBIR started at the National Institutes of Health (NIH), there has been a profound change in the agency's vision for itself. Most fundamentally, NIH is now more interested in and committed to "translational research"—activities that will help to move technologies from the laboratory into the marketplace. Among many initiatives, NIH has formed an entire organization devoted to this effort, the National Center for Advancing Translational Sciences (NCATS).

The NIH Institutes and Centers (ICs) have in general become more interested in SBIR/STTR in part because of this greater commitment to translational research. Not all ICs have made major changes to their operations in response, but some have done so, and new models of program management are emerging at some of the larger ICs as a result of the new focus on translational research.

This chapter focuses on two of the largest ICs—the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI). It also reviews some of the other agency-wide initiatives, most notably the occasional provision of awards considerably larger than stated in the SBA guidelines (these awards are legal on the basis of waivers provided by SBA).

NEW MANAGEMENT MODELS FOR SBIR/STTR

For almost all ICs, the traditional management model for SBIR/STTR at NIH has been to employ one or two staff members to act as expert advisors in relation to program questions. They complement program officers with broad responsibility for administering the SBIR and STTR programs.

This model has some advantages. It is relatively low cost, which has been an especially important consideration when administrative funding was not available through the SBIR/STTR programs and when ICs tended to see the programs as a tax on their other research activities. The model also ensures that program officers with deep expertise in IC interests and priorities manage SBIR/STTR awards. Some of the larger ICs did assign the management of SBIR awards to an individual staff member who effectively became the program officer for SBIR/STTR, but this was not a standard model. Most ICs found that they had too few awards to justify such a full-time assignment.

However, this approach has two disadvantages: first, it leaves companies connected directly to program officers that are experts in the research areas that they fund but likely with little commercialization experience; and, second, it does not provide for the accrual of expertise—for example, on regulations or marketing—within the IC.

Beginning in the mid-2000s, some ICs developed new models for managing SBIR/STTR. At NCI, the NCI SBIR Development Center has become the locus for all SBIR activities, including awards and the company liaison.[1] At NHLBI, the Office of Translational Alliances and Coordination (OTAC) has become a provider of deep expertise to both program officers and companies in the many areas that impinge on biomedical commercialization, including intellectual property, capital acquisition, marketing, and regulation by the U.S. Food and Drug Administration (FDA). Other ICs are developing their own models, but these two approaches affect two of the biggest ICs and are most developed. They are discussed in more detail below.

The NCI Model: Building on the National Science Foundation (NSF) Management Model

Starting in 2007, NCI moved rapidly to shift the traditional NIH management model for SBIR/STTR to one much closer to that pioneered by NSF.[2] NCI is the largest IC at NIH and accounts for about $119 million in SBIR/STTR funding, out of about $750 million at NIH overall.

The new model is deployed through the NCI SBIR Development Center (NCIDC). NCIDC funds nine full-time program directors, each of whom holds a doctorate and is working in a particular technical area within NCI's portfolio of activities. The NCIDC is led by a full-time director and currently hosts two AAAS Science and Technology Policy Fellows.

The NCIDC activities cover the entire timeline of SBIR activities. Staff are responsible for outreach to applicants and for coaching potential applicants to

[1]This is in many respects similar to the NSF model discussed in the committee's forthcoming report on SBIR at the National Science Foundation.

[2]See National Academies of Sciences, Engineering, and Medicine, *SBIR at the National Science Foundation*, Washington, DC: The National Academies Press, forthcoming.

improve the quality of applications. They oversee and actively manage currently funded projects, replacing the Program Manager who fulfills this function at other ICs. As the award ends, NCIDC staff help to match awardees with potential sources of Phase III funding. This model is indeed very close to that developed at NSF.

In addition, NCI has developed a new funding strategy—Bridge awards—and a new investor forum for bringing together NCI SBIR/STTR companies and potential investors.

Bridge Awards

NCI has pioneered a variant on Phase IIB awards, which are designed to support companies entering clinical trials (see Chapter 4 for more detail). It has made 16 $3 million Bridge awards since the program started in FY2009. One-half are in imaging and devices, and about one-quarter are in therapeutics and diagnostics respectively (see Figure 3-1). These awards account for about 15 percent of all Phase IIB awards made by NIH during fiscal years (FY) 2009-2014 (see Chapter 4).

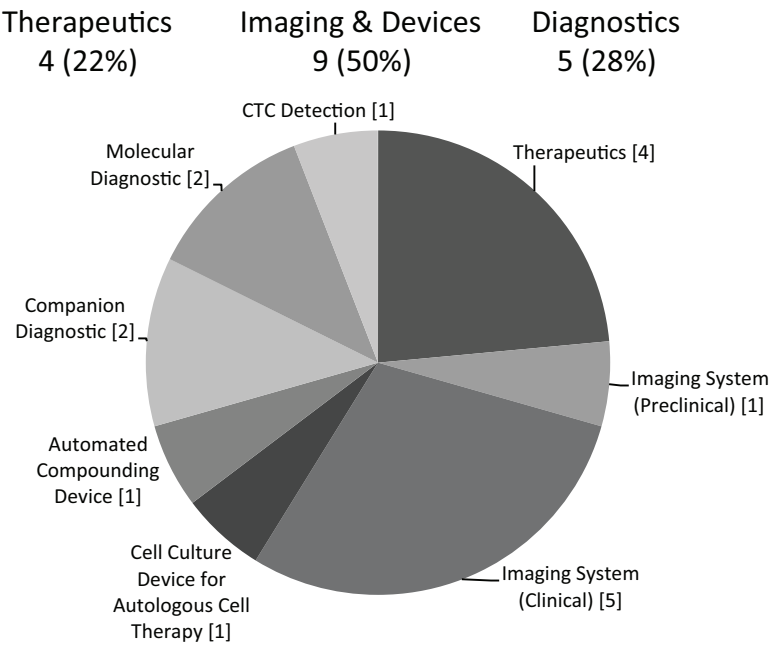

FIGURE 3-1 Distribution of NCI Bridge awards by sub-sector, FY2009-2013
SOURCE: Michael Weingarten, "Bridging Technologies from the Lab to Market: the NCI SBIR program," November 13, 2014.

Bridge awards provide SBIR/STTR firms up to $1 million per year for up to 3 years. They are specifically designed to help companies prepare for and enter the clinical trials process. They help companies connect with potential funders and strategic partners earlier in the process than would normally be the case by providing partners with a boost to the company that does not dilute their equity. While a funding match by a private-sector investor is not strictly required, companies with a match can and do have a competitive advantage.

In some cases, investors and other third parties have generated large matching funds. Overall leverage is slightly better than 2:1 (see Figure 3-2), and most Bridge projects report more than the "recommended" 1:1 match. About 40 percent comes from venture investors, 30 percent from strategic partners, and 20 percent from angel investors.

To date, participating companies have reported positive experiences with Bridge awards. Dr. Roger Sabbadini of the firm Lpath, contacted for this report, said that other Institutes should follow NCI's example. He is sufficiently convinced of its value now that he serves as reviewer for NCI Bridge awards.

However, acquiring the matching funds for these awards is a time- and resource-intensive endeavor for companies. Forty-three respondents from the 2014 Survey reported that they had to find matching funds. Of these, 44 per-

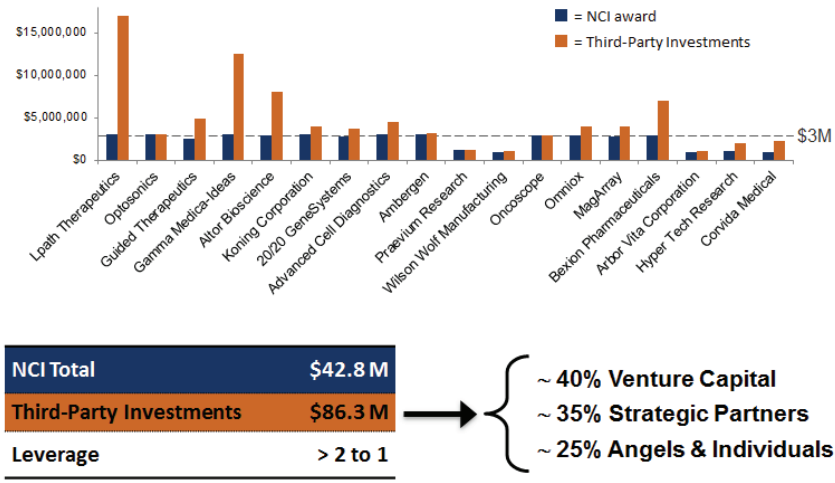

FIGURE 3-2 Matching investments for Bridge awards at NCI.
NOTE: See the Lpath case study in Appendix E.
SOURCE: Michael Weingarten, "Bridging Technologies from the Lab to Market: the NCI SBIR program," November 13, 2014.

cent said that it took at least 2 months of full-time equivalent effort for senior management.[3]

There are also potential pitfalls to selecting SBIR/STTR projects in a process akin to that of a small venture firm. In particular, the risk exists that interests in short-term commercial perspectives will predominate over the potential for more broadly spread societal benefits. Also, venture firms often provide extensive ongoing management support and marketing connections, neither of which NCI provides. Further, venture firms are, of course, the source of further rounds of funding.

I-Corps

The I-Corps program is described in more detail under NIH-wide innovations below. However, it is important to note here that the I-Corps initiative, although open to all ICs, has been driven in large part by NCI SBIR leadership, and that NCI continues to utilize most of the available slots in the program.

Investor Forums

Again building on initiatives from other agencies, NCI has organized a number of investor forums in recent years. Like the Navy Opportunity Forum, these aim to bring together companies and potential investors. At the November 2014 forum in Santa Clara, California, for example, 28 companies presented their technologies, with more than 200 people in attendance.

According to NCI, the investor forums have overall generated more than $300 million in deals, with $230 million in 2010 alone, primarily through a $200 million deal between Zacharon and Pfizer. In 2013 Zacharon was acquired by BioMarin for $10 million.

The NHLBI Model[4]

The new approach at NHLBI emerged from a growing understanding that commercialization for biomedical innovation presented major challenges that the original SBIR/STTR program management model was not addressing. An initial assessment of the issue was undertaken by a high-level committee, which included staff familiar with the SBIR program and senior IC management. The team produced a detailed and far-reaching report titled *Enhancing the Return on*

[3]2014 Survey, Question 29, N=43.

[4]Information in this section is drawn from internal agency documents made available as well as two briefings provided to the NRC committee by NHLBI staff.

the NHLBI SBIR/STTR Investment Team (ERNSIT),[5] which became the basis for a number of pilots and changes at NHLBI.

The report identified some key challenges for biomedical commercialization in general, and also some particular challenges for those working in the technical areas covered by NHLBI. Key general challenges included the following:

- Funding gaps exist before and after SBIR/STTR programs.
- Small businesses lack biomedical product development and business knowledge.
- Outreach and monitoring results are challenging because many small businesses get started, shut down, move, change names.
- NIH policies (e.g., review) do not always align with what is needed for SBIR/STTR awardee success.
- In some cases, program officers and grants management specialists might lack expertise in advising small businesses on commercialization issues and managing awards.

ERNSIT recommended some significant changes, most notably that NHLBI should introduce an entirely new office staffed with personnel dedicated to program activities, which would provide "scientific, business management, regulatory, and outreach expertise to coordinate and accelerate translational activities at the NHLBI."[6]

Within this new structure, ERNSIT also recommended:

- Enhanced and expanded partnerships for outreach
- More strategic use of funding opportunity announcements to align SBIR/STTR with Institute priorities
- Strategies to address pre- and post-SBIR funding gaps
- Improved evaluation and assessment

All of these recommendations were adopted by the NHLBI governing council in May 2010, and NHLBI's Office of Translational Alliances and Coordination (OTAC) started work in 2011.

The work of OTAC can be divided into four broad areas: expert advice to program officers and companies; outreach and training before Phase I; Phase I and Phase II commercialization support; and support after Phase II.

[5]The ERNSIT report was an internal report to the director of NCI. A summary of the ERNSIT report recommendations were provided by NHLBI in the NHLBI Office of Translational Alliances and Coordination and the SBIR/STTR Program, "Lab to Health," presentation to Academies, May 26, 2015, p. 7.

[6]The NHLBI Office of Translational Alliances and Coordination and the SBIR/STTR Program, "Lab to Health," presentation to Academies, May 26, 2015, p.7.

Expert Advice

Expert advice requires access to experts, and OTAC has hired and otherwise acquired a portfolio of expertise well suited to the needs of SBIR/STTR participants. These include as full-time staff:

- A regulatory specialist with 8 years of experience at the U.S. Food and Drug Administration (FDA);
- An entrepreneur in residence who has worked at a large pharmaceutical company and is an investor;
- An entrepreneur in residence who is also an early-stage investor and serial entrepreneur;
- A grants management specialist; and
- A business development/marketing expert with more than 15 years' experience with small innovative businesses and startups.

OTAC also includes a patent examiner on detail from the U.S. Patent and Trademark Office with extensive experience in intellectual property issues (additional expertise in some of these areas is also available from the National Institute of Occupational Safety and Health, a part of the Centers for Disease Control).

Proof-of-Concept Programs (pre Phase I)

OTAC operates two proof-of-concept programs: the NIH Centers for Accelerated Innovation (NCAI) and the Research Evaluation and Commercialization Hubs (REACH) program.[7] These programs aim to address three issues identified by the ERNSIT report: lack of funding for very early-stage commercialization activities; lack of commercialization expertise among scientists; and lack of access to additional commercialization resources.

There are three NCAI Centers located respectively at the Boston Biomedical Innovation Center, the Cleveland Clinic, and the University of California in Los Angeles, and three REACH centers located respectively at the University of Minnesota, the Long Island Biomedical Hub, and the University of Louisville.

Figure 3-3 shows the pipeline from letters of interest from researchers through company formation and SBIR application. It shows the different screening filters from the REACH and NCAI processes.

Targeted Funding Opportunities

The ERNSIT report recommended that NHLBI try to target its SBIR resources more strategically. Efforts to do so have focused on improved definition

[7]REACH is a trans-NIH program that is managed by a trans-NIH oversight committee, chaired by NHLBI based on their experience with these issues. NHLBI does not operate the REACH program.

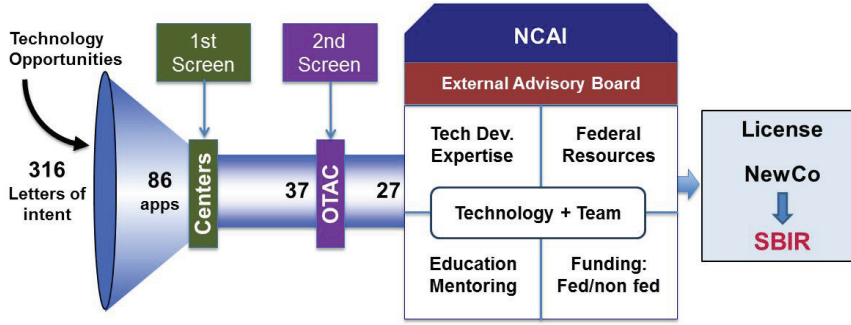

FIGURE 3-3 NCAI proof-of-concept support.
SOURCE: National Heart, Lung, and Blood Institute.

of topics and expanded use of targeted funding opportunity announcements (FOAs). While there is a set-aside budget associated with targeted FOAs, NHLBI staff consulted for this study note that detailed research proposals still come from the investigator community. Targeted FOAs are usually reviewed in-house by the IC using its own review panels, which some NHLBI staff believe offer a substantial advantage for SBIR/STTR applications over NIH's Center for Scientific Review (CSR) reviews. They note that this approach allows NHLBI to select reviewers with the appropriate combination of product development and scientific expertise necessary to effectively review small business program applications. Finally, budgets can be set aside for the targeted areas, which is not the case for standard topics provided through the annual Omnibus Solicitation. Some ICs such as NHLBI and NCI view the annual contract solicitation as an opportunity for targeted funding announcements, because it meets all of the criteria for such identified above.

It appears that funding for targeted FOAs is increasing as a percentage of SBIR/STTR funding. Estimates by NHLBI staff suggest that, excluding contracts, targeted funding opportunities now account for perhaps 15 percent of SBIR/STTR funding (see Box 3-1 for examples).

Training for Awardees

In addition to the I-Corps pilot program led by NCI, NHLBI participates in the Coulter College Commercializing Innovation (C3i) program. Covering topics such as market assessments, patentability assessments, and regulatory reviews, the C3i commercialization planning program seeks to support collaborative research that addresses unmet clinical needs in health care.[8] NHLBI also partners

[8]C3i was launched in 2014 by the National Institute of Biomedical Imaging and Bioengineering and the Wallace H. Coulter Foundation. Biomedical Engineering Society, Coulter College. http://bmes.org/coulter, accessed October 1, 2015.

BOX 3-1
Examples of NHLBI Targeted Funding Opportunities

- Stem Cell-Derived Blood Products for Therapeutic Use: Technology Improvement (STTR RFA-HL-15-029, SBIR RFA-HL-15-030)
- Onsite Tools & Technologies for Clinical Research Point-of-Care (STTR RFA-HL-14-017, SBIR RFA-HL-14-011)
- Bioreactors for Reparative Medicine (STTR RFA-HL-15-004, SBIR RFA-HL-15-008)
- Human Cellular Models for Predicting Individual Responses to CFTR-Directed Therapeutics (STTR RFA-HL-15-026, SBIR RFA-HL-15-027)

SOURCE: NIH Annual SBIR Request for Applications.

with a range of national investor showcases and events, including those run by BIO, the American Capital Association, and AdvaMed. This effort to align with industry sector conferences focused on early-stage activities is a potentially important initiative.

Post Phase II Awards

NHLBI operates two award programs to help bridge the gap between the end of SBIR/STTR Phase II and full commercial opportunities. The Bridge awards are very similar to those provided through NCI and described in detail above. Bridge awards are for $3 million over 3 years, with an expectation of a 1:1 match from a third party.[9]

Uniquely, NHLBI also operates Small Market awards. These are focused on rare diseases and pediatric populations. Recognizing that these are more challenging areas for commercialization, the match expectation here is 1:3, that is, outside matches must total $1 million for a $3 million award (as with NCI, matches must be in cash and not in-kind and must come from outside the award-recipient company).[10] Of course, awardees still have full access to the portfolio of experts working through the NHLBI OTAC.

Outreach Initiatives

To complement the outreach activities coordinated by the NIH Program Office (see Chapter 2, Program Management), the larger ICs have in some cases implemented their own activities. NHLBI has been especially innovative in using

[9]See RFA-HL-16-009 for details on the current request for Bridge proposals.
[10]See RFA-HL-14-012 for details on the current request for Small Market proposals.

social media for this purpose. It has hosted a series of virtual meetings using Google Hangouts, which have covered regulatory issues, commercialization, and intellectual property, thus providing access to OTAC experts in these areas.

OTAC has also developed a series of explanatory videos that are hosted on YouTube.[11] These, in particular, permit access from locations far from Washington, and the two videos on managing processes prescribed by FDA have attracted 1,649 and 1,329 views, respectively.[12]

NHLBI hosts the Regional Innovation Conferences, partnering with local resources to put them on. These conferences serve a variety of purposes, including connecting SBIR companies to potential sources of Phase III funding. According to NHLBI, the most recent Boston Regional Innovation Conference allowed 19 local companies to present their SBIR technologies, of which 3 entered into materials transfer agreements and 1 received a $1 million funding round led by a venture firm.[13] NHLBI also runs its own disease-specific conferences and worships, which have recently included workshops on Translating New Therapeutics for Sickle Cell Disease to the Market Place and Precision Therapeutics Delivery for Lung Diseases.

One of the challenges for small biosciences companies is to make the appropriate connections with what are effectively the primary sources of funding for clinical trials and then product development and marketing: big pharmaceutical companies. Given the enormous costs of drug development (estimated by the recent Tufts study as $2.6 billion on average[14]), connecting to the big pharmaceutical companies is essential but frequently difficult. In 2014, NHLBI sponsored a workshop on building an industry-government-academic partnership that attracted a large number of the world's major pharmaceutical companies. While the impact of the SBIR/STTR programs remains to be seen, the committee believes that improving the pathway for connections between small companies and big pharma is of substantial value.

Building an IT Platform to Track and Manage Multiple Initiatives

As ICs develop more complex and ambitious programs, especially for outreach, it becomes necessary to develop an information technology (IT) platform that can accommodate and track all of these new activities and participants. NHLBI is now exploring the use of Salesforce as a technical tool to bring together a PI, an entrepreneurial lead, and a mentor.

[11] See http://bit.ly/NHLBI-YouTube.

[12] NHLBI, Small Biz Hangouts, "Conquering the (Regulatory) Basics—Navigating the FDA Website" and "First Contact with FDA," accessed July 15, 2015. (See http://bit.ly/NHLBI-YouTube.)

[13] NHLBI op. cit. p.37

[14] Tufts Center for the Study of Drug Development, 2014 CCSD Report, http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study, accessed June 16, 2015.

New Management Models: Summary

Both NCI and NHLBI have developed new management models for their SBIR/STTR programs that quite fundamentally challenge the standard model at NIH. The standard approach often suffers from a lack of commercial expertise among program officers. Meanwhile, survey evidence and case study discussions revealed considerable demand among awardees for more support in relation to commercialization—including in relation to FDA approval for clinical trials.

Of course, because they were initiated recently, it is too soon to determine whether these new approaches, while addressing a key challenge, are having a net positive impact on program outcomes, and indeed whether that impact is worth the additional cost of the more focused management structures that they require.

NIH-WIDE INNOVATIONS

Awardee Training and Education: The I-Corps Pilot Program

After a number of years during which NIH relied on a third-party provider to offer commercialization training for awardees (see Chapter 2, Program Management), the agency introduced in FY2014 a version of the I-Corps program previously deployed at NSF. The NSF I-Corps program brings together awardees, a marketing partner (usually a graduate student in business or a marketing professional), and a mentor for a concentrated period of commercialization analysis and planning. The program is based on a teaching curriculum called the Lean Launchpad, developed by Steve Blank, a serial entrepreneur at Stanford University. I-Corps offers participants an intensive entrepreneurial immersion course that uses the participants' companies as the core learning medium. The 2014 I-Corps course had 11 class sessions and required a considerable commitment of time and effort from the participating teams. Final presentations were due 11 weeks after the initial meeting.

A key feature of the course is the requirement that participants must undertake at least 100 interviews with potential customers and partners. This extended listening exercise is designed to provide companies with important business information well before the product is ready to launch.

At NCI, the lead IC for the I-Corps program, participants are awarded a $25,000 supplemental award to pay for their participation. This participation provides the three-member teams with access to both instruction and peer connections via an I-Corps node (provided via a university). These teams include a C-level executive (e.g., CEO, CFO) from the company, an outside industry expert, and the principal investigator on the SBIR/STTR award.

The I-Corps program is tailored to the specific needs of life sciences companies. It is organized around three tracks: therapeutics, diagnostics, and medical devices, each of which has a specialized instructor. ICs may participate in one or more of the tracks—NCI is the only IC to participate in all three (see Figure 3-4).

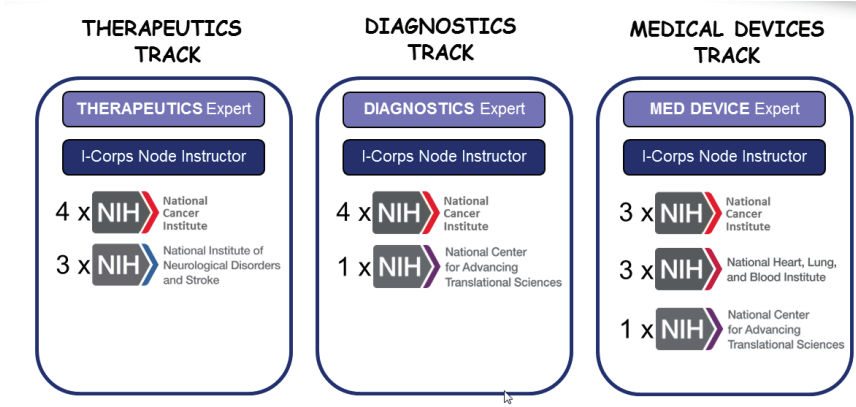

FIGURE 3-4 First-year participation in NIH I-Corps program, by track and IC.
NOTE: X = participants.
SOURCE: Andrew Kurtz, "The NCI SBIR Program: An Overview of New Funding Opportunities and Strategies for Employing Lean Startup Tools to Drive Success in Your Small Business," AACR presentation, April 20, 2015.

Multiple ICs participated in the first cohort (including NHLBI). The initial cohort of 19 companies included 3 awardees from NHLBI. IC staff expect this program to expand substantially in the near future, assuming results are as projected.

NCI has provided a review of initial outcomes from the first pilot program in FY2014. The 19 teams conducted a total of 2,128 "discovery" interviews. More than 80 percent found the I-Corps program to be good or excellent and would recommend it to other companies involved in the NIH SBIR program.[15] Companies developed specific hypotheses that underpin their business models and then found ways to test them, especially against feedback from customers and partners. The process was carefully structured and tracked on a weekly basis.

More generally, participation in the program improves company knowledge about core aspects of their business. Figure 3-5 shows the before and after state of knowledge for participating companies in relation to key aspects of their operations.

These data indicate an impressive improvement in understanding for participants. This improvement is also evident in areas that are directly relevant to life sciences companies as shown in Figure 3-6. For example, the improvement shown for medical reimbursement—a key revenue concern in life science markets—is especially impressive.

[15] Andrew Kurtz, "The NCI SBIR Program: An Overview of New Funding Opportunities and Strategies for Employing Lean Startup Tools to Drive Success in Your Small Business," AACR presentation, April 20, 2015.

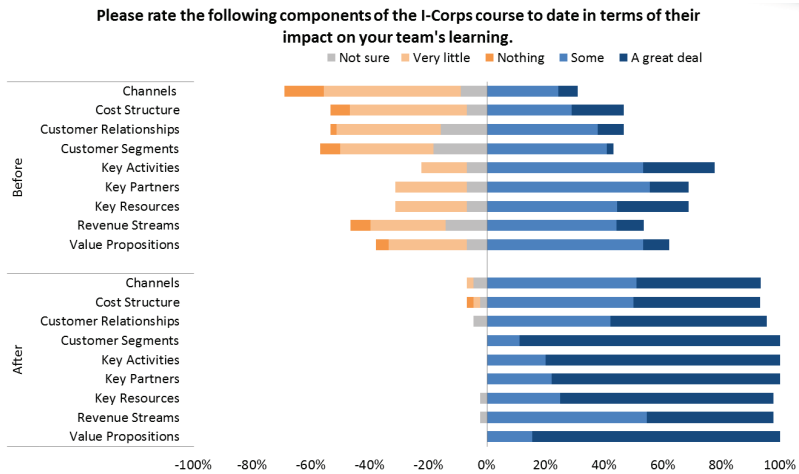

FIGURE 3-5 State of participant knowledge, before and after I-Corps participation. SOURCE: Andrew Kurtz, "The NCI SBIR Program: An Overview of New Funding Opportunities and Strategies for Employing Lean Startup Tools to Drive Success in Your Small Business," AACR presentation, April 20, 2015, p. 35.

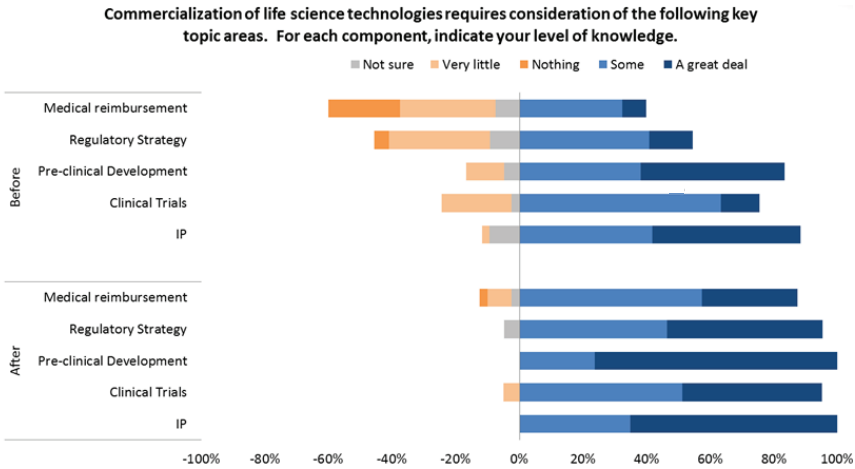

FIGURE 3-6 Change in life science business understanding after I-Corps participation. SOURCE: Andrew Kurtz, "The NCI SBIR Program: An Overview of New Funding Opportunities and Strategies for Employing Lean Startup Tools to Drive Success in Your Small Business," AACR presentation, April 20, 2015, p. 36.

The FY2014 cohort was a pilot. Results such as those described above have led NCI and other ICs to expand the pilot. However, the program currently serves only a small fraction of Phase I companies at NIH, and it is unclear whether there are either plans or resources to expand the program to serve larger numbers.

Phase IIB

This program is designed to provide additional support for development efforts pursued in a previously funded NIH SBIR Phase II, often for grant for products or technologies that require ultimate approval by a Federal regulatory agency.[16] Although the amount of funding needed for a trial varies substantially, Phase IIB is not designed to fully fund the process through the end of Phase 3 clinical trials. According to Dr. Matthew Portnoy, the NIH SBIR/STTR Program Director, Phase IIB is designed to get companies close to or to the end of Phase 2 clinical trials (in most cases, Phase 3 is much more expensive).[17]

Phase IIB started in FY2003 as a small pilot and as of FY2014 provided about $50 million in funding a year for about 50 projects (see Figure 3-7).

Data from the 2014 Survey show that the primary purpose of SBIR/STTR Phase IIB—supporting companies partially through clinical trials—is to a considerable extent being achieved. About three-quarters of Phase IIB survey respondents reported that their project required FDA approval (a surprisingly low number given that Phase IIB is supposed to be allocated only to projects that require FDA approval). Table 3-1 shows that Phase IIB companies were more successful in completing Phase 3 clinical trials than were other awardees, and they abandoned the process at a much lower rate.

More than one-third of respondent Phase II companies had abandoned the clinical trials process by the time of the survey; this was true for only 5 percent of respondent Phase IIB companies. Conversely, 10 percent of respondent Phase II and 21 percent of respondent Phase IIB companies had completed the entire clinical trials process. These encouraging numbers suggest that Phase IIB is having a positive impact, although the small numbers tracked through the survey suggest caution in interpreting these results (see Table 3-1).

[16]According to the NIH Grants Policy Statement, Revised March 31, 2015, "Some NIH ICs offer Phase II SBIR/STTR awardees the opportunity to apply for Phase IIB Competing Renewal awards. These are available for those projects that require extraordinary time and effort in the R&D phase and may or may not require FDA approval for the development of such projects, including drugs, devices, vaccines, therapeutics, and medical implants related to the mission of the IC." Access at *<http://grants.nih.gov/grants/policy/nihgps/HTML5/section_18/18.5_small_business_innovation_research_and_small_business_technology_transfer_programs.htm>*.

[17]Discussion with Dr. Matthew Portnoy, NIH SBIR/STTR Program Director, June 17, 2015.

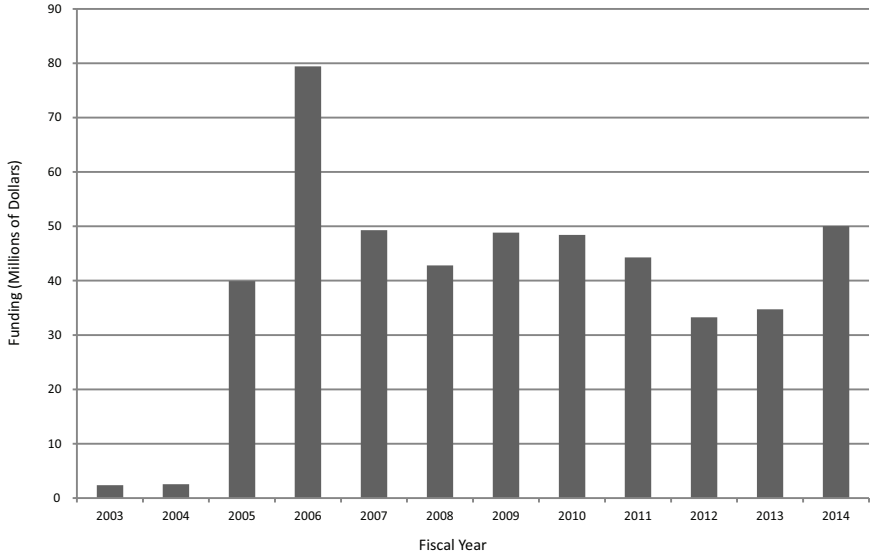

FIGURE 3-7 Phase IIB funding at NIH, FY2003-2014.
SOURCE: Based on data from National Institutes of Health.

TABLE 3-1 Phase IIB and Clinical Trials

	Percentage of Respondents			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Process abandoned	35.5	35.9	33.3	5.3
Preparation under way for clinical trials	34.4	35.5	28.2	47.4
IND granted	4.7	4.1	7.7	10.5
In Phase 1 clinical trials	4.7	5.1	2.6	
In Phase 2 clinical trials	9.4	7.4	20.5	15.8
In Phase 3 clinical trials	2.3	1.8	5.1	
Completed clinical trials	9.0	10.1	2.6	21.1
BASE: NIH PROJECTS REQUIRING FDA APPROVAL	256	217	39	19

NOTE: If the large portion of awardees who were not able to be reached by the survey contained a large percentage of companies that went out of business because they could not proceed with FDA approval, the survey results may understate the number of those requiring FDA approval and the percentage who did not proceed with FDA approval.
SOURCE: 2014 Survey, Question 41.

BOX 3-2
Award Size Rules for SBIR/STTR

After the 2011 reauthorization, 15 U.S.C. §138 raises the basic limits on award sizes to $150,000 and $1 million for Phase I and Phase II, respectively. The agencies are allowed to go 50 percent higher (to $225,000 and $1.5 million) without authorization from SBA. SBA may issue waivers to go higher than the upper limits on specific topics. As of September 2013, NIH had received six waivers approved by SBA, five for specific topics and one for the HHS/NIH Annual Omnibus SBIR and STTR solicitations. SBA granted the waiver under the following conditions:

- NIH may allocate no more than 5 percent of its SBIR funds to fund the portion of SBIR awards (Phase I and Phase II) that exceed the guidelines.
- NIH may allocate no more than 5 percent of its STTR funds to fund the portion of STTR awards (Phase I and Phase II) that exceed the guidelines.
- Based on the SBIR and STTR Policy Directives, NIH may also use non-SBIR funds to fund the portion of SBIR awards that exceed the SBIR guidelines, and may use non-STTR funds to fund the portion of STTR awards that exceeds the STTR guidelines.

SOURCE: Gregory A. Davis, Karen D. Gordon, Ellory E. Matzner, and Daniel E. Basco, "Preliminary Evaluation of Small Business Innovation Research (SBIR) Program Limits on Award Size at the National Institutes of Health," Science and Technology Policy Institute memo, September 9, 2013.

Extra-large Awards

NIH is well known in the SBIR community for providing awards that are larger than those set forth in SBA guidelines (see Box 3-2 for size rules). Such awards are permitted under waivers received from SBA. In September 2013, the Science and Technology Policy Institute (STPI) provided an initial report to the White House Officer of Science and Technology Policy on over-sized awards at NIH.[18] The STPI report focused primarily on the rationale for larger awards. Key findings from the study include the following:

- Biomedical research is expensive (see the Tufts study noted above).
- The cost of drug development has doubled about every 9 years since 1950.
- Venture funding in life sciences has moved downstream, reducing the funding available for early-stage companies.

[18]Gregory A. David, Karen D. Gordon, Ellory E. Matzner, and Daniel E. Basco, "Preliminary Evaluation of Small Business Innovation Research (SBIR) Program Limits on Award Size at the National Institutes of Health," Science and Technology Policy Institute memo, September 9, 2013.

TABLE 3-2 Extra-large Awards at NIH, FY2009-2012

Rank by size	Company Name	Award Years	Total Award Dollars
1	ADVANTAGENE, INC	3	$5,293,474
2	LENTIGEN CORPORATION	3	$5,082,389
3	VISTAGEN THERAPEUTICS, INC.	3	$4,604,082
4	SELEXYS PHARMACEUTICALS CORPORATION	3	$4,380,425
5	TRANSCENDENT INTERNATIONAL LLC	3	$4,228,802
6	OMNIOX, INC.	4	$3,978,944
7	SANARIA, INC.	4	$3,963,532
8	AUTOMMUNE TECHNOLOGIES, LLC	3	$3,938,686
9	MICROTRANSPONDER, INC	7	$3,828,360
10	CIRCULITE, INC.	3	$3,785,688
11	LYCEAN TECHNOLOGIES, INC.	2	$3,756,977
12	PHARMACOGENETICS DIAGNOSTIC LABORATORIES	4	$3,653,414
13	INVIVO SCIENCES, LLC	4	$3,647,125
14	SIGNUM BIOSCIENCES	4	$3,620,902
15	REGENEREX, LLC	2	$3,588,048
16	ADVANCED CELL DIAGNOSTICS INC.	4	$3,530,276
17	GEL-DEL TECHNOLOGIES	3	$3,492,034
18	ANGION BIOMEDICA	3	$3,491,534
19	AMBERGEN, INC.	4	$3,468,150
20	ETUBICS CORPORATION	3	$3,353,817
21	STRATATECH CORPORATION	3	$3,312,268
22	ARIETIS	4	$3,265,574
23	GLYSENS, INC.	4	$3,228,959

SOURCE: Gregory A. Davis, Karen D. Gordon, Ellory E. Matzner, and Daniel E. Basco, "Preliminary Evaluation of Small Business Innovation Research (SBIR) Program Limits on Award Size at the National Institutes of Health," Science and Technology Policy Institute memo, September 9, 2013, pp. B-1–B-2.

- Unlike the Department of Defense, there is no rationale for NIH to provide non-SBIR funds to further develop promising ideas.[19]

The STPI report also provided some useful data about the incidence of extra-large awards, focused on FY2009-2012. Table 3-2 shows the 23 awards

[19]Ibid., pp. iii-iv.

identified by STPI as exceeding the maximum total allowed under reauthorization ($3.25 million).

The STPI report concludes that the amounts provided are appropriate in the context of rising costs and that they are sufficiently rare (8 percent of awards) that they do not undermine program requirements to provide funding for a wide range of companies.

A review of the STPI report does, however, raise some further questions. The current maximum total allowed of $3.25 million has been the case only since FY2013. Applying current benchmarks retrospectively seems inappropriate. In addition, the program has been providing extra-large awards for many years, but the STPI review was limited to FY2009-2013.

Perhaps more importantly, though, the STPI report does not address the key question: what did NIH get for the additional funds? Are larger awards necessarily associated with better outcomes? If not, then it is difficult to make a case for them. There is also a related question: because review panels do not weigh the proposed budgets for projects against each other, there may be an inherent bias within the application process that links better scores to more ambitious/more expensive projects.

Extra-large Awards: Data from Agency Records

The STPI report focuses only on a narrow definition and time frame. It may be more useful—and providing of better context—to use a different set of metrics and a longer time frame.

STPI defines extra-large awards as those that provide total funding of over $3.25 million. However, it is difficult to define a "project" when there is often substantial overlap between different awards—companies often receive multiple awards for the development of technologies that are closely related to each other. Therefore, it is useful to focus this analysis specifically on the size of individual SBIR/STTR Phase II awards. It is acknowledged that some Phase I awards are also extra-large, but the financial impact of these awards on the program as a whole is much less than that of Phase II awards, which are on average an order of magnitude larger than Phase I. Using data provided by NIH for FY2001-2014 provides a more extended view of patterns of extra-large awards. Excluding from the analysis Phase IIB awards, which are designed for a specific purpose and are by definition larger than standard Phase II awards, as well as supplementary awards, also helps focus on Phase II awards. The data have been cross-checked against data submitted to SBA by NIH and available from the SBA website.

Overall, the number of larger awards grew steadily from FY2001 to FY2011. At about the time of the 2011 reauthorization of the SBIR/STTR programs, when new limits were imposed and blanket agency level waivers were no longer permitted, the number of larger awards stopped growing and, in 2014, dropped 24 percent. Table 3-3 shows awards over $1.5 million during the period FY2001-2014.

TABLE 3-3 NIH Phase II Awards of More than $1.5 million, FY2001-2014

	SBIR		STTR		Total	
Fiscal Year	Number of Awards	Amount of Funding (Dollars)	Number of Awards	Amount of Funding (Dollars)	Number of Awards	Amount of Funding (Dollars)
2001	14	30,478,132			14	30,478,132
2002	17	32,303,153	1	2,073,798	18	34,376,951
2003	35	95,717,136	1	1,846,876	36	97,564,012
2004	50	121,764,850	5	11,802,203	55	133,567,053
2005	39	95,651,702	6	11,872,663	45	107,524,365
2006	54	128,836,919	4	9,724,432	58	138,561,351
2007	34	74,395,458	6	11,739,773	40	86,135,231
2008	46	101,489,214	6	12,856,978	52	114,346,192
2009	79	181,126,549	2	3,354,070	81	184,480,619
2010	65	145,922,317	11	25,015,316	76	170,937,633
2011	86	192,849,665	9	22,215,213	95	215,064,878
2012	84	190,537,470	11	23,462,720	95	214,000,190
2013	93	205,117,540	3	5,798,604	96	210,916,144
2014	64	141,686,526	9	18,637,007	73	160,323,533
Total	760	1,737,876,631	74	160,399,653	834	1,898,276,284

SOURCE: Based on data from the National Institutes of Health.

The steady growth trend in both larger awards and their associated funding should be put in context. Table 3-4 shows these larger Phase II awards as a percentage of total awards and funding for Phase II during this period. The share of awards of $1.5 million or more increased from 3.1 percent of the total in FY2001 to 29.9 percent in FY2013, before declining to 19.2 percent in FY2014. The growth in funding shares was even greater, from 8.8 percent in FY2001 to 50.6 percent in FY2013, before declining to 33.3 percent in FY2014. These data suggest that the limits imposed under reauthorization have already had an impact.

Some awards are, however, considerably larger than the average. Table 3-5 shows the number of awards and associated funding for awards that are more than $2.25 million. The data for extra-large awards largely track with those for larger awards in general. Both the number of awards and their funding peaked in FY2011-2012, and have since declined. It is worth noting that these extra-large awards became possible quite suddenly in FY2003.

Overall, Figure 3-8 shows both the steady growth in importance of large awards within the SBIR/STTR programs and also the impact of the new limits.

TABLE 3-4 NIH Phase II Awards of More than $1.5 million as a Percentage of All Awards and Funding, FY2001-2014

	SBIR		STTR		Total	
Fiscal Year	Percentage of All Awards	Percentage of All Funding	Percentage of All Awards	Percentage of All Funding	Percentage of All Awards	Percentage of All Funding
2001	3.3	9.2	0.0	0.0	3.1	8.8
2002	4.1	9.9	3.3	9.9	4.1	9.9
2003	8.0	24.6	4.2	13.4	7.8	24.2
2004	12.3	31.5	9.3	27.9	12.0	31.2
2005	10.2	23.9	11.3	26.1	10.3	24.1
2006	13.0	27.7	8.7	24.9	12.6	27.4
2007	9.6	20.8	11.1	23.1	9.8	21.1
2008	11.9	25.6	11.1	23.4	11.8	25.3
2009	21.9	41.2	4.7	9.0	20.0	38.7
2010	18.2	36.2	22.9	47.7	18.8	37.5
2011	27.7	46.3	18.8	37.6	26.5	45.2
2012	25.9	46.1	25.0	48.8	25.8	46.4
2013	33.2	53.9	7.3	15.9	29.9	50.6
2014	19.2	33.5	18.8	32.4	19.2	33.3
Total	14.7	31.4	12.0	27.9	14.4	31.1

SOURCE: Based on data from the National Institutes of Health.

Outcomes from Larger Awards

The 2014 survey can be used, at least on a preliminary basis, to examine the relationships between award size and outcomes, as well as NIH selection scoring and outcomes. The latter is discussed in Chapter 4 (Quantitative Outcomes).

During the 14 years covered by this analysis, awards in excess of $1.5 million cost a total of $1.9 billion, which is 31 percent of the total spending on Phase II awards (excluding Phase IIB and supplementary awards). The marginal cost—the cost over and above that incurred had these awards been set at $1.5 million—was $647 million. Given that the average award size across this period was $864,000, this funding could have provided an additional 749 standard-sized awards—or an increase of about 13 percent in the number of Phase II awards. So the question is whether NIH received good value for these investments. In reality, funding additional awards would likely have meant funding weaker applications, as acceptance moved farther down the list of fundable applications. Therefore, it is

TABLE 3-5 NIH Phase II Awards of More than $2.25 million, FY2001-2014

	SBIR		STTR		Total	
Fiscal Year	Number of Awards	Amount of Funding (Dollars)	Number of Awards	Amount of Funding (Dollars)	Number of Awards	Amount of Funding (Dollars)
2001	3	11,614,499			3	11,614,499
2002	3	7,584,883			3	7,584,883
2003	20	68,656,403			20	68,656,403
2004	19	65,090,916	3	7,855,839	22	72,946,755
2005	17	55,821,258	1	2,623,076	18	58,444,334
2006	23	72,500,887	1	3,983,527	24	76,484,414
2007	14	38,945,205	1	2,657,177	15	41,602,382
2008	17	48,632,474	2	5,292,673	19	53,925,147
2009	31	95,419,468			31	95,419,468
2010	26	74,351,334	6	16,220,796	32	90,572,130
2011	37	105,817,941	4	12,120,122	41	117,938,063
2012	36	105,014,427	4	11,209,092	40	116,223,519
2013	32	94,170,229	1	2,561,843	33	96,732,072
2014	27	77,154,871	1	2,983,056	28	80,137,927
Total	305	920,774,795	24	67,507,201	329	988,281,996

SOURCE: Based on data from the National Institutes of Health.

not likely that the additional awards would have generated a return as high as the average return on the existing portfolio of funded projects.

The simplest outcomes to consider are sales revenues and the acquisition of additional investment funding. For this analysis, the outcomes for projects that received $1.5 million or less in SBIR Phase II awards (excluding Phase IIB) and those that received more than $1.5 million are compared. Figure 3-9 shows sales for the 252 respondent companies that reported some sales.

Thirty-one companies reported receipt of larger awards. This number approximately aligns with the percentage of extra-large awards during this period (see agency data section above). This relatively small number means that caution should be employed in interpreting these outcomes. However, it is notable that three of the four projects reporting at least $50 million in related sales received larger awards and that this group accounted for four of the nine projects reporting at least $20 million in sales.

This is only the first review of this issue. We urge that NIH reproduce and extend this analysis using data as they become available. However, the results do

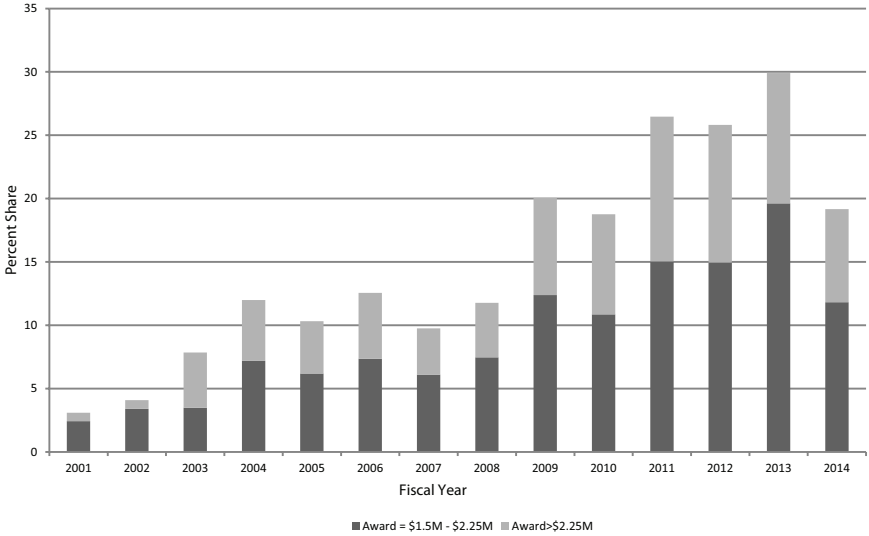

FIGURE 3-8 Share of large and extra-large awards in all NIH SBIR/STTR funding for Phase II (excluding Phase IIB), FY2001-2014.
SOURCE: Based on data from the National Institutes of Health.

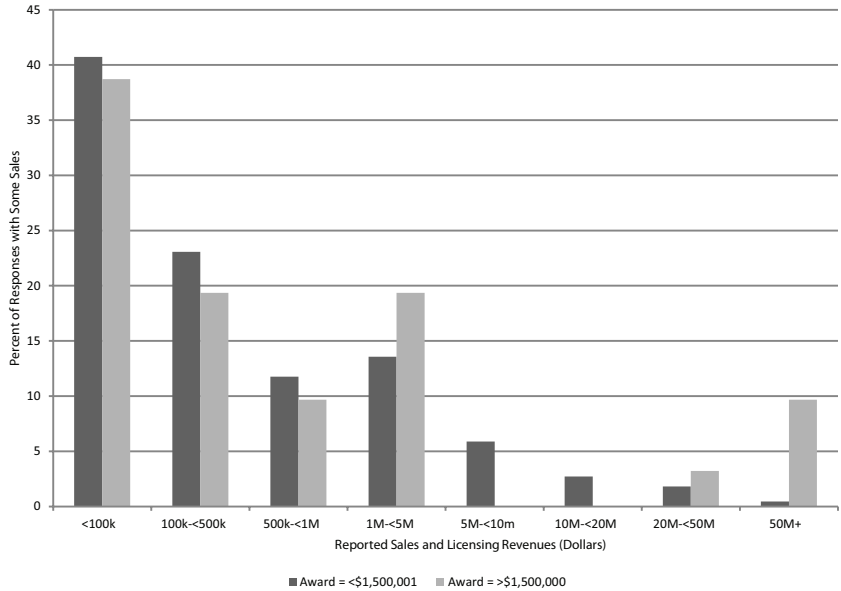

FIGURE 3-9 Sales reported for standard and extra-large projects, by range, FY2001-2010.
SOURCE: Based on NIH awards data and 2014 Survey (N=221 [<$1,500,001] and N=31 [>$1,500,000]).

suggest that even though there is little difference in outcomes for most awards, the large award companies generated more of the largest reported outcomes than their share of all awards would lead us to expect.

4

SBIR and STTR Awards at NIH

The NIH SBIR/STTR programs are the second largest after the Department of Defense (DoD). In fiscal year (FY) 2014, the programs provided more than $800 million in funding, an increase of more than $100 million from FY2013 following implementation of changes made in the 2011 reauthorization of the SBIR/STTR programs (see Chapter 1).

The FY2014 total can be broken down as follows (see Table 4-1):

- The SBIR program provided $711.1 million (88.3 percent of total funding).
- The STTR program provided $94.4 million (11.7 percent of total funding).
- SBIR grants accounted for $602.0 million. The recently expanded SBIR contracts accounted for $109.1 million.
- SBIR and STTR Fast Track grants totaled $54.4 million (6.8 percent of total funding).
- SBIR and STTR Phase I awards (excluding Fast Track) were $246.7 million (30.6 percent of total funding).
- SBIR and STTR Phase II awards (excluding Fast Track) were $504.4 million (62.6 percent of total funding).

A more extended analysis of the data is provided in the Annex to this chapter. This summary provides an overview of applications and awards for the NIH SBIR/STTR programs, including a review of trends, the distribution of awards by state, and participation by companies new to the program.

TABLE 4-1 SBIR/STTR Funding by Program, Phase, and Funding Mechanism, FY2014

	Funding (Millions of Dollars)				
	Phase I	Phase II	Fast Track (Phases I and II combined)	Total	Percentage of Total Funding
SBIR grants					
competing (new)	146.1	170.4		316.5	39.3
non-competing (renewals)	26.0	212.5		238.5	29.6
Fast Track (new)			17.1	17.1	2.1
Fast Track (renewals)			29.9	29.9	3.7
SBIR grants total	172.1	382.9	47.0	602.0	74.7
STTR grants					
competing (new)	35.8	21.7		57.5	7.1
non-competing (renewals)	5.6	23.9		29.5	3.7
Fast Track (new)			1.1	1.1	0.1
Fast Track (renewals)			6.3	6.3	0.8
STTR total	41.4	45.6	7.4	94.4	11.7
SBIR contracts	33.2	75.9		109.1	13.5
Total	246.7	504.4	54.4	805.5	100.0
SBIR total	205.3	458.8	47	711.1	88.3
STTR total	41.4	45.6	7.4	94.4	11.7

SOURCE: NIH Reporter database, Table 126.

SBIR PHASE I

SBIR Phase I Grants: Applications and Awards

SBIR Phase I applications at NIH have declined over time, despite a rebound during the period following the financial crisis of 2008-2009. This trend, not unique to NIH, has occurred at other agencies. Applications in FY2014 were at about 4,500, down from well over 5,500 in FY2010 and FY2011.

Over the period as a whole, the success rate for SBIR Phase I applications was 17.5 percent, ranging from a low of 13.7 percent in FY2010 to a high of 27.1 percent in FY2008. Given that funding over the period was relatively flat, year-to-year changes in success rate are largely driven by changes in the number of applications.

SBIR Phase I grants remain the primary gateway into the program. Until FY2014, only Phase I winners could apply for Phase II funding. On average

about 650 new Phase I awards were made each year of the study period, although the number declined slightly in recent years. Funding for Phase I grants remained largely flat at about $120 million annually, although increases in FY2012 and FY2014 above $140 million suggest that a new increased level might be emerging, based perhaps on the expansion in overall funding mandated under reauthorization.

While the number of awards declined, the average size of new Phase I awards increased, from about $150,000 in FY2005 to more than $220,000 for FY2011-2014. About 12 percent of Phase I winners received additional funding through supplementary awards. These awards average about $270,000, so they constitute a sharp expansion in the amount of Phase I funding for those projects that receive supplements.

SBIR Phase I Contracts

Contracts have until recently constituted a small share of the SBIR program at NIH (there are no STTR contracts). Traditionally, the focus has been on grants, with contracts being used for technologies that might then be used or needed within NIH. That changed in FY2014 following a substantial shift from grants to contracts at the National Cancer Institute (NCI), where approximately 35 percent of Phase I awards are now made through contracts. (This change is discussed in detail in Chapter 2.) Prior to FY2014, the number of Phase I contracts increased somewhat but remained well below 80 per year (except for FY2010). In FY2014 there were 129 contracts. Funding amounts increased from $20 million in FY2013 to $33 million in FY2014. In general, the size of contracts tracked closely with the size of grants on a year-by-year basis.

SBIR PHASE II

To a considerable degree, the distribution of SBIR Phase II awards is driven by the distribution of Phase I awards. Until FY2015, all Phase II awards went to projects that had already received a Phase I award (except for Fast Track awards, see Fast Track section below). This section covers both grants and contracts because they are not disaggregated in the NIH dataset.

As with Phase I, there was a decline in Phase II applications across the study period (FY2005-2014), mitigated by the apparent response to the financial crash in 2009-2010. Overall, the number of applications declined from about 850 in FY2005 to 566 in FY2014. Success rates for Phase II grant applications varied by year but averaged about 35 percent across the period.

The number of new Phase II SBIR grants also declined over the study period, from a high of 355 in FY2006 to 229 in FY2014, with a low of 183 in FY2013. This trend is a matter of some concern, because Phase II grants have historically provided the core of the program and are the source of most commercial innova-

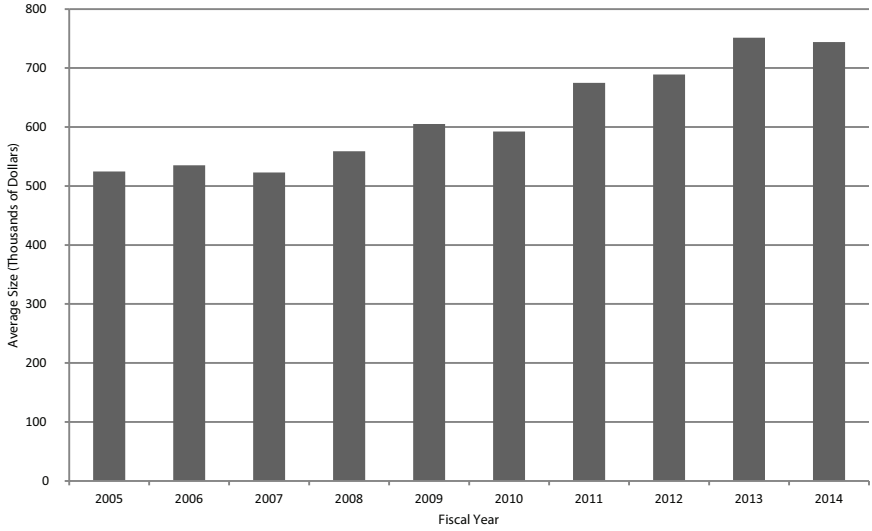

FIGURE 4-1 Average size of competing Phase II SBIR grant, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

tion within it. A number of possible explanations exist for this trend, which occurred in a context in which funding for the program as a whole increased by 12 percent. Explanations include a shift of program funds to the out years of grants and to contracts. However, the most immediate explanation lies in the increased size of SBIR Phase II grants. Figure 4-1 shows the growth in the average size of year 1 funding for new Phase II grants.

During the study period, average funding increased almost 42 percent from $525,000 in FY2005 to $744,000 in FY2014. Larger awards are indeed made at the cost of more awards, even in an environment where funding has increased. Out-year funding—which NIH calls noncompeting awards—grew proportionally, from about $500,000 per award on an annual basis to about $700,000.

Phase IIB Grants

NIH has initiated a special funding program within the SBIR program to help companies address the formidable financial hurdles involved in meeting the clinical trials requirements imposed by the U.S. Food and Drug Administration (FDA) before products can be brought to market. Phase IIB (formerly known as competing continuation awards) provide up to $1 million annually for 3 years to support companies engaged with the clinical trials process. After the pilot phase in FY2003 and FY2004, the number of Phase IIB SBIR awards settled at about 20 per year.

Aside from an outlier in FY2006, annual funding for Phase IIB was between $40 million and $50 million, or 5-6 percent of total program funding. Prior to the 2011 reauthorization, companies could receive more than one Phase IIB award (22 did so, with two companies receiving four such awards).

SBIR Phase II Contracts

Until very recently NIH awarded a relatively small number of Phase II contracts. Between FY2005 and FY2013, they averaged fewer than 30 per year. In FY2014, there was a sharp increase, to more than 70. Funding shifted in tandem, growing from $30 million in FY2013 to about $75 million in FY2014. This is almost entirely the result of a change in policy at NCI, which accounted for almost all of the additional awards. This policy change is discussed further in Chapter 2.

Fast Track

NIH has permitted Fast Track applications for over a decade. If approved, a Fast Track award transitions qualified projects directly from Phase I to Phase II, and no further application is required. Milestones that signal the successful completion of Phase I feasibility studies must be met. The program aims to provide a more rapid transition for projects where the company can present convincing evidence of feasibility, including in many cases preliminary data.

The number of Fast Track awards grew steadily and substantially over the study period, and in FY2014 there were more than 70 Fast Track awards, constituting almost 25 percent of all Phase II awards (computed with Fast Track awards included in the denominator).

What was an experimental or pilot program now appears to be well embedded in the SBIR/STTR programs at NIH. The Fast Track program has multiple potential benefits: it reduces the load on reviewers, provides more certainty for the firm, and essentially eliminates the Phase I-Phase II funding gap that can pose real problems for small companies.

STTR

There are no STTR contracts, so all STTR awards are made in the form of grants. There were about 500 Phase I STTR applications annually from FY2009-2013, before increasingly sharply to almost 800 in FY2014. Applications tended to have slightly higher success rates than those for Phase I SBIR; there was no clear pattern over time, with STTR rates moving randomly between about 14 percent and 22 percent. The number of STTR Phase II awards tracked Phase I with a lag and accounted for about 70 percent of STTR program funding.

STTR is funded at about 10 percent of SBIR. There were 1,209 new STTR awards over the period, accounting for about 14 percent of all Phase I grants.

Funding for STTR awards declined from FY2005 to FY2011, from $32 million to just over $21 million, before increasing in each year since to reach $41 million in FY2014.

NEW ENTRANTS

About one-third of companies submitting Phase I SBIR/STTR applications were new to the program, and they accounted for between 20 and 25 percent of applications. These companies also accounted for about 30 percent of Phase I awardees and, in recent years, more than 25 percent of awards, which suggests that the program is open to new entrants and that existing companies do not have a substantial advantage in pursuing funding (see Figure 4-2).

AWARDS AND THE STATES

Awards are not distributed equally across the states, and Congress has indicated concern about the levels of awards to low-award states. However, statistical analysis indicates a strong correlation between the number of applications per 100,000 population and the number of scientists and engineers employed in the state per 1,000 population (Pearson correlation = 0.67).

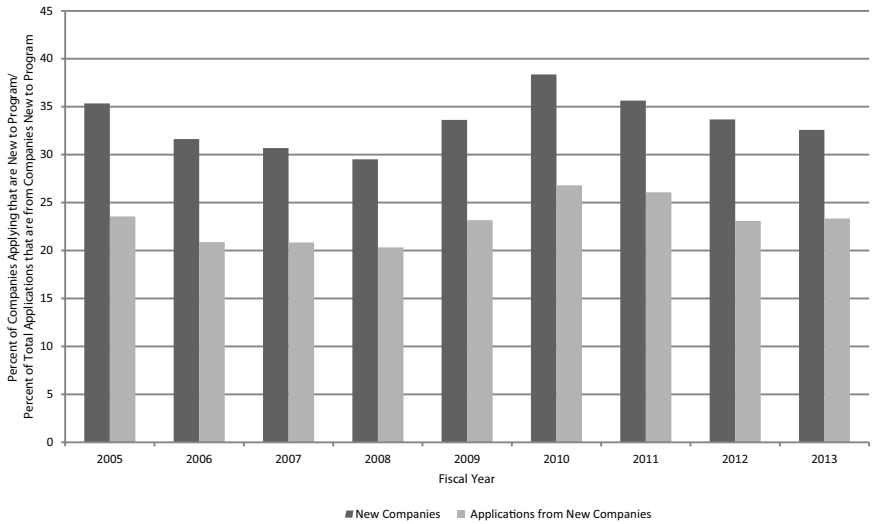

FIGURE 4-2 Share of NIH SBIR/STTR applications and awards from previously nonparticipating companies, FY2005-2013.
SOURCE: NIH data provided by the NIH SBIR/STTR Program Office.

Normalizing for population shows that applications are received at very different rates from the states. Massachusetts firms generated an average of 850 Phase I SBIR applications per 100,000 population annually across the study period. In contrast, six states generated fewer than 50 per 100,000 population.

The number of applications from a given state largely drives the number of awards to that state, but some states are more successful on average than others. Success rates vary from a high of 32 percent to a low of less than 10 percent for four states. Unlike application rates, success rates are not well correlated with the share of scientists and engineers in the workforce (Pearson correlation = 0.28). However, the states with very low employment rates for scientists and engineers also report low success rates, so there may be an effect at the lower end of the distribution.

ANNEX 4-A: SBIR AND STTR AWARDS AT NIH

Introduction

This annex describes and analyzes SBIR and STTR awards made by NIH. In order to focus on more recent awards while ensuring that longer-term trends are addressed, the period of analysis in this case is FY2005-2014 inclusive. A 10-year period seems sufficient for trend analysis, particularly given the important changes to the program during that period.

This annex covers Phase I and Phase II awards, and awards through SBIR and STTR separately. It considers awards from a range of perspectives, including distribution by state, the impact of multiple awards to individual companies, and applications and success rates.

Table 4-2 shows funding by program and phase for FY2014; Figure 4-3 shows a summary of this information in chart format. Overall the rate of increase

TABLE 4-2 SBIR/STTR Funding by Program, Phase, and Funding Mechanism, FY2014

	Funding (Millions of Dollars)				
	Phase I	Phase II	Fast Track (Phases I and II combined)	Total	Percentage of Total Funding
SBIR grants					
competing (new)	146.1	170.4		316.5	39.3
non-competing (renewals)	26.0	212.5		238.5	29.6
Fast Track (new)			17.1	17.1	2.1
Fast Track (renewals)			29.9	29.9	3.7
SBIR grants total	172.1	382.9	47.0	602.0	74.7
STTR grants					
competing (new)	35.8	21.7		57.5	7.1
non-competing (renewals)	5.6	23.9		29.5	3.7
Fast Track (new)			1.1	1.1	0.1
Fast Track (renewals)			6.3	6.3	0.8
STTR total	41.4	45.6	7.4	94.4	11.7
SBIR contracts	33.2	75.9		109.1	13.5
Total	246.7	504.4	54.4	805.5	100.0
SBIR total	205.3	458.8	47	711.1	88.3
STTR total	41.4	45.6	7.4	94.4	11.7

SOURCE: NIH Reporter database, Table 126.

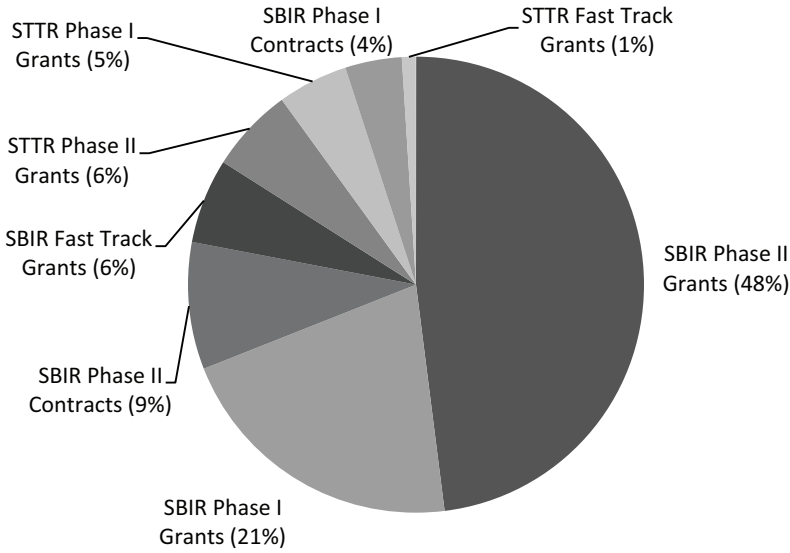

FIGURE 4-3 SBIR/STTR funding by program, phase, and funding mechanism, FY2014.
SOURCE: NIH RePorter database, Table 126.

in funding for the SBIR/STTR programs during the study period approximately matched inflation rates for the economy as a whole, although biomedical inflation has been higher. Figure 4-4 shows total SBIR/STTR funding for FY2005-2014. The increase in FY2014 reflects additional funding added through reauthorization.

SBIR

SBIR Phase I

Most funding and awards have historically been provided through the standard NIH SBIR grant mechanism. In FY2014, however, funding for contracts effectively doubled, driven almost entirely by changes in strategy at NCI, one of the largest Institutes and Centers (ICs). For reasons described in more detail in Chapter 2, contracts and grants are quite different and are thus described separately in this chapter.

SBIR Phase I Applications and Success Rates

Figure 4-5 shows the number of Phase I SBIR applications received by NIH in FY2005-2014 (data in this section covers both grants and contracts because they are not disaggregated in the NIH dataset). The number of applications fell steadily from FY2005 to FY2008 before rebounding sharply in FY2010. The

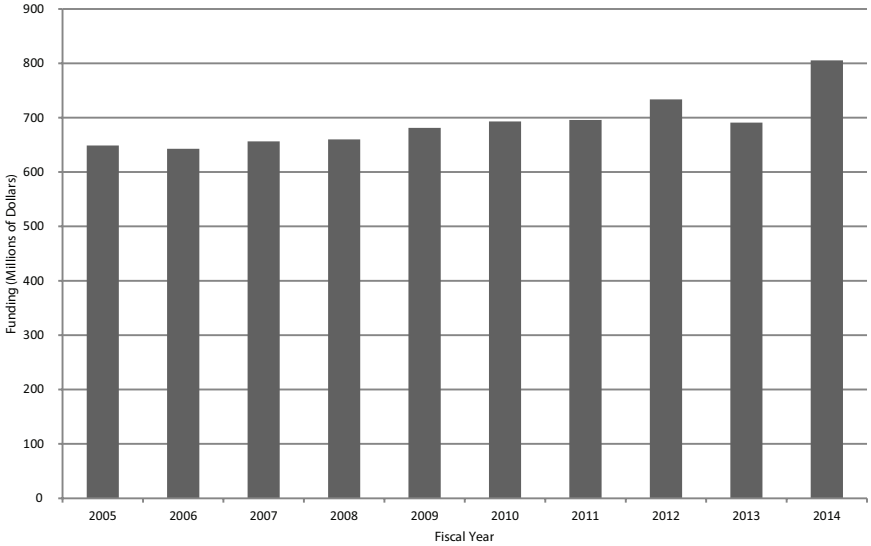

FIGURE 4-4 Total funding for SBIR/STTR, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

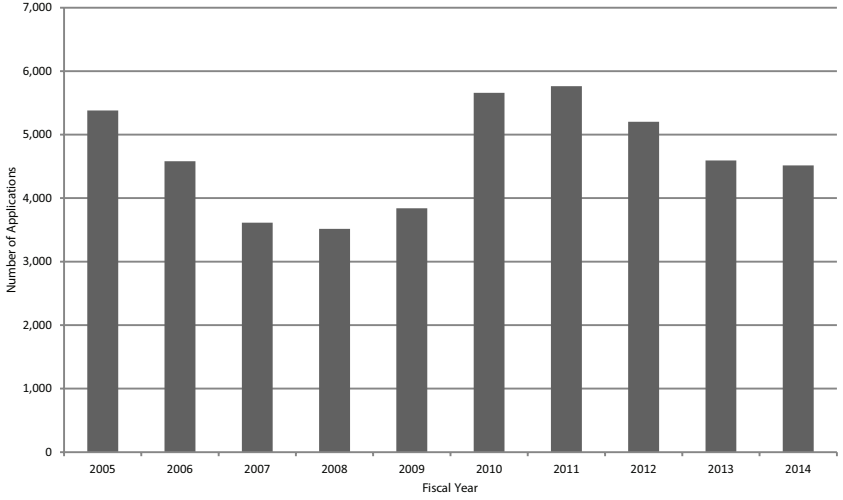

FIGURE 4-5 Number of SBIR Phase I applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 216.

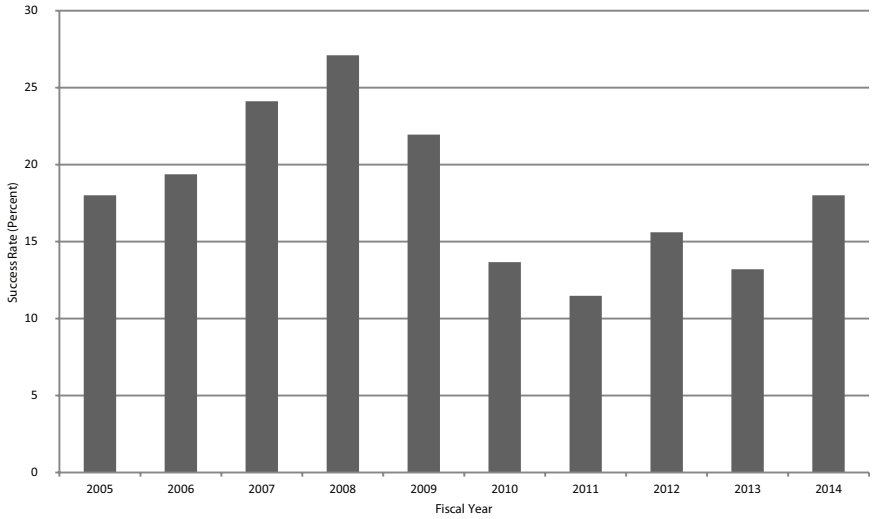

FIGURE 4-6 Success rates for SBIR Phase I applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 216.

number declined again, although not to the low of FY2008. Although detailed analysis was not performed, it seems likely that applications are inversely correlated with the availability of seed and venture funding in the wider economy. These sources were squeezed in the financial crash of FY2009-2010.

Over the period as a whole, the average success rate for SBIR Phase I applications was 17.5 percent. Figure 4-6 shows that the rate varied from a low of 11.5 percent in FY2011 to a high of 27.1 percent in FY2008. Given that funding was relatively flat, changes in success rate were largely driven by changes in the number of applications.

SBIR Phase I Grants

SBIR Phase I is the primary gateway into the program. Until FY2014, only Phase I winners could apply for Phase II funding. Figures 4-7 and 4-8 show the number of SBIR Phase I awards and the total amount of funding by year. Figure 4-7 includes competing awards (the initial Phase I award) and noncompeting awards (supplements or add-ons to the initial award). There was an annual average of about 650 new Phase I awards during the study period, although the number declined slightly in recent years. Total funding for new SBIR Phase I grants remained largely flat during the study period, as shown in Figure 4-8, with some recent increases perhaps signaling a new trend toward the end of the period (FY2012 and FY2014).

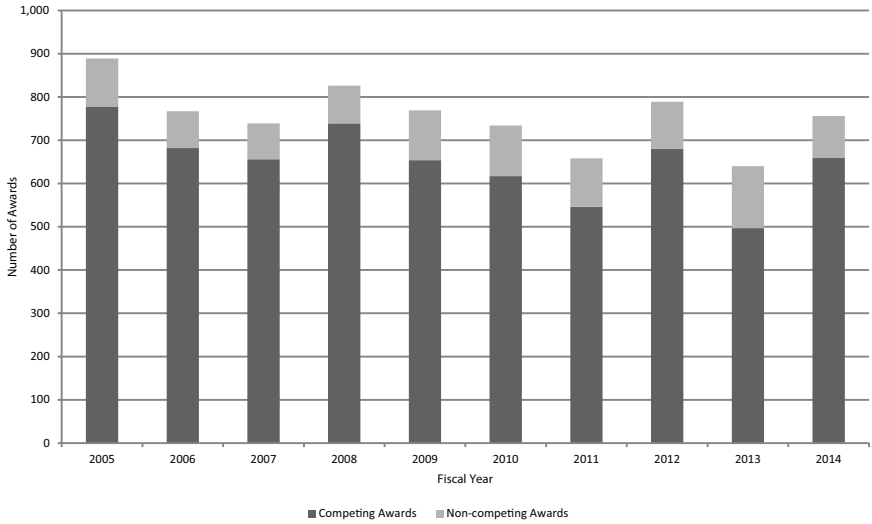

FIGURE 4-7 Number of SBIR Phase I competing and noncompeting grants, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

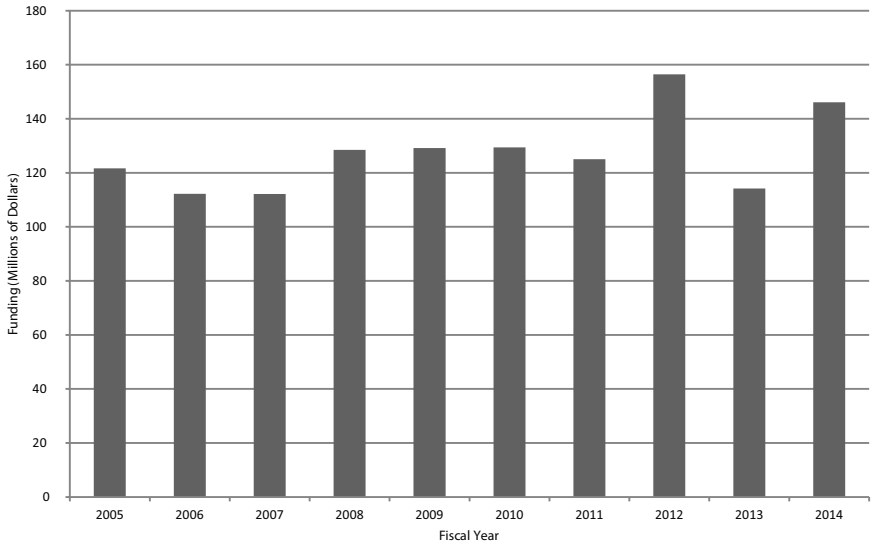

FIGURE 4-8 Total funding for new SBIR Phase I awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

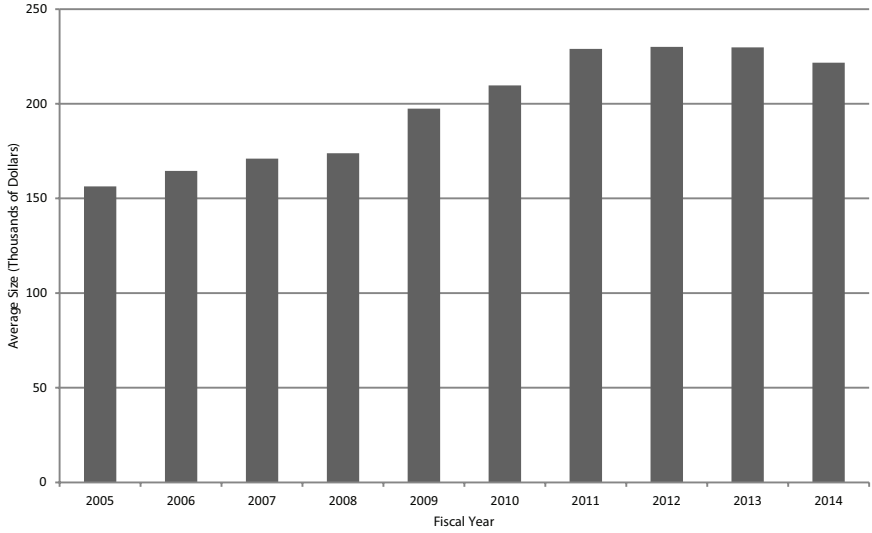

FIGURE 4-9 Average size of new SBIR Phase I awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

The decline in the number of new Phase I grants during the study period is reflected in the growth of the average award size, which has been more than $200,000 since FY2010, averaging about $230,000 during FY2010-2014 (see Figure 4-9).

In addition to competing awards, projects may receive noncompeting awards as supplements of various kinds. Although on average only about 12 percent of new SBIR Phase I awards receive additional support through noncompeting awards, that additional support tends to be larger—an average of $270,000.

SBIR Phase I Contracts

Contracts have until recently constituted a small share of the NIH SBIR program. Traditionally, the focus has been on grants, with contracts being used for technologies that might then be used or needed within NIH. As Figures 4-10 and 4-11 show, that focus changed in FY2014 following a substantial shift from grants to contracts at NCI, where approximately 35 percent of Phase I awards are now made through contracts.

The number of contracts awarded increased during the second half of the study period, with FY2005-2009 averaging 47 annually and FY2010-2013 averaging 77. FY2014 experienced a sharp jump, with the number doubling within that year. Funding levels from contracts showed a smoother growth path, again until FY2014, as shown in Figure 4-11.

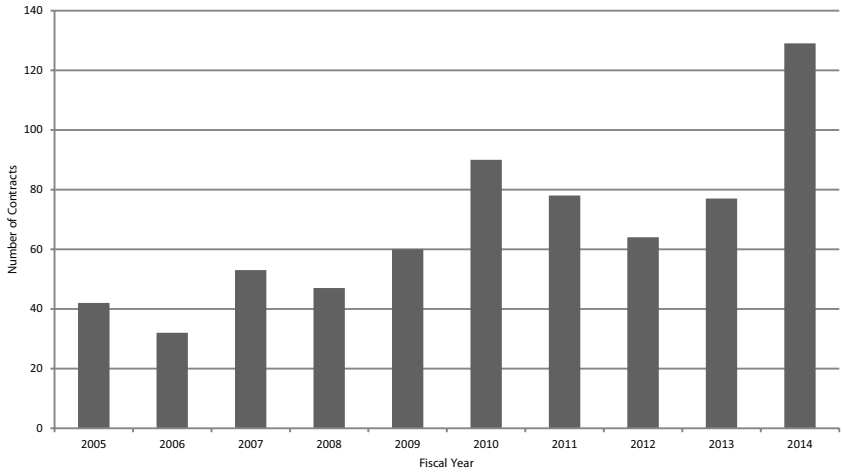

FIGURE 4-10 Number of SBIR Phase I contracts awarded at NIH, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

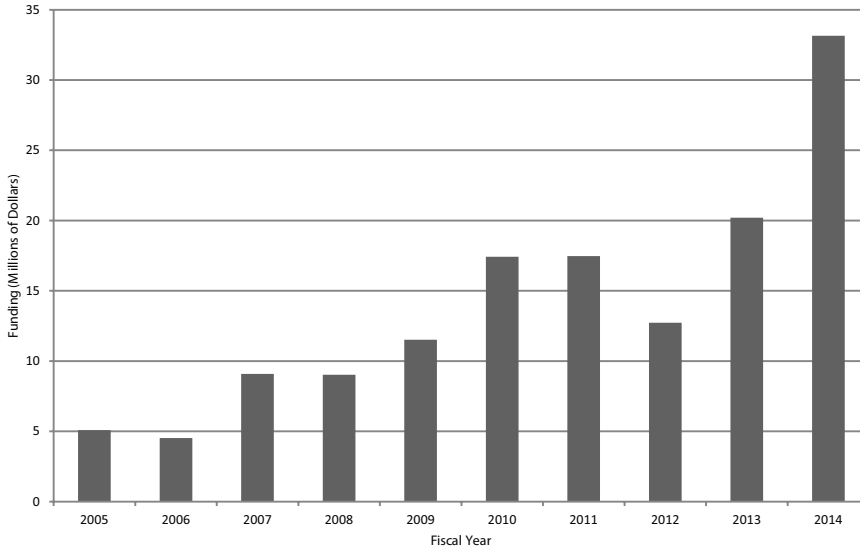

FIGURE 4-11 Funding for SBIR Phase I contracts at NIH, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

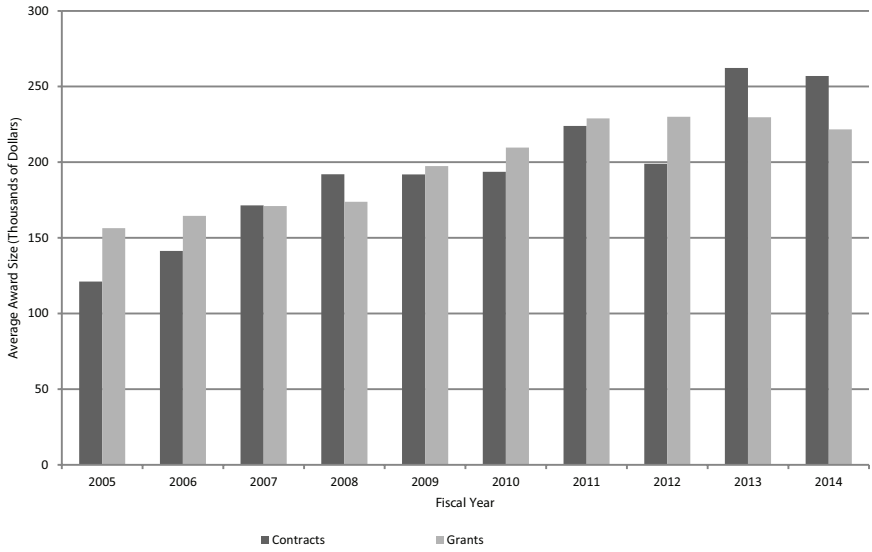

FIGURE 4-12 Average size of new SBIR Phase I contracts and grants at NIH, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

On average, new Phase I contracts did not appear to be either larger or smaller than new Phase I grants, as shown in Figure 4-12. However, contracts were on average larger in FY2013 and FY2014, so it is possible that a new trend is emerging.

Discussions with NCI staff indicate that NCI appears focused on contracts because this mechanism leaves control of selection entirely with the IC (the Center for Scientific Review is not involved in study sections) and because it offers tighter control of the project itself, where payments are linked to milestones not just time and materials.[1]

SBIR Phase II

To a considerable degree, the distribution of SBIR Phase II awards is driven by the distribution of Phase I awards. Until FY2015, all Phase II awards went to projects that had already received a Phase I award (except for Fast Track awards, see Fast Track section below).

[1]See the discussion of contract funding in Chapter 2.

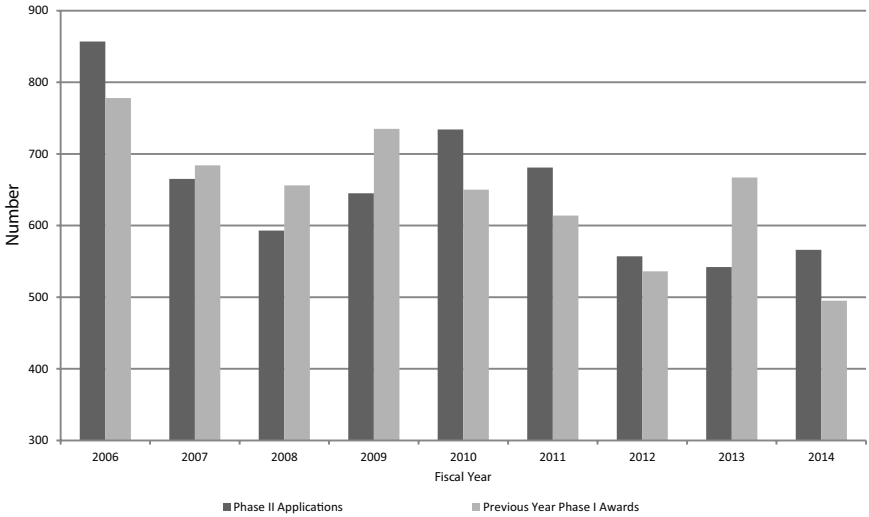

FIGURE 4-13 SBIR Phase II applications and SBIR Phase I awards (lagged 1 year), FY2006-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 216.

SBIR Phase II Applications and Success Rates

This section covers both grants and contracts because they are not disaggregated in the NIH dataset. As with Phase I, there was a decline across the study period in Phase II applications, mitigated by the apparent response to the financial crash in 2009-2010. Figure 4-13 shows the number of Phase II SBIR applications for FY2006-2014, charted with SBIR Phase I awards lagged by 1 year (so that Phase I awards are matched up with subsequent Phase II applications).[2] The Pearson Rho value for this (small) sample is 0.67, indicating strong correlation.

As expected, success rates for Phase II are much higher than those for Phase I. At NIH, these rates are the obverse of application rates: because funding has been largely flat for Phase II, the uptick in applications during the crash led to lower success rates during the study period. Overall, however, rates held between 30 and 40 percent (see Figure 4-14).

SBIR Phase II Grants

Tracking Phase II awards at NIH is a complicated endeavor. The agency distinguishes initially between competing and noncompeting awards. Compet-

[2]In some cases the lag is shorter or longer than 1 year, so these data should be viewed as illustrative, not definitive, of the linkage between Phase I awards and Phase II applications.

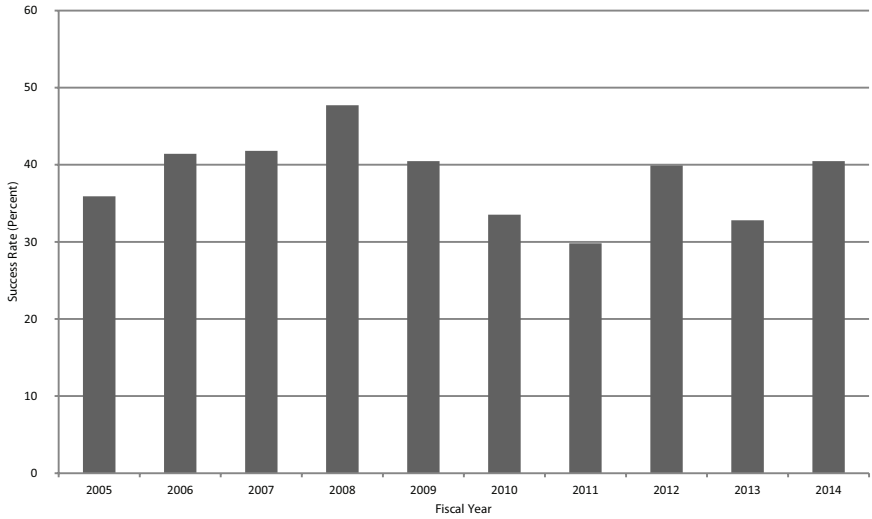

FIGURE 4-14 SBIR Phase II success rates, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 216.

ing awards represent the first year of the Phase II award. Noncompeting awards include the second year of the award, subsequent years of a longer award, supplementary awards of various kinds, and Phase IIB awards. This section differentiates between competing awards, Phase IIB awards, and other noncompeting awards.

SBIR Phase II Grants—Competing Awards

By tracking competing awards, the number of new SBIR Phase II grants by fiscal year can be determined (see Figure 4-15). The number of new SBIR Phase II grants has been declining quite steadily at NIH, from a peak of more than 350 in FY2006 to a low of about 180 in FY2013 before rebounding somewhat to 229 in FY2014. This represents a decline of almost 50 percent, and even smoothing the data suggests that the number of awards has declined by about one-third during the period. Given that overall funding for the program increased by about 12 percent during the study period in nominal terms, the decline in funding for new Phase II grants has several possible explanations, including a shift of program funds to the out years of grants, a shift of funds to contracts, and an increase in funding for STTR.

However, the most immediate explanation lies in the increased size of SBIR Phase II grants. Considering only competing awards (i.e., the first year of a Phase II grant) the average award size increased by about 50 percent over the study period (see Figure 4-16), which almost entirely explains the one-third decline in the number of awards.

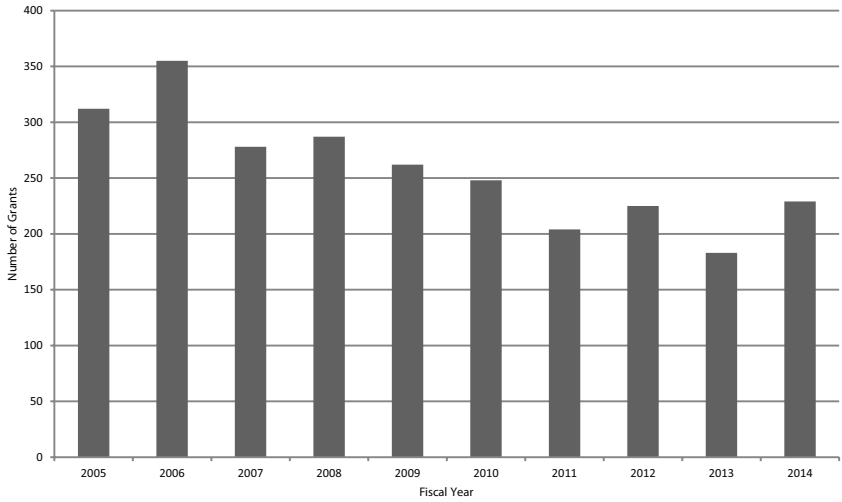

FIGURE 4-15 New NIH Phase II SBIR grants, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

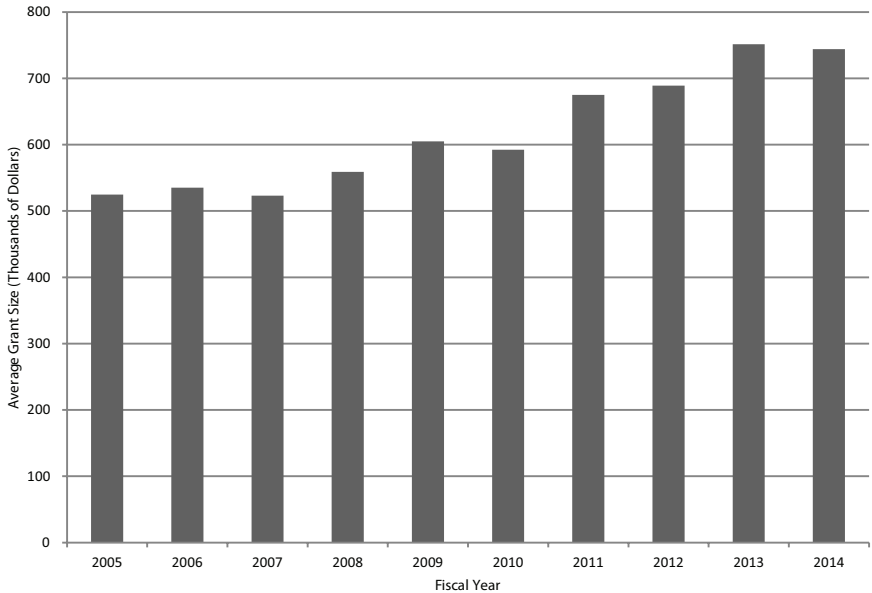

FIGURE 4-16 Average size of first year of competing Phase II SBIR grant, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

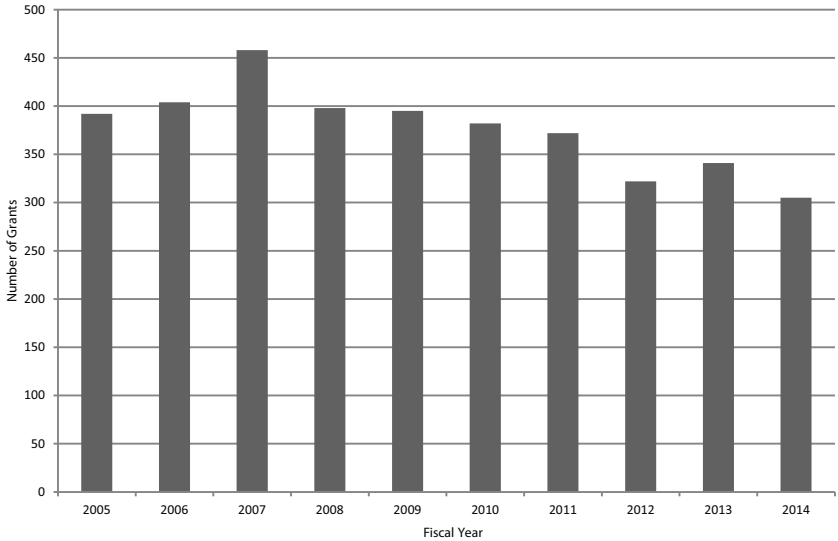

FIGURE 4-17 Number of noncompeting SBIR Phase II grants, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

SBIR Phase II Grants—Non-competing Awards

The aggregate data provided by NIH includes all noncompeting awards, including Phase IIB awards, which are discussed separately below. The data show that, similar to competing awards, the number of noncompeting awards has been declining (see Figure 4-17). Once again, much of the decline is explained by an increase in the average award size, from about $500,000 in FY2005 and FY2006 to almost $700,000 in FY2014 (see Figure 4-18).

SBIR Phase II Contracts

The number of SBIR Phase II contracts more than doubled in FY2014 (see Figure 4-19). This increase is almost entirely accounted for by NCI's adoption of contracts as an important mechanism. Funding amounts moved in close alignment with the number of awards, again more than doubling in FY2014 (see Figure 4-20). NCI's use of contracts is discussed above in the section on Phase I contracts.

SBIR Phase IIB Grants

NIH has initiated a special funding program within SBIR to help companies address the formidable financial hurdles involved in meeting the clinical trials requirements imposed by the FDA before products can be brought to market (see Box 4-1). Phase IIB awards (formerly known as competing continuation awards)

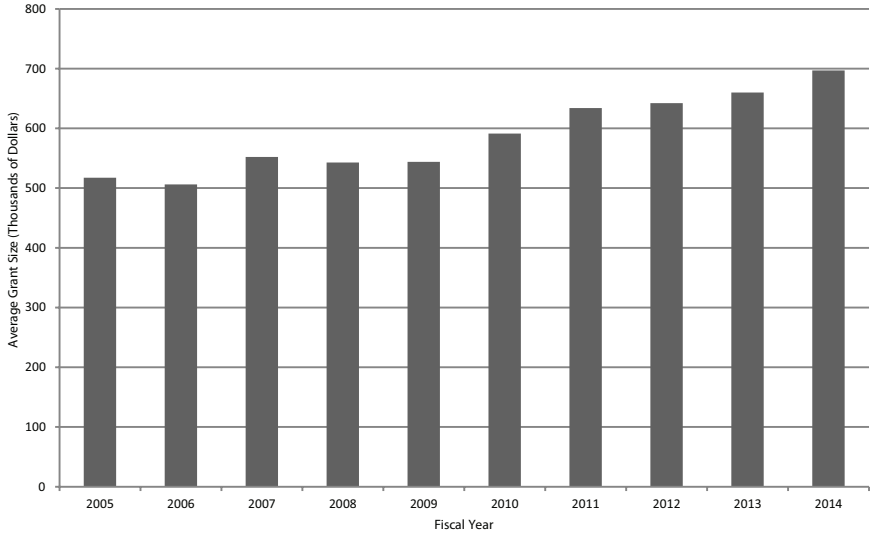

FIGURE 4-18 Average size of SBIR Phase II noncompeting award by fiscal year, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

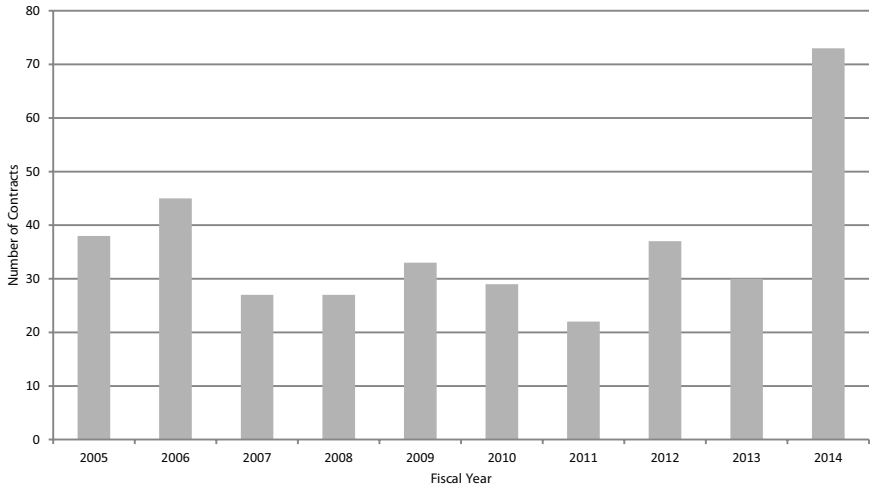

FIGURE 4-19 Number of Phase II SBIR contracts, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

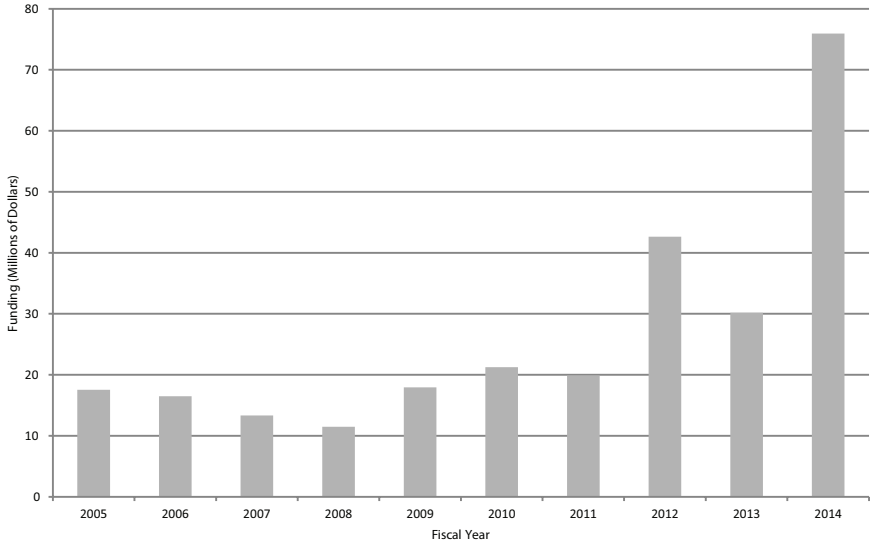

FIGURE 4-20 Funding for SBIR Phase II contracts, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

provide up to $1 million annually for 3 years to support companies engaged with the clinical trials process. Figure 4-21 shows that after the pilot phase in FY2003 and FY2004, the number of Phase IIB SBIR awards settled at about 20 per year. Funding for the program has varied, peaking in FY2006 at almost $80 million, or about 14 percent of total program funding (see Figure 4-22).

Companies can receive more than one Phase IIB award. Two companies received 4 awards, and 22 received 2 or more. Fourteen companies received at least $5 million in Phase IIB funding, which in aggregate was about 20 percent of all program funding (a number of companies with Phase IIB awards are described in Appendix E).

Fast Track

NIH has permitted Fast Track applications for over a decade now. If approved, then a Fast Track award transitions directly from Phase I to Phase II, and no further application is required. Milestones that signal the successful completion of Phase I feasibility studies must be met. The program aims to provide a more rapid transition for projects where the company can present convincing evidence of feasibility, including in many cases preliminary data. Figure 4-23 shows the number of Fast Track SBIR awards, which grew substantially over the study period.

BOX 4-1
Types and Phases of Clinical Trials

There are major differences in the approval procedures for drugs and medical devices. Medical devices are approved by the U.S. Food and Drug Administration (FDA) through the Premarket Approval (PMA) application process. Often a single confirmatory study is sufficient for approval. Drugs are approved through the New Drug Application (NDA) process, which requires a series of clinical trials. In the United States, clinical trials are generally divided into the following phases:

- Preclinical. Experiments involving nonhuman subjects to gather efficacy, toxicity, and pharmacokinetic information.
- Phase 1. Small-scale trials to test a drug on human subjects, often starting with sub-therapeutic doses but then increasing as safety is established. The objective is to determine the safety of the drug for humans.
- Phase 2. Larger scale testing on volunteers (typically 100-300 subjects) to test for efficacy, using a therapeutic dose of the drug.
- Phase 3. Larger scale testing on patients (typically 1,000-2,000 subjects) to determine the drug's therapeutic effect.
- Phase 4. Sentry studies after the drug is in the marketplace to ensure that new safety or efficacy concerns have not emerged.
- Large-scale clinical trials can be very expensive, running to tens of millions of dollars in some cases.

SOURCE: FDA Drug Approval process, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm, accessed February 20, 2014.

This growth means that the share of Fast Track in the broader population of Phase II awards has also grown. Figure 4-24 shows that Fast Track awards are now almost 25 percent of the collective population of Fast Track and Phase II SBIR awards. This growth also means that what was an experimental or pilot program is now well embedded in the NIH SBIR/STTR programs. Given its growing popularity, other agencies should consider pilot projects of their own, because the Fast Track program has multiple potential benefits. It reduces the load on reviewers, provides more certainty for the firm, and essentially eliminates the Phase I-Phase II gap that can pose real problems for small companies. However, it would be important to ensure that the milestones at the end of Phase I are successfully completed and that transition to Phase II does not become a formality. There is no evidence that there are problems in this area.

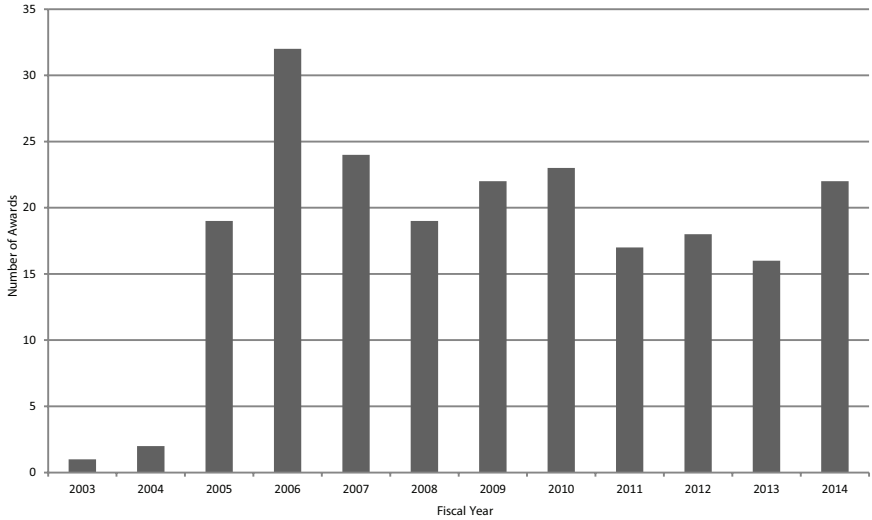

FIGURE 4-21 Number of Phase IIB awards, FY2003-2014.
SOURCE: NIH data provided to NAS, September 2014.

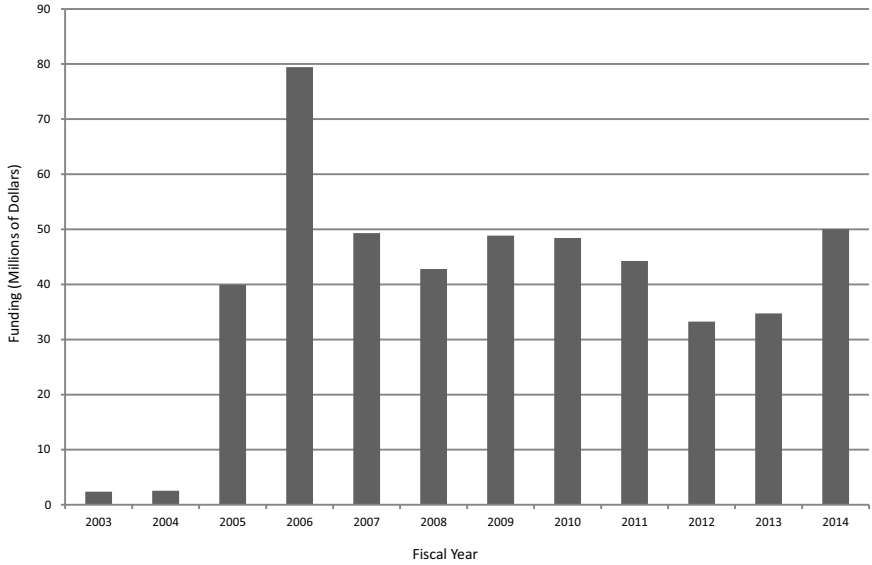

FIGURE 4-22 Funding for Phase IIB awards, FY2003-2014.
SOURCE: NIH data provided to NAS, September 2014.

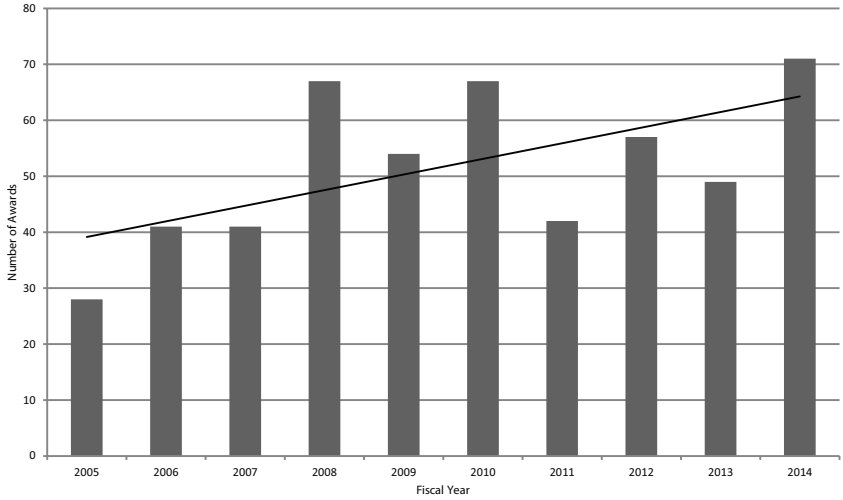

FIGURE 4-23 Number of Fast Track SBIR awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

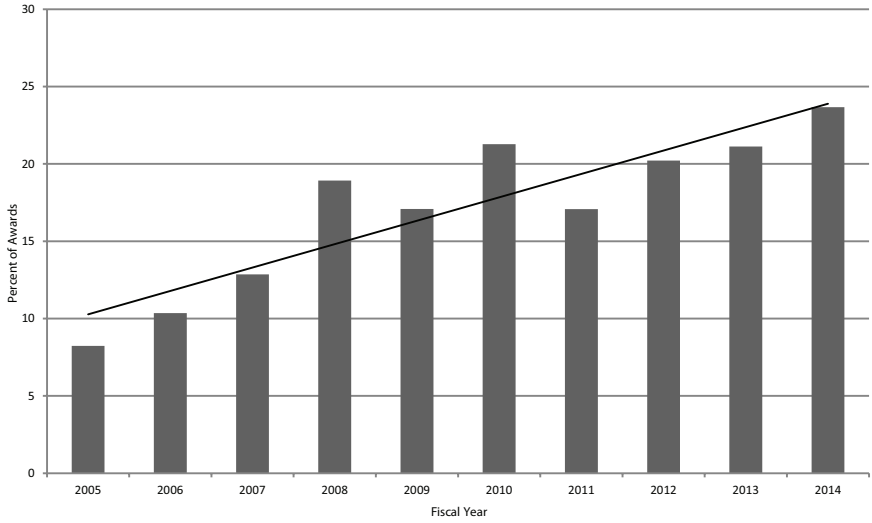

FIGURE 4-24 Fast Track awards as a percentage of Fast Track plus Phase II SBIR awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

STTR

STTR Phase I Grants

STTR Phase I Applications and Success Rates

Until FY2013, trends in STTR Phase I applications tracked quite closely with those for SBIR applications. In FY2013 and FY2014, SBIR applications decreased while STTR applications increased, quite sharply in FY2014 (see Figure 4-25). In FY2014, applications increased by more than 50 percent from the low of 508 in FY2011, reaching almost 800 in total. Figure 4-26 compares success rates for STTR Phase I applications and SBIR Phase I applications. In 7 of the 10 years, STTR Phase I had higher success rates, and in 3 years, SBIR Phase I had higher success rates. STTR success rates ranged between about 14 percent and 22 percent, while SBIR success rates ranged between about 12 percent and 27 percent.

STTR Phase I Grants

All STTR awards at NIH are made as grants, so there are no STTR contracts. STTR differs from SBIR in a number of respects. STTR funding is approximately 10 percent of SBIR funding. Across the study period, there was a total of 1,209 new Phase I STTR awards (Figure 4-27), compared with 6,508 new Phase I grants and 672 new Phase I contracts. STTR thus accounted for about 14 percent of all new Phase I awards from FY2005-2014. Funding for STTR Phase I awards de-

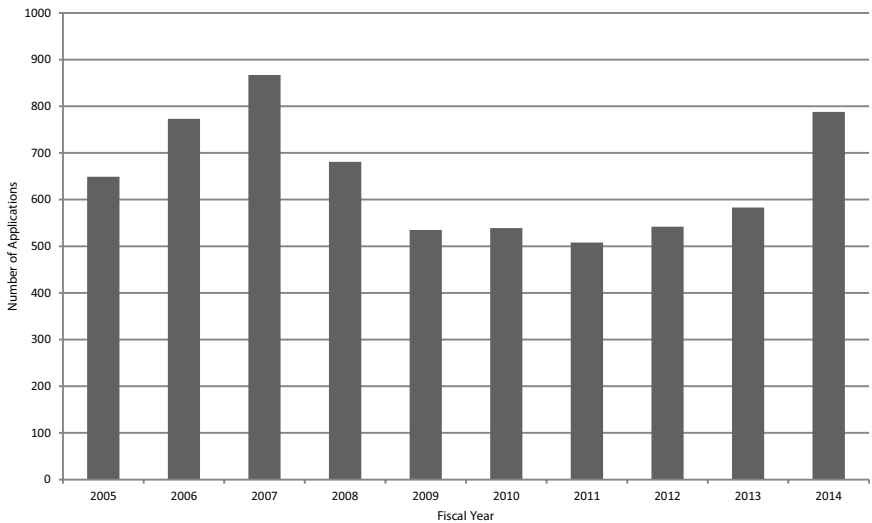

FIGURE 4-25 Number of STTR Phase I applications, FY2005-2015.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 215.

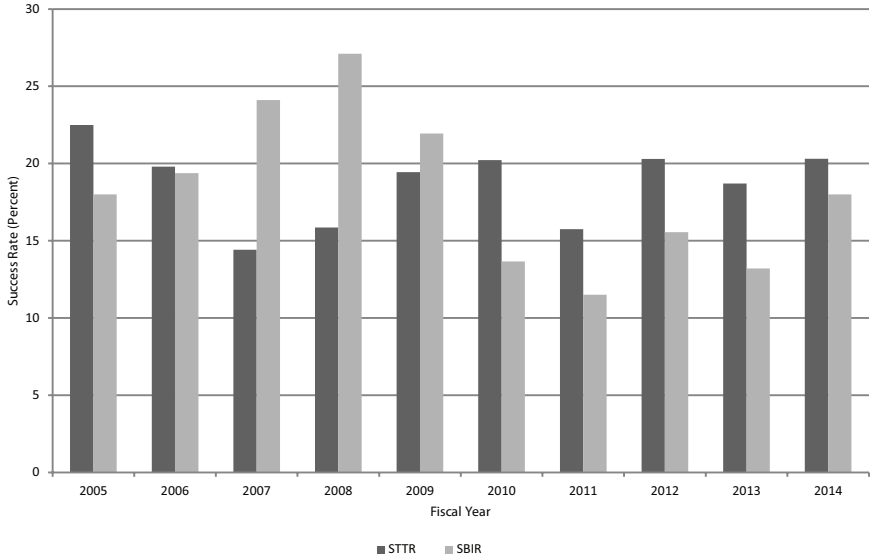

FIGURE 4-26 Success rates for SBIR and STTR Phase I applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 215.

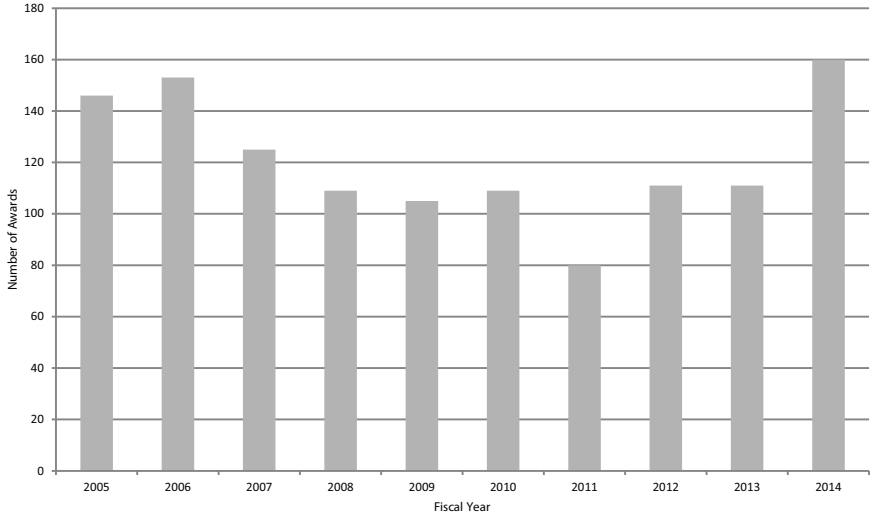

FIGURE 4-27 Number of new STTR Phase I awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

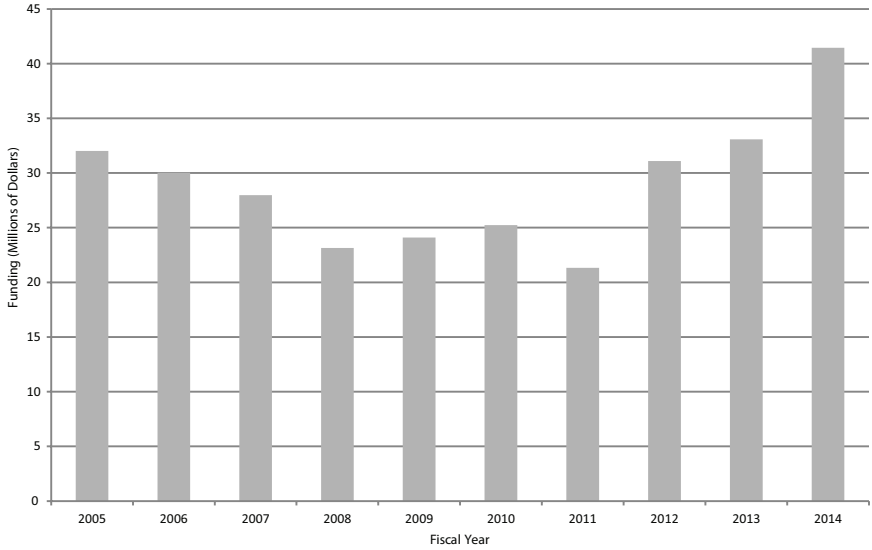

FIGURE 4-28 Funding for NIH STTR awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

creased by greater than one-third between FY2006 and FY2011 before increasing quite rapidly, reaching $40 million for the first time in FY2014 (see Figure 4-28).

STTR Phase II

Like SBIR, Phase II accounts for the lion's share of program funding. However, unlike STTR Phase I, there has been no recent increase in funding for Phase II (see Figure 4-29). Moreover, unlike SBIR—where Phase II awards account for about 70 percent of overall program funding—STTR funding is now divided equally between Phase I and Phase II. Over the same period, the number of new Phase II awards declined somewhat (see Figure 4-30), but this may reverse now that more Phase I grants are being awarded.

New Entrants into the Program and Multiple Award Winners

New Entrants

One important metric for program management is the extent to which the program is open to new applicants and awardees. At NIH every year, about one-third of the companies submitting proposals are new to the program, and about one-quarter of the proposals are from new companies (on average, more expe-

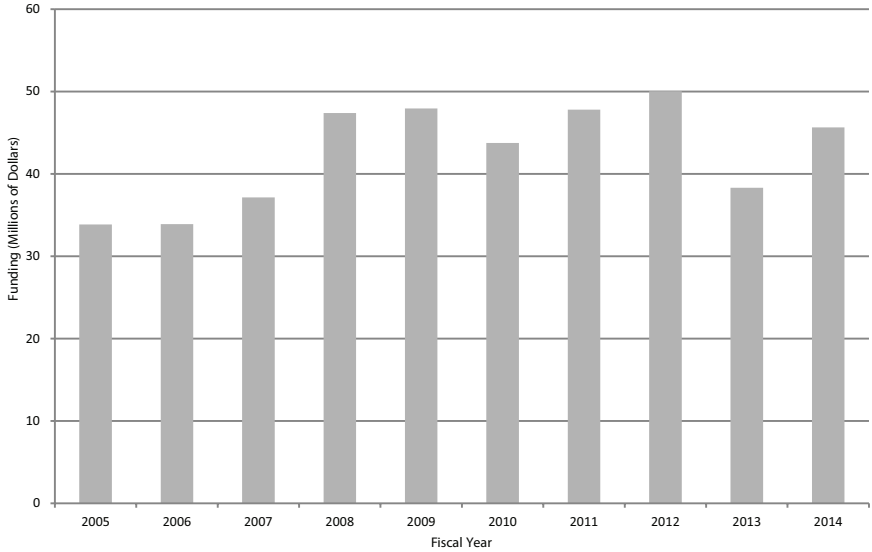

FIGURE 4-29 Funding for STTR Phase II awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

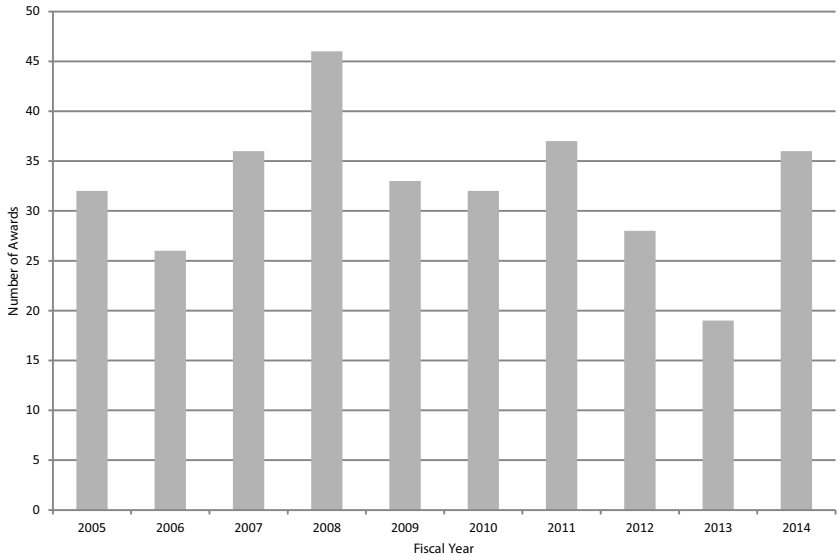

FIGURE 4-30 Number of new Phase II awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 126.

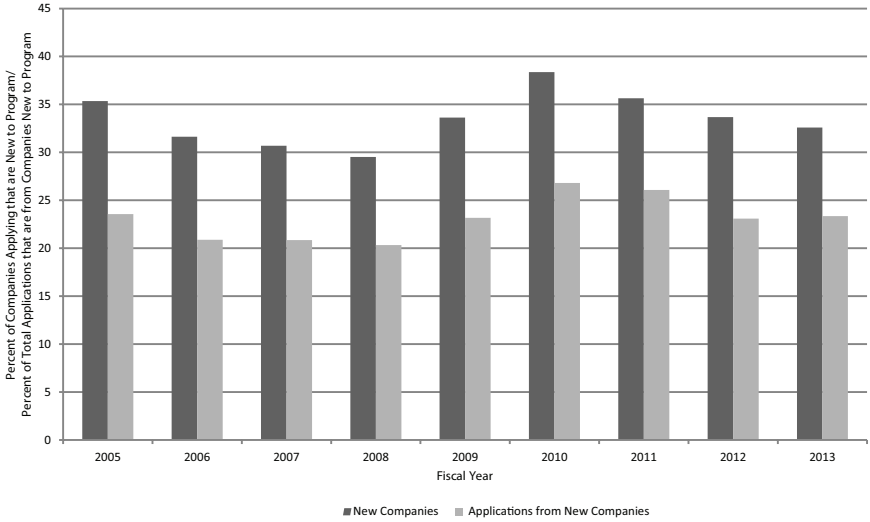

FIGURE 4-31 NIH SBIR/STTR Phase I grants, FY2005-2013: Applications from companies not previously funded by NIH SBIR/STTR.
SOURCE: NIH SBIR Program Office.

rienced companies tend to submit more proposals annually). Figure 4-31 shows the share of new applicant companies and applications from new companies. There was a modest increase in FY2010 (perhaps as other funding became more difficult to find), but overall the figures remained stable over the study period.

The percentage of awarded companies that are new to the program and the percentage of grants made to those companies as a percentage of all grants tracked quite closely with the shares of proposals described above (see Figure 4-32). This suggests that companies with experience in the program do not have a substantial advantage in acquiring funding for subsequent projects. In fact, new companies account for a slightly higher share of grants made than applications submitted, suggesting that they fare slightly better than existing participants in the selection process.

Multiple Award Winners

NIH spreads its awards widely. Table 4-3 shows the Phase I awards and funding provided to the top 20 NIH SBIR/STTR Phase I award winners for FY2005-2014. The most prolific company, Lynntech, received 44 Phase I awards during the 10-year period. Overall, the top 20 companies accounted for 7.7 percent of SBIR/STTR Phase I awards and 8.1 percent of funding. The distribution of Phase II awards and funding is similarly spread out (Table 4-4). The most

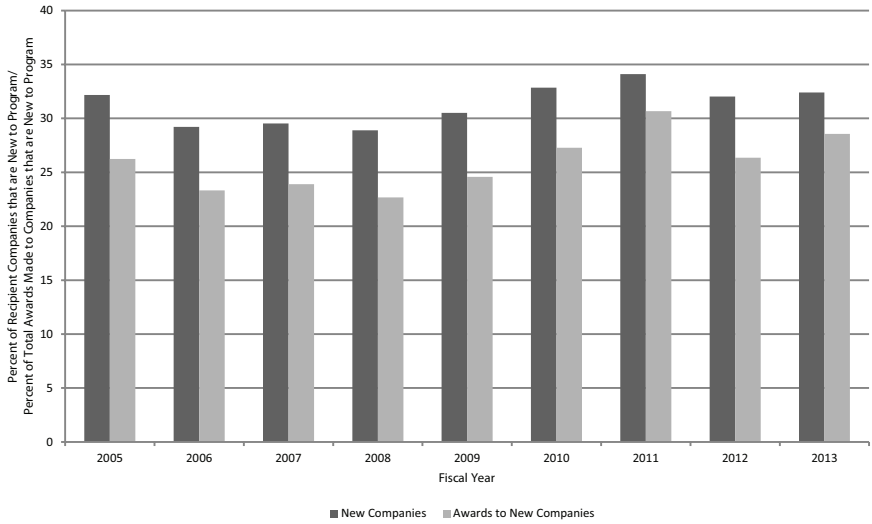

FIGURE 4-32 NIH SBIR/STTR Phase I grants, FY2005-2013: Awards to companies not previously funded by NIH SBIR/STTR.
SOURCE: NIH SBR-STTR Program Office.

prolific Phase II companies, Radiation Monitoring and Praxis, each received 24 awards during the 10-year period. The top 20 awardees (plus one tie) accounted for 9.9 percent of awards and 8.2 percent of funding made during this period. Together, these data show that awards are not heavily concentrated at the company level at NIH. Both the number of awards and the share of awards to the top 20 winners are low relative to other agencies. At DoD for example the top 20 winners accounted for 14.3 percent of awards and 14.4 percent of funding of SBIR Phase I winners.[3]

Awards and the States

The distribution of awards among states has been a matter of concern for Congress and was discussed extensively in the context of the recent reauthorization. Agencies are now required to report on their effort to encourage applications from underserved states. SBIR awards are not distributed equally among the states, which is not surprising given the uneven distribution of resources and scientific and technical talent across the nation and the merit-based approach of the SBIR program.

[3]National Research Council, *SBIR at the Department of Defense*, Washington, DC: The National Academies Press, 2015, Table 2-3.

TABLE 4-3 Awards and Funding, Top 20 NIH SBIR/STTR Phase I Award Winners, FY2005-2014

Company Name	Number of Awards	Funding (Dollars)
LYNNTECH, INC.	44	9,025,700
PANORAMA RESEARCH, INC.	43	9,060,220
RADIATION MONITORING DEVICES, INC.	40	6,010,950
MICROBIOTIX, INC.	38	21,567,426
ADVANCED MEDICAL ELECTRONICS CORPORATION	38	7,153,653
PHYSICAL SCIENCES, INC.	37	7,753,637
OREGON CENTER FOR APPLIED SCIENCE, INC.	33	6,869,913
ANGION BIOMEDICA CORPORATION	32	8,477,366
P2D, INC.	28	7,893,568
KORONIS BIOMEDICAL TECHNOLOGIES CORPORATION	27	4,416,605
RADIKAL THERAPEUTICS, INC.	26	7,210,799
L2 DIAGNOSTICS, LLC	25	9,351,615
AFFINERGY, INC	25	6,775,632
PROGENRA, INC.	23	6,035,889
INFLEXXION, INC.	23	4,048,479
CLEVELAND MEDICAL DEVICES, INC.	23	6,259,675
SOCIOMETRICS CORPORATION	22	4,829,713
LUCIGEN CORPORATION	22	4,368,269
COGNOSCI, INC.	22	5,723,741
BARRON ASSOCIATES, INC.	20	3,347,622
Total	591	146,180,472

SOURCE: NIH data provided by NIH SBIR/STTR Program Office.

SBIR Phase I awards and applications for each state from FY2005-2014 are provided in Table 4-5. As expected the large states and research-intensive states had more applications and more awards. In addition, the success rates of different states varied widely.

However, reviewing the number of awards alone is of little analytic use: that number is largely driven by state population, so initial analysis must consider applications normalized for population. That rate is provided in Table 4-5 and reveals very large disparities. At the top end, Massachusetts generated more than 850 Phase I SBIR applications per 100,000 population, and both Wisconsin and Maryland generated more than 550. Six states (Nevada, Louisiana, Mississippi, Idaho, Alaska, and West Virginia) generated fewer than 50 such applications.

TABLE 4-4 Awards and Funding, Top 20 NIH SBIR/STTR Phase II Award Winners, FY2005-2014

Company Name	Number of Awards	Funding (Dollars)
RADIATION MONITORING DEVICES, INC.	24	21,820,506
PRAXIS, INC.	24	16,397,125
OREGON CENTER FOR APPLIED SCIENCE, INC.	21	26,136,560
PHYSICAL SCIENCES, INC.	15	13,105,723
NEW ENGLAND BIOLABS, INC.	15	8,504,170
INFLEXXION, INC.	15	18,262,357
TRANSCENDENT INTERNATIONAL, LLC	14	16,799,671
ADVANCED MEDICAL ELECTRONICS CORPORATION	14	14,262,176
ANGION BIOMEDICA CORPORATION	13	22,843,573
NOVELMED THERAPEUTICS, INC.	12	9,817,808
BARRON ASSOCIATES, INC.	12	10,261,347
SOCIOMETRICS CORPORATION	11	9,043,544
MC3, INC.	11	6,987,602
LYNNTECH, INC.	11	11,309,483
KDH RESEARCH AND COMMUNICATION, INC.	11	6,100,073
TALARIA, INC.	10	11,133,879
ISA ASSOCIATES, INC.	10	6,363,783
3-C INSTITUTE FOR SOCIAL DEVELOPMENT	10	10,600,351
QUANTUMBIO, INC.	9	4,596,024
DNA SOFTWARE, INC.	9	3,093,901
BIOSTATISTICAL PROGRAMMING ASSOC, INC.	9	5,489,489
Total	280	252,929,145

SOURCE: NIH data provided by NIH SBIR/STTR program office.

This disparity in application rates may be explained by the small share of working scientists and engineers in low-award states. Figure 4-33 presents a scatterplot of applications per 100,000 population and number of science and engineering PhDs per 1,000 population. Statistical analysis using the Pearson test generates a result of 0.67, which indicates strong correlation between the number of applications (normalized) and the presence of PhD scientists and engineers.

Two outliers are excluded from the chart to permit a clearer visualization of the data for the remaining states. (The District of Columbia is excluded because its share of PhDs is four times greater than any other state, and Massachusetts has 50 percent more applications per capita than any other state. Both are included in

TABLE 4-5 NIH SBIR Phase I Applications and Awards, by State, FY2005-2014

State	Number of Applications	Number of Awards	Success Rate (Percent)	Applications per 100,000 Population
AL	539	96	17.8	112.8
AK	12	2	16.7	16.9
AR	608	130	21.4	95.1
AZ	348	81	23.3	119.3
CA	10,907	2,143	19.6	292.8
CO	1,435	293	20.4	285.3
CT	787	164	20.8	220.2
DE	195	37	19.0	324.1
DC	145	28	19.3	161.5
FL	1,224	193	15.8	65.1
GA	890	182	20.4	91.9
HI	103	12	11.7	75.7
ID	40	7	17.5	25.5
IL	965	204	21.1	75.2
IN	744	145	19.5	114.7
IO	303	58	19.1	99.5
KS	196	43	21.9	68.7
KY	652	136	20.9	150.3
LA	223	29	13.0	49.2
ME	121	20	16.5	91.1
MD	3,280	595	18.1	568.1
MA	5,601	1,301	23.2	855.4
MI	1,287	295	22.9	130.2
MN	1,145	263	23.0	215.9
MS	80	6	7.5	27.0
MO	635	121	19.1	106.0
MT	194	37	19.1	196.1
NE	181	32	17.7	99.1
NV	130	14	10.8	48.1
NH	392	85	21.7	297.8
NJ	1,521	246	16.2	173.0
NM	422	85	20.1	204.9
NY	2,834	594	21.0	146.2

TABLE 4-5 Continued

State	Number of Applications	Number of Awards	Success Rate (Percent)	Applications per 100,000 Population
NC	2,064	502	24.3	216.5
ND	52	12	23.1	77.3
OH	1,704	330	19.4	147.7
OK	271	51	18.8	72.2
OR	976	321	32.9	254.8
PA	2,429	513	21.1	191.2
RI	267	57	21.3	253.7
SC	391	78	19.9	84.5
SD	81	4	4.9	99.5
TN	399	63	15.8	62.9
TX	2,599	469	18.0	103.4
UT	694	127	18.3	251.1
VT	154	45	29.2	246.1
VA	1,529	258	16.9	191.1
WA	1,546	359	23.2	229.9
WV	64	2	3.1	11.3
WI	1,055	283	26.8	569.3
WY	63	8	12.7	111.8
Total	54,477	11,159	20.5	176.4

the Pearson analysis above.) Aside from New Mexico, where the share of science and engineering PhDs is inflated by the presence of Los Alamos, and Maryland and Wisconsin, which are outliers in generating more than their share of applications, the picture is very consistent: the presence of more scientists and engineers is closely correlated with more applications. It is also true that S&T resources are not uniformly distributed within a state, but rather tend to cluster around universities or research parks or research labs, and it is from those clusters that most applications come. This would suggest that substantial outreach to increase the number of applications from underserved states may not be successful in generating awards.

Unsurprisingly, given their large shares of applications, Massachusetts, Maryland, and Wisconsin also accounted for the largest shares of awards normalized for population, all with more than 10 awards per 100,000 population. Conversely, 10 states had 1 or fewer awards per 100,000 population. The average number for all states was 3.6 per 100,000 population. Success rates for applica-

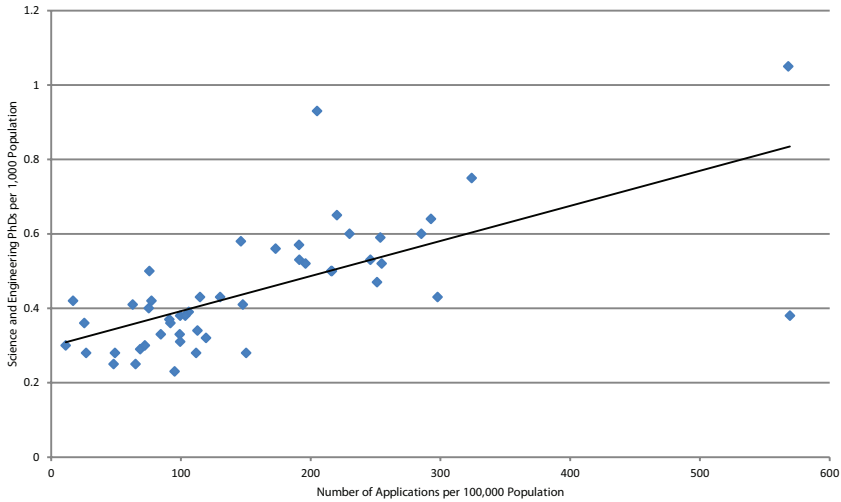

FIGURE 4-33 NIH SBIR Phase I: Distribution of applications by science and engineering PhDs, normalized for population.
SOURCE: NIH applications data (Table 216) and NSF Science and Engineer Indicators.

tions varied substantially from a high of 32 percent for Oregon to a low of less than 10 percent for West Virginia, Mississippi, and South Dakota. The average for all states was slightly greater than 20 percent across the study period.

Perhaps surprisingly, success rates across all states are not particularly well correlated with science and engineering PhDs in the workforce (see Figure 4-34). The Pearson value is 0.28. However, it is also apparent that states with very low shares of scientists and engineers also tend to have very low success rates—see circled group in Figure 4-34, where seven of the eight states with the lowest success rates also have low shares of scientists and engineers. Therefore, it appears there may be a threshold effect in which a certain density of science and engineering PhDs are necessary to develop sufficiently attractive applicants.

Understanding Low-award States

Three factors appear to play a role, to different degrees for different states, in why some states receive fewer NIH SBIR awards.

1. Some states do not have a great deal of science and engineering resources. The average number of science and engineering PhDs per thousand employed for all states is 0.55. For the 10 lowest award states, it is 0.37.

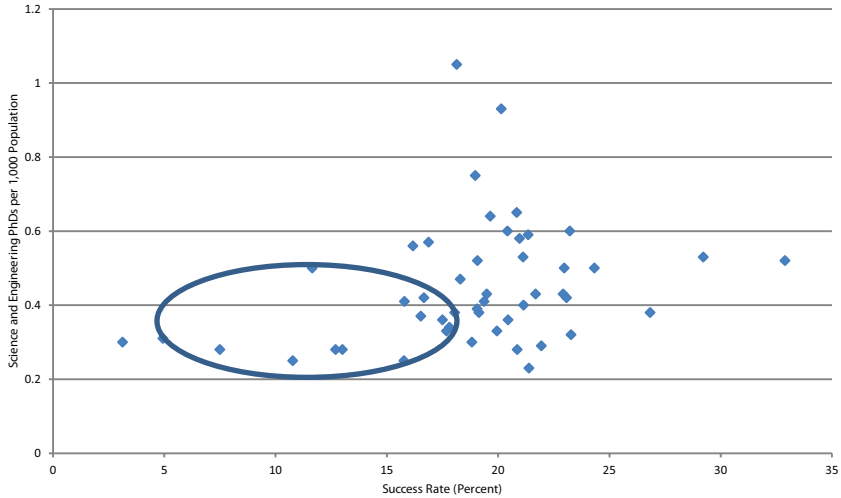

FIGURE 4-34 NIH SBIR Phase I: Distribution of state success rates by science and engineering PhDs, normalized for population.
SOURCE: NIH applications data (Table 216) and National Science Board, *Science and Engineer Indicators 2014*, Arlington, VA: National Science Foundation, Chapter 4.

2. Fewer applications. Less science and engineering resources likely leads in part to the second direct factor—fewer applications. The 10 lowest award states generated an average of 48.1 applications per 100,000 population over the study period. The average for all states (including low performers) was 176.4.
3. Lower success rates. The average success rate for all states was 20.1 percent. For the lowest award states, it was 14.1 percent. The state with the highest application rate among this group (South Dakota) had one of the lowest success rates. Although the numbers are small, it is apparent that there is no correlation between application rates and success rates for the low award states (Pearson Rho = -0.07).

The evidence overall suggests that low application rates do tend to generate low numbers of awards, but that low application rates themselves result partly from demographics (population) and partly from the distribution of science and engineering resources in the workforce. In attempting to generate more applications from low-award states, a strategy will be to target outreach at identifiable clusters of science and engineering resources within a state.

5

Quantitative Outcomes

This chapter analyzes outcomes related to the efforts by NIH to address the congressional mandate to increase commercialization of federally funded research and to stimulate technological innovation under its SBIR and STTR programs.[1]

This chapter reviews quantitative data provided through the 2014 Survey of Phase II SBIR/STTR recipients at NIH. It focuses primarily on the commercialization outcomes and knowledge effects from SBIR/STTR awards, as well as the longer term impact on the companies themselves. The chapter is followed by an Annex that includes more detailed descriptions and analysis.

There is evidence that NIH has achieved some success in tracking outcomes of SBIR/STTR awards, but more work needs to be done. NIH is currently building electronic links to the Small Business Administration (SBA) outcomes database now under development and working to develop its own outcomes tracking system (see Chapter 3); however, data from these sources are not yet available. Thus, the analysis of outcomes in this report is based primarily on the 2014 Survey by the Academies, which tried to survey all SBIR and STTR Phase II awardees for the period FY2001-2010 inclusive.[2]

A detailed description of the methodology underlying the 2014 survey is provided in Appendix A of this report (see Box 5-1). The full text of the survey is provided in Appendix C. Overall, the survey of NIH Phase II SBIR/STTR award recipients generated 726 responses. In cases where company information, as opposed to individual project information, was collected, multiple responses

[1]The participation of women and minorities is discussed in Chapter 6, and although some data are presented here on SBIR/STTR and agency mission, those are discussed further in Chapter 2.

[2]See Appendix A for a detailed description of the survey methodology used in this report.

BOX 5-1
Workshop on Improving University-SBIR/STTR Linkages

A workshop convened on February 5, 2014, by the committee considered a range of issues concerning universities and the SBIR/STTR programs.[a] Participants at this workshop addressed a range of topics including:

- Improving linkages between SBIR/STTR programs at agencies and the universities,
- Aligning with university accelerator initiatives,
- Supporting improved links between state and local innovation and entrepreneurship programs and the universities, and
- Supporting shifts in culture at universities to incentivize faculty to pursue SBIR/STTR funding.[b]

[a] See http://sites.nationalacademies.org/PGA/step/sbir/PGA_086819.htm.
[b] These issues and others related to the SBIR/STTR programs and universities will be addressed in detail in the upcoming NASA report on the STTR program.

from the same company were aggregated and then averaged to provide a better view of company-level activities.

A more detailed presentation of the data collected via the survey, including response rates, is included at the end of this chapter in Annex 5-A.

COMMERICIALIZATION

As with our other reports on the SBIR program, we have adopted a broad view of commercialization, taking it to include additional investments from outside the SBIR/STTR programs as well as sales and licensing revenues. In addition, given the long time to market required for many life sciences technologies, we have been careful to include a range of benchmarks and metrics, having determined that no single metric can appropriately capture such a broad concept.

That said, we focus first on different ways of measuring sales and other types of commercial revenue as well as further investment. In line with previous studies by the Academies and consistent practice at all agencies, investment beyond Phase II is recognized as acknowledgement by third parties that the project has developed technologies of marketable value. For many projects, further investment is required before commercial sales can begin. An extended discussion of approaches to measuring commercialization is contained in the Annex to this chapter.

NIH is also in some ways a special case for commercialization. Because NIH is not an agency where the SBIR/STTR programs are designed to generate

technologies for use by the agency itself, markets have to be found outside the agency. The path to such markets is particularly difficult for the large percentage of projects that require U.S. Food and Drug Administration (FDA) approval; such approval was required for 45 percent of the surveyed projects. Regulatory approval is expensive—sometimes extremely expensive—and time consuming. These are two formidable challenges for small companies. It is therefore especially important to capture milestones along the way to commercialization as well as commercial sales and related revenues.

Sales and Revenues

Perhaps the single most used metric for assessing SBIR-type programs is revenue or licensing fees. As recommended in a previous Academies' report[3] overreliance on this particular metric may lead to incorrect conclusions about the program, although they are important considerations.

Reaching the Market

The first question in this section concerns reaching the market: Did the project generate any sales, and if not, are sales expected (a necessary question given the long cycle time of some projects)? Responses are summarized in Figure 5-1.

Overall, just less than one-half of projects reported some sales or licensing revenues, and a further 25 percent expected sales in the future. These data are similar to those generated by the previous survey of NIH SBIR-only awardees by the National Research Council (NRC)[4] in 2005.[5]

Amount of Sales and Licensing Revenues

Simply identifying the percentage of projects reaching the market is an important metric, but it is not sufficient; it is also necessary to understand the scale and distribution of sales. The 2014 survey asked those who reported some sales of the technology developed for the surveyed project to report the amount of sales, grouped into ranges. These data are summarized in Figure 5-2.

Most reported sales at the lower end of the scale: 62 percent were less than $500,000 and more than one-half of those sales (39 percent of the total) were under $100,000. Four percent reported revenues of at least $20 million, while 8 percent reported sales of between $5 million and $20 million.

[3]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, Washington, DC: The National Academies Press, 2009.

[4]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council or NRC are used in an historic context identifying programs prior to July 1.

[5]National Research Council, A*n Assessment of the SBIR Program at the National Institutes of Health*.

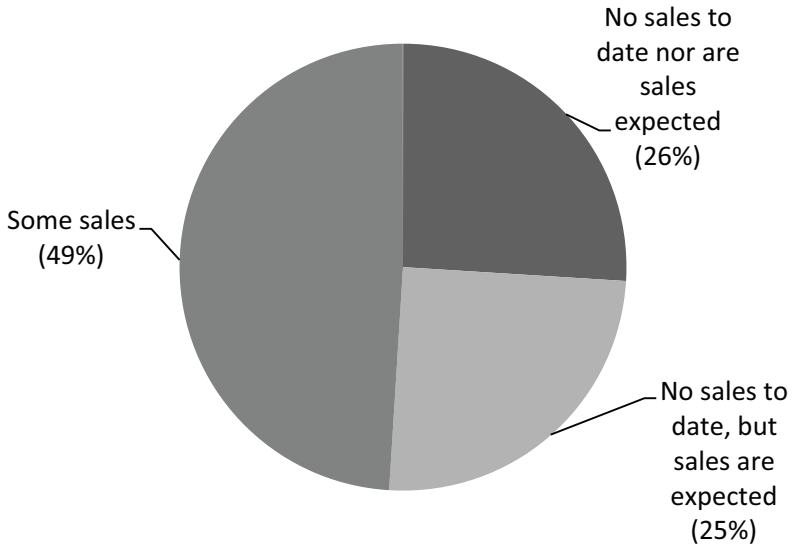

FIGURE 5-1 NIH SBIR/STTR sales and licensing revenues (percentage of respondents).
NOTE: N=602. See Table 5-7 in the chapter annex for details.
SOURCE: 2014 Survey, Question 32.

Markets by Sector

The 2014 Survey also asked respondents about the market sectors in which sales were made. Overall, 58 percent identified the private sector, followed by export markets (17 percent). Sales to federal agencies comprised 6 percent of sales (see Figure 5-3).

Further Investment

The ability of SBIR/STTR projects and companies to attract further investment has traditionally been an important measure of SBIR/STTR commercialization outcomes.[6] There has also been interest in the sources of additional funding for high-tech innovation. Although the United States has historically been a leader in venture capital and angel investment, these are not the only or even the primary sources of additional investment funding for NIH SBIR/STTR projects.

Overall, more than 80 percent of respondents indicated that their project received additional investment in the technology related to the surveyed project.[7] As

[6]See National Research Council, *An Assessment of the SBIR Program*, Washington, DC: The National Academies Press, 2008.

[7]2014 Survey, Question 30. N=572.

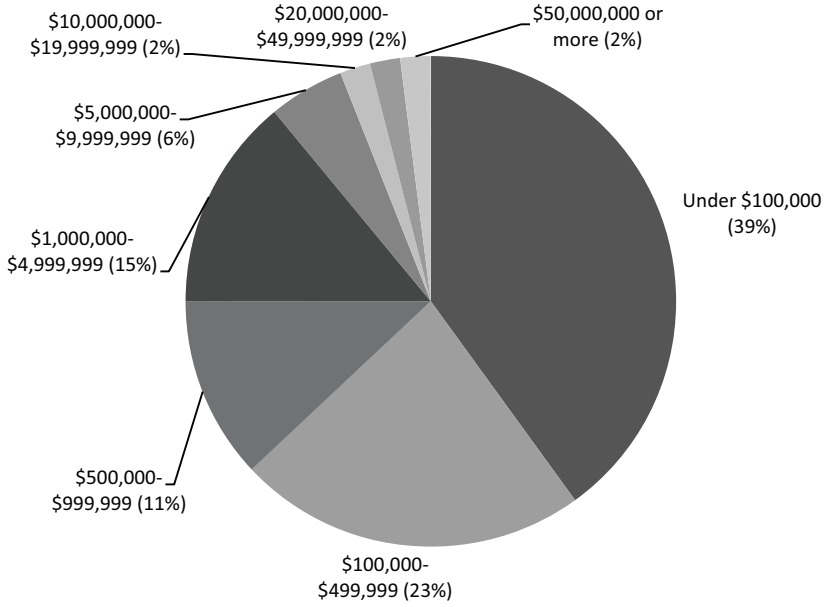

FIGURE 5-2 Distribution of total sales and licensing revenues by range (percentage of respondents reporting sales).
NOTE: N=263 (projects reporting sales). See Table 5-8 in the chapter annex for details.
SOURCE: 2014 Survey, Question 34.

with prior surveys, the data show small amounts of additional funding are most likely. Table 5-1 shows the amount of funding received. About 76 percent of all projects received less than $1 million in additional investment with the median amount of additional funding equaling $300,000. Four respondents (less than 1 percent) reported receiving $50 million or more in additional funding, while 9 percent reported receiving $5 million or more. These data highlight funding challenges for these companies because the cost of Phase III clinical trials has recently been estimated at $26,000 per patient.[8] Phase III trials can require the enrollment of more than 1,000 patients.[9]

Of the 470 respondents that reported additional funding, 44 percent was from private-sector sources, 9 percent was from venture capital sources, and 14 percent was from angel and other private equity investors. Twenty-one percent reported strategic investments from partners, which is especially important in the context

[8]Jon Hess, "Clinical Operations: Accelerating Trials, Allocating Resources and Measuring Performance," *Cutting Edge Information*, October 12, 2014.

[9]Avik S. Roy, "Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials," FDP Project Report 5, Manhattan Institute, April 2012.

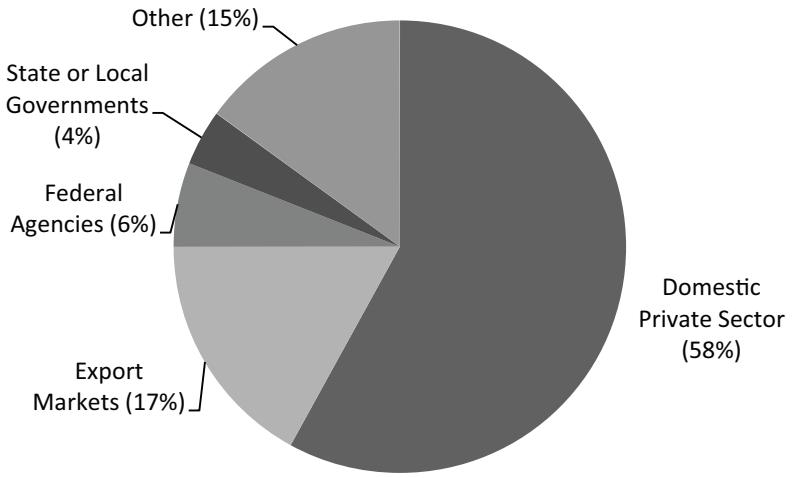

FIGURE 5-3 Markets for NIH SBIR/STTR products and services: Percentage of total sales (mean of all responses/category).
NOTE: N=265 (projects reporting sales). See Table 5-9 in the chapter annex. For this question, each respondent reports a percentage distribution. Values above are calculated by deriving the mean value for all the responses received for each category.
SOURCE: 2014 Survey, Question 36.

TABLE 5-1 Additional Funding Received by Funding Mechanism and Amount

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
None ($0)	17.8	19.0	11.2	3.4
Under $100,000	24.3	23.2	30.3	6.9
$100,000-$499,999	21.7	21.5	22.5	13.8
$500,000-$999,999	11.7	11.4	13.5	20.7
$1,000,000-$4,999,999	15.7	15.5	16.9	31.0
$5,000,000-$9,999,999	3.5	3.7	2.2	10.3
$10,000,000-$19,999,999	2.3	2.5	1.1	10.3
$20,000,000-$49,999,999	2.3	2.3	2.2	3.4
$50,000,000 or more	0.7	0.8		
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	572	483	89	29
Mean	2,560	2,698	1,813	4,666
Median	300	300	300	3,000

SOURCE: 2014 Survey, Question 30.

TABLE 5-2 Distribution of Responses Related to Additional Investment Funding by Source of Funds

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Non-SBIR/STTR federal funds	25.2	21.9	41.4	28.6
Private Investment: U.S. Sources	44.2	45.7	36.8	67.9
Venture capital (VC)	9.5	9.5	9.2	21.4
U.S. angel funding or other private equity investment (not VC)	13.6	14.5	9.2	14.3
Friends and family	11.4	11.4	11.5	10.7
Strategic investors/partners	20.5	21.0	18.4	17.9
Other sources	9.1	9.3	8.0	17.9
Foreign Investment	5.5	5.5	5.7	
Financial investors	2.4	2.4	2.3	
Strategic investors/partners	3.7	3.3	5.7	
Foundations	3.6	2.9	6.9	

SOURCE: 2014 Survey, Question 31.

of life sciences where large pharmaceutical and medical device companies are a critical part of the path to market (see Table 5-2).

Twenty-five percent of respondents reported funding from non-SBIR/STTR federal sources, which would include such potential funders as BARDA, the Centers for Medicare & Medicaid Services, and the Veterans Administration, or the Department of Defense.

As shown in Table 5-13 in the chapter annex, 24 percent of respondents reported funding from other external sources, including 16 percent from state and local governments and 9 percent from research institutions. Overall, the most utilized funding source was the company itself (58 percent) and in many cases personal funds (26 percent).

SBIR/STTR and Clinical Trials

Many NIH-funded projects face the challenge of proceeding through clinical trials before they can seek success in the marketplace. Survey responses indicate that this was true for 46 percent of projects.[10] For these companies, the road to successful conclusion of clinical trials is very challenging (Table 5-3). More than one-third of projects had abandoned the process, and about another one-third

[10]2014 Survey, Question 40. N=584.

TABLE 5-3 Outcomes for Projects Requiring FDA Approval

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
FDA process abandoned	35.5	35.9	33.3	5.3
Preparation under way for clinical trials	34.4	35.5	28.2	47.4
IND granted	4.7	4.1	7.7	10.5
In Phase 1 clinical trials	4.7	5.1	2.6	
In Phase 2 clinical trials	9.4	7.4	20.5	15.8
In Phase 3 clinical trials	2.3	1.8	5.1	
Completed clinical trials	9.0	10.1	2.6	21.1
BASE: NIH PROJECTS REQUIRING FDA APPROVAL	256	217	39	19

SOURCE: 2014 Survey, Question 41.
NOTE: IND refers to Investigational New Drug

were preparing for entry into clinical trials. Nine percent of projects had completed clinical trials (21 percent of Phase IIB projects).

These figures are difficult to interpret because the survey covered a 10-year period. Newer projects are more likely to be preparing for clinical trials or in earlier stages than are older projects. Still, it is fair to conclude that a majority of those requiring approval will not in the end receive it given that the probability of a project being abandoned increases with its age.

These data can be compared with the general set of outcomes for all efforts to receive FDA approval. Table 5-4 shows that 8 percent of those projects entering the clinical trials process eventually received approval, while 30 percent of projects were approved for Phase 1 clinical trials. Survey responses match these estimates quite closely, which is noteworthy given that Table 5-4 includes data from larger and much better funded companies.

SBIR/STTR companies utilize a wide range of funding sources to meet the demands of clinical trials. Figure 5-4 shows that the largest single source was internal company funding (51 percent) followed by SBIR/STTR itself (32 percent) and Phase IIB (22 percent). Angel funding, venture funding, and strategic funding from other companies were each mentioned by 15 percent of respondents.

For those receiving SBIR/STTR support of some kind for clinical trials, 48 percent thought that the funding was extremely or very useful, while 33 percent said it was not at all useful.[11] Among those who received Phase IIB funding, positive responses were higher—more than three quarters of respondents said that

[11]2014 Survey, Question 45. N=79.

TABLE 5-4 Outcomes for FDA Applications at Different Phases

Stage	Overall Probability of Success	Conditional Probability of Success	Approximate Time
Preclinical			
Toxicology			1 to 6 years
Clinical			6 to 11 years
Investigational New Drug Application		40%	
Phase I	30%	75%	
Phase II	14%	48%	
Phase II	9%	64%	
Approval			0.6 to 2 years
New Drug Application	8%	90%	
Market			11 to 14 years
Phase IV/Post-Market surveillence			

NOTES: "Overall probability of success" is the unconditional probability of researching a given stage. For example, 30 percent of drugs make it to Phase I testing. "Conditional probability of success" shows the probability of advancing to the next stage of the process conditional on reaching a given stage. For example, the probability of advancing to Phase III testing conditional on starting Phase II testing is 48 percent.
SOURCE: Adapted from Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22:151-85, 2003.

it made a "tremendous difference," while 24 percent said that it made little or no difference (N=21, so responses should be treated with caution).[12]

However, while the additional funding was regarded as helpful, it was not seen as sufficient. Figure 5-5 shows that of the 21 Phase IIB responses, one-third thought the funding was not sufficient even to complete preparation for clinical trials, and a further 29 percent thought it was sufficient only for completion of those preparations. Five percent (one respondent) thought it was sufficient for Phase 3 trials.

KNOWLEDGE EFFECTS

One of the four congressionally mandated objectives for the SBIR/STTR programs is to "stimulate technological innovation." Although patents and peer-reviewed papers are not the only useful way to assess the development and transmission of knowledge by small high-tech companies, they offer a useful starting point.

[12]2014 Survey, Question 46. N=21.

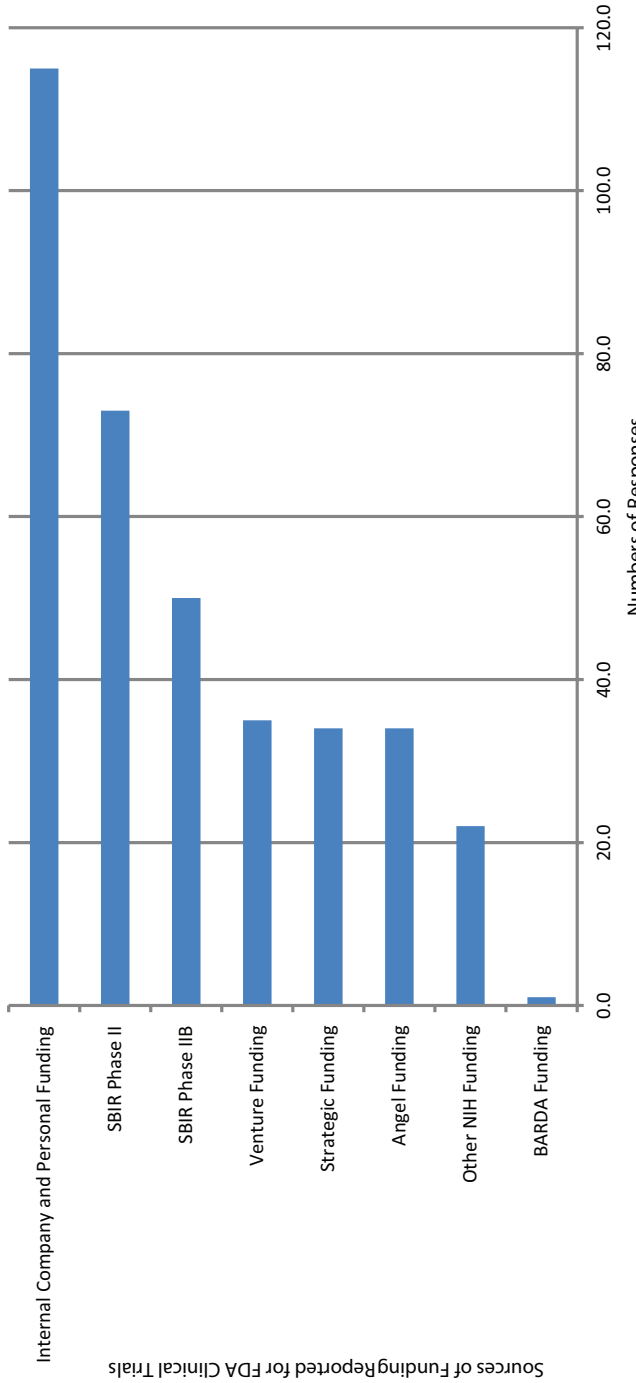

FIGURE 5-4 Sources of funding reported for FDA clinical trials (numbers of responses).
NOTE: N=226 (projects requiring FDA approval). Numbers do not sum to 226 because respondents could select more than one answer. BARDA is the Biomedical Advanced Research and Development Authority. It "provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies." http://www.phe.gov/about/BARDA/Pages/default.aspx, accessed August 8, 2015.
SOURCE: 2014 Survey, Question 4.

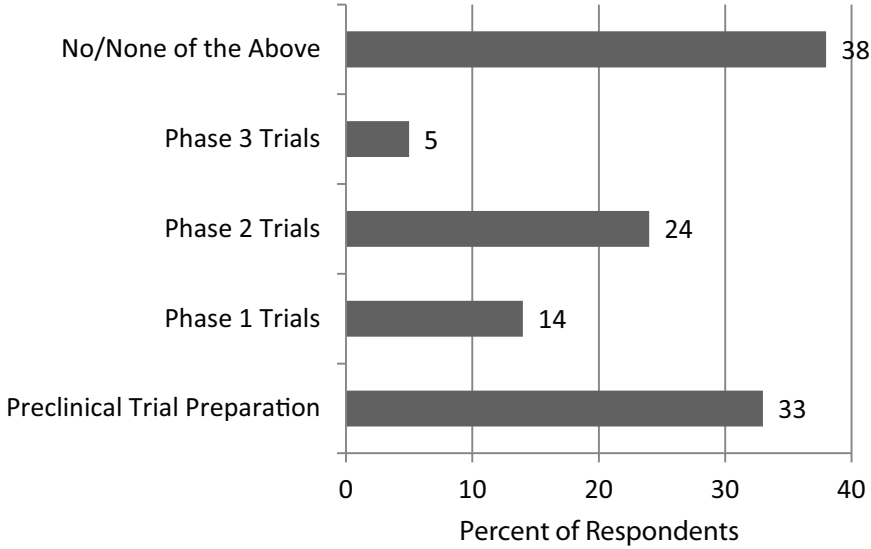

FIGURE 5-5 Sufficiency of Phase IIB funding for different phases of clinical trials (percentage of respondents).
NOTE: N=21.
SOURCE: 2014 Survey, Question 47.

Figure 5-6 shows the number of patents related to all SBIR/STTR awards reported by companies participating in the 2014 Survey. About two-thirds of respondent companies received at least one such patent, and about 13 percent received 10 or more.

The survey also asked about patents related to the specific project being surveyed. About 53 percent of respondents reported at least one patent related to the project, and 4 percent reported at least 10 (see Table 5-5).[13]

In addition to patents, the survey asked about articles in peer-reviewed journals. Meetings with company executives indicated that, for many companies, even though technical knowledge and trade secrets are very important, the company strongly supported peer-reviewed publication. In part, companies saw this as marketing among peers, both for eventual products and a means of attracting talent. Eighty percent of survey respondents reported publishing at least one peer-reviewed article related to the surveyed project. Forty-two percent reported publishing at least three articles, as shown in Figure 5-7. As shown in Table 5-19 in the annex section of this chapter, two-thirds of Phase IIB responses reported publishing at least 3 articles and 21 percent reported publishing at least 10.

[13]2014 Survey, Question 39.1.2. N=186.

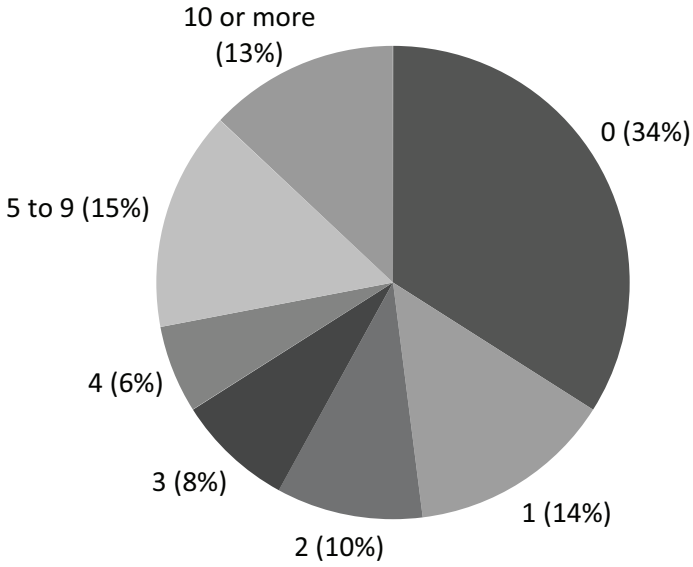

FIGURE 5-6 Number of patents reported related to all company SBIR/STTR awards (percentage of company-weighted responses).
NOTE: N=409.
SOURCE: 2014 Survey, Question 12.

TABLE 5-5 Number of Patents Received Related to Surveyed Project

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	47.0	47.2	46.3	25.9
1	23.7	23.0	27.5	22.2
2	12.0	12.1	11.3	7.4
3 or 4	8.2	7.6	11.3	22.2
5 to 9	5.2	5.9	1.3	14.8
10 or more	4.0	4.3	2.5	7.4
1 or more	53	52.8	53.8	74.1
Mean	1.63	1.71	1.23	3.11
Median	1	1	1	2
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	502	422	80	27

SOURCE: 2014 Survey, Question 38.1.

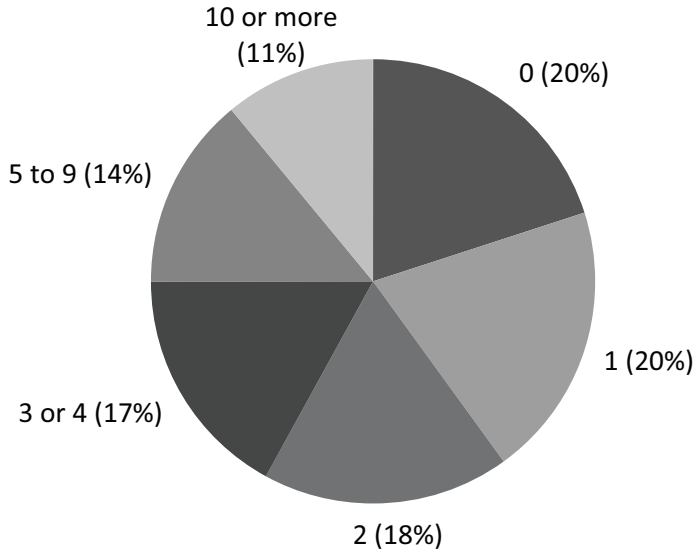

FIGURE 5-7 Number of peer-reviewed articles relating to surveyed project (percentage of respondents).
NOTE: N=508.
SOURCE: 2014 Survey, Question 38.

Another mechanism for knowledge transfer is the development of links between SBIR/STTR companies and their projects with research institutions (RIs). Sixty-five percent of SBIR respondents reported some connection to an RI. All STTR respondents are required to partner with an RI. Many reported that RI faculty worked on the surveyed project (39 percent used faculty as consultants), while a smaller number reported that the technology was originally developed at and/or was licensed from the RI (see Table 5-6).

COUNTERFACTUALS

Because there is no available matched set of companies that did not receive SBIR/STTR Phase II funding at precisely the point in time that surveyed companies did receive funding, it is not possible to develop an appropriate control group against which to measure impacts (see discussion of the Academies efforts to do so in Appendix A). However, it is at least possible to ask—as previous surveys by the Academies and the Government Accountability Office (GAO) have done—what the company itself believed might have happened had SBIR/STTR funding not been available. While this is of course subjective, the company is best suited to provide these answers.

TABLE 5-6 Connections to Research Institutions (RIs) and SBIR/STTR Awards

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
The PI for this project was at the time of the project an RI faculty member	17.4	6.1	77.8	3.6
The PI for this project was at the time of the project an RI adjunct faculty member	10.4	12.1	1.1	17.9
Faculty member(s) or adjunct faculty member(s) worked on this project in a role other than PI	38.7	38.2	41.1	35.7
Graduate students worked on this project	22.3	21.3	27.8	21.4
The technology for this project was licensed from an RI	16.0	14.0	26.7	17.9
The technology for this project was originally developed at an RI by one of the participants in this project	20.2	17.1	36.7	17.9
An RI was a subcontractor on this project	37.4	35.5	47.8	53.6
None of the above	29.7	35.1	1.1	32.1
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	569	479	90	28

SOURCE: 2014 Survey, Question 71.

Because alternative funding especially for long-cycle projects and those requiring FDA approval is difficult to acquire, it is not surprising that 7 percent of respondents believed that the project would definitely or possibly have proceeded without funding. Conversely, almost three-quarters of respondents said that it would likely or definitely not have proceeded.[14]

These data have interesting wider implications for debates about early-stage funding; notably, they suggest poor support for the "crowding out" hypothesis (that public funding displaces private investment). Awardees in our survey—presumably those with the closest knowledge of funding prospects for the project—overwhelmingly believed it to be unlikely that alternative private funding would be found. These results also underscore the importance of SBIR/STTR funding for these small companies.

[14]2014 Survey, Question 24. See Table 5-31 in the chapter annex.

COMPANY IMPACTS

Although the effect of SBIR/STTR funding on the company is not directly included in the congressional objectives for the program, helping small companies to become self-sufficient (and in some cases to grow rapidly) does have implications for program impacts and are therefore included in our analysis.

Small high-tech companies are often fluid in structure, and the 2014 Survey found that many participating companies changed structurally in recent years. Thirty-five percent established strategic partnerships with major players, while 21 percent spun off at least one company and 16 percent were acquired by or merged with another firm.[15]

Ideally, companies that receive SBIR/STTR funding become more stable and develop contracts that are not SBIR-related over time. This appears to be the case for NIH SBIR/STTR companies as dependence on SBIR/STTR funding is limited. Overall, 42 percent of respondents indicated that the SBIR/STTR programs were currently funding 10 percent or less of the company's total research and development (R&D) effort, while about 34 percent indicated that they were funding more than one-half.[16] This picture is reinforced by data on sources of company revenues. Thirty-four percent of responding companies reported zero SBIR/STTR revenues, while about 27 percent reported receiving more than one-half of the company's revenues from SBIR/STTR.[17]

The survey also asked about the overall impact of SBIR/STTR on the company. As Figure 5-8 shows, 62 percent saw a highly positive or transformative effect, and another 35 percent reported a positive impact. Two respondents reported a negative or highly negative impact.

[15]2014 Survey, Question 11. N=436 (companies). See Table 5-14.
[16]2014 Survey, Question 10. N=421 (companies). See Table 5-25.
[17]2014 Survey, Question 9. N=409 (companies). See Table 5-26.

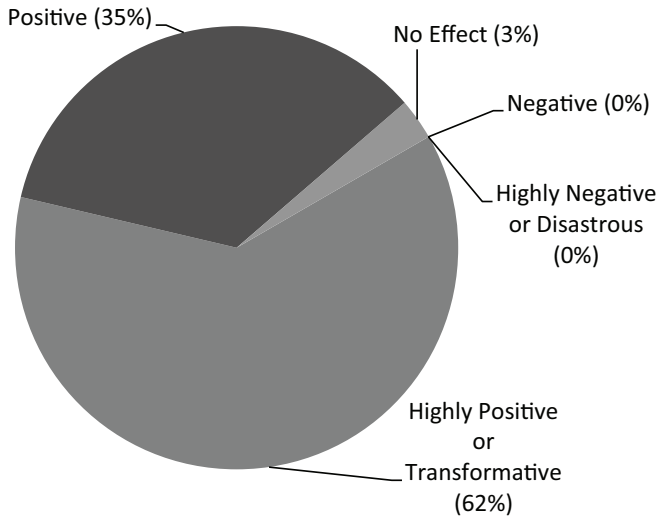

FIGURE 5-8 Long-term impact of SBIR/STTR on companies (percentage of respondents).
NOTE: N=580.
SOURCE: 2014 Survey, Question 57.

ANNEX 5-A: QUANTITATIVE OUTCOMES

This annex elaborates the results of the 2014 survey of quantitative outcomes of the NIH SBIR/STTR programs, summarized in Chapter 5. As noted earlier, this quantitative assessment of outcomes from the NIH SBIR/STTR programs focuses primarily on two of the four congressionally mandated objectives for the program: commercialization of federally funded research and stimulation of technological innovation. Data on the participation of women and minorities is included in Chapter 6. Data on program management is included in Chapter 2.

FOCUS ON COMMERICALIZATION OUTCOMES

Although there are four statutory goals for the SBIR/STTR programs, subsequent legislation passed by Congress, as well as administrative policies pursued by NIH and the other major SBIR/STTR agencies focus primarily on the commercialization of SBIR/STTR technologies.[18] Moreover, given that commercialization is among the more measurable outcomes of the SBIR/STTR programs, it has become a primary benchmark for program performance. The focus on commercialization, however, should not eclipse the requirement that the program meet all four congressionally mandated objectives. This Annex provides additional details of the commercial outcomes of the NIH SBIR/STTR programs, as well as quantitative outcome measures related to stimulating technological innovation.

SOURCES OF DATA

Although NIH was an early adopter of survey-driven outcomes research, the agency has not thereafter led the way on tracking outcomes. Other agencies have moved more rapidly to meet the need for data:

- The Department of Defense (DoD) maintains the Company Commercialization Record, which requires all companies applying for DoD SBIR/STTR funding to update outcomes for all prior awards.
- The National Science Foundation (NSF) utilizes a consultant to undertake phone interviews with recipients at set times several years after the end of the award.
- The Department of Energy (DoE) internally tracks award outcomes for several years using its own metrics and methodologies.
- The National Aeronautics and Space Administration (NASA) developed a tracking module as part of its Electronic Handbook, which has been used in recent years collect outcomes data.

[18]SBA Section 1.(c), SBIR/STTR Policy Directive, October 18, 2012, p. 3.

NIH managers are aware of this situation and have recently moved to correct this deficiency. According to the NIH SBIR/STTR Program Office, NIH has undertaken a twin-track approach. It has built an electronic bridge between the new SBA outcomes database (which is not yet online as of this writing). In addition, it is investing in a new module for its own internal Performance Outcomes Data System (PODS) database, which will address outcomes. These issues are discussed in more detail in Chapter 2 (Program Management).

Given the lack of available data from NIH, the quantitative data presented in this chapter are derived from the 2014 Survey of award recipients. We stress, however, that these data are descriptive only and should be regarded as providing insights into outcomes rather than definitive conclusions.[19]

The 2014 Survey is based primarily on the 2005 survey, with some additions and modifications. This 2014 survey was sent to two distinct populations: (1) all principal investigators (PIs) who received an NIH SBIR or STTR Phase II award between FY2001 and FY2010 inclusive and (2) in cases where PIs could not be reached, alternate company contacts at the targeted companies. Results from this survey provide quantitative insights that permit the analysis provided in this chapter. They are, where appropriate, compared to the results from the 2005 Survey.[20]

Appendix A provides a detailed discussion of the survey methodology, including response rates and potential survey bias. Below, a series of tables summarize Phase II responses for SBIR, STTR, and Phase IIB recipients.[21] The 2014 Survey is reproduced in Appendix C. References to Phase II refers to SBIR and STTR awards, not including Phase IIB.

OUTCOMES

Commercialization

At NIH, the priority for SBIR/STTR is to support the development and commercialization of technologies that will improve the nation's health. In contrast to DoD and NASA, it is not expected that SBIR/STTR technologies will be used by the agency itself. Sales are primarily made into the domestic private sector, although sales to other health-related government agencies are also quite substantial.

NIH SBIR/STTR companies also face a particular challenge, aside from the difficulties faced by all small companies as they seek to gain market traction for

[19]The committee previously sought to develop statistical comparisons with similar companies in similar sectors at similar stages of development, but these efforts were eventually abandoned as unworkable. See Appendix A for a discussion of this effort. A full description of the methodology employed for this survey and the resulting analysis is also provided in Appendix A.

[20]All comparisons to the 2005 survey are based on data from tables and analysis in National Research Council, *An Assessment of the Small Business Innovation Research Program at the National Institutes of Health*, Washington, DC: The National Academies Press, 2009, Chapter 4 and Appendix B.

[21]Phase IIB is an award made to some firms at the end of Phase II. It supports those working to complete clinical trials. A discussion of Phase IIB is included in Chapter 3 (Program Initiatives).

their products. Survey responses indicate that nearly one-half of respondent companies anticipated that they would need to successfully complete FDA clinical trials before their product could be marketed. Academic papers indicate that about 8 percent of products that file for clinical trials make it to the end of Phase 3, so these challenges are real and pervasive for these companies.

That said, SBIR/STTR program participants at NIH are—as at other agencies—small for-profit companies, and they must proceed in ways that do in the end provide a sustainable path forward for the business.

Defining "Commercialization"

Several important conceptual challenges emerge when seeking to define "commercialization" for the purposes of the SBIR/STTR programs. Like many apparently simple concepts, commercialization becomes progressively more difficult and complex as it is subjected to further scrutiny. For example:

- Should commercialization include just sales or other kinds of revenue, such as licensing fees and funding for further development?
- Should commercialization include only certain kinds of sales—excluding for example sales to government agencies?
- What is the appropriate benchmark for sales? Is it any sales whatsoever, sufficient sales to cover the costs of awards, sales that lead to breaking even on a project, or sales that reflect a commercial level of success and viability? The last at least would likely be different for each project in each company.
- Should commercialization include sales by licensees, which may be many multiples of the revenues provided to, but are largely reported by, the licensors?

For the purposes of this study, we deployed a broad net to capture a range of potentially useful data. Once acquired, these data can be analyzed in a variety of ways to provide multiple insights into this complex topic.[22]

Sales and Revenues

Perhaps the single most used metric for assessing SBIR-type programs is revenue or licensing fees. Although we have already cautioned against overuse of this metric—warnings that are applicable to the wide range of metrics adopted for use in the current assessment—sales and revenues are still important considerations.[23]

[22]For an overview of the commercialization metrics and survey used in this study, see Appendix A.

[23]Similar warnings can be found in the 2009 report on the NIH SBIR program—National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 2009, 81.

Reaching the market. The first survey question in this area concerns reaching the market: Did the project generate any sales, and if not, are sales expected (a necessary question given the long cycle time of some projects)? Responses are summarized in Table 5-7. About one-half of respondents reported some sales or licensing revenues, and a further one-quarter expected sales in the future. The percentage reporting sales to date was lower than for the 2005 Survey (57 percent). Those expecting sales in the future increased from 19 percent for the 2005 Survey to 25 percent (SBIR-only) for the 2014 Survey.

The 2005 Survey of SBIR companies found that 24 percent of respondent companies had no sales and expected none, 19 percent had no sales but expected sales in the future, and 57 percent had already generated sales from the surveyed project.[24]

Amount of sales and licensing revenues. Simply identifying the percentage of projects reaching the market is an important metric, but it is not sufficient. In addition, it is important to understand the distribution of sales. The survey also asked those who reported some sales of the technology developed for the surveyed project to report the amount of sales, segregated by tiers. These data are summarized in Table 5-8. Overall, 26 percent of SBIR respondents reported sales of at least $1 million.

Markets by sector. Because NIH is not itself a significant market, it is not surprising that most sales are made to the domestic private sector. Furthermore, because health care products are increasingly a global business, it is also not surprising that export markets accounted for 17 percent of sales (see Table 5-9). These figures are very similar to those for the 2005 Survey.[25]

Employment

As with prior surveys, the 2014 Survey asked respondents both about the size of the company at the time of the award and the current size, in terms of number of employees. At the time of the award, 60 percent of responding companies had fewer than 10 employees. The median was 7 employees (see Table 5-10).

The survey also asked about current employment (as of 2014). Respondents reported that the median size of companies was still 7 employees, but that the mean size had grown significantly, from 19 to 88. Among the 7 percent of

[24]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 249.

[25]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 251.

TABLE 5-7 NIH SBIR/STTR Sales Outcomes

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
No sales to date	50.8	50.9	50.5	48.3
No sales to date nor are sales expected	25.9	25.9	25.8	10.3
No sales to date, but sales are expected	24.9	25.0	24.7	37.9
Any sales to date	49.2	49.1	49.5	51.7
Sales of product(s)	38.7	38.3	40.9	48.3
Sales of process(es)	2.8	2.8	3.2	
Sales of services(s)	17.4	17.7	16.1	17.2
Other sales (e.g. rights to technology, licensing, etc.)	9.1	8.4	12.9	6.9
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	602	509	93	29

NOTE: Respondents could report multiple types of sales for a single project, so the types of sales do not sum to "Any sales to date."
SOURCE: 2014 Survey, Question 32.

TABLE 5-8 Distribution of Total Sales Dollars, by Range

	STTR	SBIR	Phase IIB
Under $100,000	34.1	40.6	23.1
$100,000-$499,999	22.0	22.6	23.1
$500,000-$999,999	17.1	10.4	
$1,000,000-$4,999,999	14.6	14.2	23.1
$5,000,000-$9,999,999		6.1	7.7
$10,000,000-$19,999,999	2.4	2.3	
$20,000,000-$49,999,999	2.4	1.9	7.7
$50,000,000 or more		1.9	15.4
BASE: ANY SALES RESULTING FROM THE PROJECT	38	212	13

NOTE: See Pie Chart in Figure 5-2.
SOURCE: 2014 Survey, Question 34.

TABLE 5-9 Markets by Sector

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Domestic private sector	57.5	57.1	60.1	49.2
Export Markets	16.9	16.3	20.5	34.6
DoD/NASA/Primes	2.0	2.0	1.4	0.0
NIH	0.9	0.7	1.8	0.4
Other federal agencies	3.4	3.4	3.1	12.0
State or local governments	4.2	4.8	0.7	2.3
Other (Specify below, if applicable)	15.2	15.6	12.4	1.5
BASE: ANY SALES RESULTING FROM THE PROJECT	265	228	37	13

SOURCE: 2014 Survey, Question 36.

TABLE 5-10 Number of Employees at Time of Award

	Percentage of Companies Responding			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	0.5	0.3	1.6	
1	3.7	3.1	6.8	
2	7.1	6.1	12.5	5.7
3 or 4	19.7	19.5	20.8	
5 to 9	29	27.7	35.9	35.4
10 to 19	19.2	20.1	14.1	24.9
20 to 49	12.5	14	4.4	12.4
50 to 99	3.6	3.7	3.1	8.6
100 or more	4.8	5.5	0.8	12.9
Mean	19	21	10	33
Median	7	8	5	12
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	418	354	64	17

NOTE: Answers from individual respondents were aggregated and averaged for each company, and company responses are reported above.
SOURCE: 2014 Survey, Question 14.1.

TABLE 5-11 Employment at Time of Survey

	Percentage of Companies Responding			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	13.3	12.5	17.3	14.4
1	5.6	5.8	4.8	
2	7.0	6.2	11.7	5.7
3 or 4	14.2	14.3	13.7	2.9
5 to 9	19.7	19.0	23.6	20.1
10 to 19	18.0	18.1	17.2	18.2
20 to 49	11.9	12.7	7.7	17.2
50 to 99	2.8	3.3		5.7
100 or more	7.4	8.0	4.0	15.8
Mean	88	101	16	47
Median	7	7	5	16
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	410	347	63	17

NOTE: Answers from individual respondents were aggregated and averaged for each company, and company responses are reported above.
SOURCE: 2014 Survey, Question 14.2.

firms now reporting at least 100 employees, some had grown substantially (see Table 5-11).[26]

Further Investment

The ability of SBIR/STTR projects and companies to attract further investment has traditionally been a defining metric for SBIR/STTR outcomes.[27] There has also been interest in the sources of additional funding for high-tech innovation. The United States has historically been a leader in venture capital and angel investment.

[26]Of related interest, see Link and Scott, Employment Growth from Public Support of Innovation in Small Firms (W.E. Upjohn Institute for Employment Research, 2012). The authors use the 2005 data and compare actual employment growth with a prediction of what would have been expected to happen without the SBIR award. Interestingly, comparing the counterfactual gains from the SBIR program across agencies, they find that the gap between the actual employment and the counterfactual predicted employment (if the SBIR award had not been received) is greatest for the NIH awards.

[27]See National Research Council, *An Assessment of the SBIR Program*, Washington, DC: The National Academies Press, 2008.

TABLE 5-12 Additional Funding by Phase and Amount

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
None ($0)	17.8	19	11.2	3.4
Under $100,000	24.3	23.2	30.3	6.9
$100,000-$499,999	21.7	21.5	22.5	13.8
$500,000-$999,999	11.7	11.4	13.5	20.7
$1,000,000-$4,999,999	15.7	15.5	16.9	31
$5,000,000-$9,999,999	3.5	3.7	2.2	10.3
$10,000,000-$19,999,999	2.3	2.5	1.1	10.3
$20,000,000-$49,999,999	2.3	2.3	2.2	3.4
$50,000,000 or more	0.7	0.8	0	0
Mean	2,560	2,698	1,813	4,666
Median	300	300	300	3,000
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	572	483	89	29

NOTE: Table includes 17.8 percent of respondents who answered in the positive to Q29 (any sales?), but then reported zero sales.
SOURCE: 2014 Survey, Question 30.

Overall, about 80 percent of respondents indicated that their company had received additional investment in the technology related to the surveyed project.[28] As with prior surveys, most respondents received small amounts of additional funding. Table 5-12 shows responses related to additional funding. Three-quarters of all NIH respondents reported receipt of less than $1 million. One percent reported receiving $50 million or more in additional funding; 9 percent reported receiving $5 million or more. Given that the cost of Phase 3 clinical trials has recently been estimated at $26,000 per patient[29] and that can require the enrollment of more than 1,000 patients,[30] the funding challenge for SBIR/STTR companies is immediately apparent.

Of those projects that received additional funding, 44 percent reported funding from U.S. private-sector sources, 25 percent from non-SBIR/STTR federal sources, and 24 percent from other external sources. Seventy percent reported additional funding from their own company, including 26 percent who reported

[28]2014 Survey, Question 30. N=572.
[29]Hess, "Clinical Operations."
[30]Roy, "Stifling New Cures."

personal investments. Overall, 10 percent and 14 percent of those who received additional funding identified U.S. venture capital and U.S. angel and other private equity investors as the sources, respectively. Twenty-one percent and 4 percent reported strategic investments from U.S. partners and foreign partners, respectively (see Table 5-13).

TABLE 5-13 Distribution of All Reported Additional Investment Funding by Source of Funds

	Percentage of Responses			
Source of Funding	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Non-SBIR/STTR Federal Funds	25.2	21.9	41.4	28.6
Private Investment: U.S. Sources	44.2	45.7	36.8	67.9
Venture capital (VC)	9.5	9.5	9.2	21.4
U.S. angel funding or other private equity investment (not VC)	13.6	14.5	9.2	14.3
Friends and family	11.4	11.4	11.5	10.7
Strategic investors/partners	20.5	21	18.4	17.9
Other sources	9.1	9.3	8.0	17.9
Foreign Investment	5.5	5.5	5.7	
Financial investors	2.4	2.4	2.3	
Strategic investors/partners	3.7	3.3	5.7	
Other External Sources	23.9	19.8	43.7	21.4
State or local governments	15.8	14.8	20.7	17.9
Research institutions (such as colleges, universities or medical centers)	9.3	5.5	27.6	3.6
Foundations	3.6	2.9	6.9	
Internal Sources	70.0	74.0	50.6	71.4
Your own company (including money you have borrowed)	58.2	62.4	37.9	57.1
Personal funds	26.0	27.4	19.5	21.4
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	507	420	87	28

SOURCE: 2014 Survey, Question 31.

TABLE 5-14 Company-Level Changes

	Percentage of Responding Companies			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Entered into strategic partnership with major industry player	34.9	35.8	30.7	35.4
Established one or more spin-off companies	20.8	22.2	13.3	18.2
Been acquired by/merged with another firm	16.0	14.4	24.1	8.6
Planning to make an initial public offering in the next 3 years	3.6	4.0	1.4	5.7
Made an initial public offering	2.6	2.5	3.5	2.9
None of the above	43.3	42.8	45.9	38.8
BASE: TOTAL COMPANIES ANSWERING QUESTION	436	365	71	17

NOTE: Responses do not sum to 100 percent because respondents could select more than one answer.
SOURCE: 2014 Survey, Question 11.

Company-Level Commercialization Through Mergers and Acquisitions

SBIR/STTR firms often commercialize their technology through mergers or other company-level activities. Greater than 43 percent of responding companies indicated that they had not been acquired, had not implemented or planned an initial public offering (IPO), and had not established a spin-off (see Table 5-14). Conversely, greater than one-third had entered into a strategic partnership with a major industry player, 21 percent had established one or more spin-off companies, and 16 percent had been acquired by or merged with another firm.

Commercialization Training and Marketing

NIH has provided commercialization training for SBIR/STTR awardees for 10 years, primarily through an arrangement with a third-party provider (see Chapter 3, Program Initiatives). Thirty-nine percent of SBIR respondents and 24 percent of STTR respondents engaged in commercialization training at NIH.[31] More than 38 percent considered the training to be valuable or extremely valuable (see Table 5-15). Conversely, about one-quarter of participants thought it was not very valuable or not at all valuable. Phase IIB respondents tended to see the training as less valuable, perhaps because they were already farther down the

[31]2014 Survey, Question 49. N=570.

TABLE 5-15 Value of Commercialization Training

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Extremely or very valuable	38.2	37.4	45.0	26.7
Extremely valuable	11.1	10.2	20.0	6.7
Very valuable	27.1	27.3	25.0	20.0
Somewhat valuable	36.2	36.9	30.0	26.7
Not very valuable	20.3	20.9	15.0	40.0
Not at all valuable	5.3	4.8	10.0	6.7
BASE: ACCEPTED COMMERCIALIZATION ASSISTANCE IN CONNECTION WITH AWARD	207	187	20	15

SOURCE: 2014 Survey, Question 51.

commercialization path. STTR recipients saw the training as slightly more valuable than did SBIR recipients, perhaps reflecting that they had less information about commercial strategy to begin with given their strong academic roots.

However, about 27 percent of respondents indicated that they were likely to use the existing agency commercialization program in the future. Forty-nine percent expressed a preference to use the funding for their own marketing efforts, as permitted under the reauthorization legislation for SBIR/STTR (see Table 5-16). This is money that the grantees must use for paying for the training.

One question added to the 2014 Survey asked whether the company has at least one full-time staff person for marketing. This question provides another metric of the extent to which the company has focused on marketing. Forty-three percent of respondant companies reported that their company had at least one full-time marketing staff.[32]

Conclusions: Commercialization at the Company Level

Evidence from the 2014 Survey provides useful insight into the commercialization record of SBIR/STTR companies at NIH, on a number of dimensions. The data confirm that a substantial percentage of projects do indeed commercialize through sales of products or services and/or through the receipt of additional development funding.

[32]2014 Survey, Question 13.

TABLE 5-16 Use of Different Commercialization Support

	Percentage of Respondents			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Continue to use the agency's program	26.8	26.6	28.1	11.1
Use the funding for your own marketing consultant	49.0	47.7	56.2	40.7
Neither	24.2	25.7	15.7	48.1
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	559	470	89	27

SOURCE: 2014 Survey, Question 52.

Forty-nine percent of respondents indicated that their company had already recorded sales of products or services derived from the awarded project. A further one-quarter of respondents were expecting sales in the future. Given the relatively short time between the award date for some of these awards and the survey date, and the long time-to-market cycle for products with regulatory requirements to meet, these expectations are not unreasonable. NIH does provide independent data against which the validity of the survey responses can be cross-checked.

Overall, the scale of commercialization is limited. About three-quarters of respondents with project-related revenues indicated that these revenues totaled $1 million or less.[33] About 10 projects reported sales greater than $50 million and another 13 or 14 reported sales between $10 million and $50 million.

Additional investment is another important metric for commercialization. Many Phase II projects are not yet ready for the marketplace at the end of the award period, especially given the need for regulatory compliance.[34] Three-quarters of all respondents reported receiving less than $1 million in additional funding. One percent reported receiving $50 million or more in additional funding; 9 percent reported receiving $5 million or more. The source of additional funding varied. About one-quarter of respondents mentioned non-SBIR/STTR federal funding, while 44 percent mentioned U.S. private-sector funding (including 10 percent for venture capital and 14 percent for angel investments). U.S. strategic investors were also important (21 percent).

In conclusion, these data support our view that SBIR/STTR funding is associated with outcomes that meet congressional mandates for commercialization. In

[33]See Figure 3-9.

[34]It is important to bear in mind that sales could continue to accumulate for many years to come, i.e., the problem may be in the assessment time frame rather than the actual return on investment.

the future, better data, especially collected by the agency, would allow for a more definitive conclusion and also more detailed understanding of the links between agency programs and initiatives and outcomes.

Knowledge Effects

One of the four congressionally mandated objectives for the SBIR/STTR programs is to "stimulate technological innovation," which is often equated with patenting activity. However, in the context of small business, this standard metric of innovation does not capture the entire story: patenting is important, but it is also expensive, and SBIR/STTR funds cannot legally be used for this purpose. During case study discussions (for this and previous reports by the Academies on SBIR), company executives explained that patents have their limitations and are expensive. As a result, they prefer to keep their technology secret or to rely on first-mover advantages and other market-based leverage to defend their technologies.

However, standard metrics provide at least a starting point for quantitative analysis. Consequently, the survey addressed several intellectual property (IP)-related metrics: patents, trademarks, copyrights, and peer-reviewed papers.[35]

Patents

Patents are to some degree the life blood of high-tech firms. Overall, about two-thirds of companies (and more than 80 percent of Phase IIB recipients) reported the award at least one patent related to any SBIR/STTR-funded technology; 13 percent reported at least 10 related patents (see Table 5-17).

The survey also asked questions about IP related to the surveyed award (Table 5-18). Greater than one-half of respondents reported receiving at least one patent related to the surveyed technology. Nine percent reported receiving 5 or more related patents, and 4 percent reported 10 or more. STTR respondents reported similar numbers. The share of respondents reporting at least one patent is slightly down from the 2005 survey (57 percent).[36]

[35]The values of these knowledge repositories vary. Any unique item, painting, photo, or music score can be copy-written for a modest fee. Trademarks include more processing, as registered trademarks need to be unique in their field so as not to impinge on another prior trademark's domain. A patent can be valuable IP, and patents have been correlated with prosperity. Refereed journal articles as a metric are not as highly valued outside of academia as inside, although company executives state in meetings that publications help to attract and keep high-quality staff and also provide additional validation for—and publicity about—their technology.

[36]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 265.

TABLE 5-17 Number of Patents Related to All Company SBIR/STTR Awards

	Percentage of Companies Responding			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	33.6	30.8	48.8	18.3
1	14.0	16.0	3.2	12.2
2	10.2	9.1	16.2	
3	8.3	8.6	6.9	25.4
4	5.8	5.0	10.3	9.1
5 to 9	15.1	16.2	9.0	10.7
10 or more	12.9	14.2	5.6	24.4
1 or more	66.4	69.2	51.2	81.7
Mean	4.74	5.22	2.11	5.40
Median	2.00	2.00	1.00	3.00
BASE: TOTAL COMPANIES ANSWERING QUESTION	409	347	63	16

SOURCE: 2014 Survey, Question 11.

TABLE 5-18 Patents Awarded Related to Surveyed Project

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	47.0	47.2	46.3	25.9
1	23.7	23.0	27.5	22.2
2	12.0	12.1	11.3	7.4
3 or 4	8.2	7.6	11.3	22.2
5 to 9	5.2	5.9	1.3	14.8
10 or more	4.0	4.3	2.5	7.4
1 or more	53	52.8	53.8	74.1
Mean	1.63	1.71	1.23	3.11
Median	1	1	1	2
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	502	422	80	27

SOURCE: 2014 Survey, Question 38.1.

Copyrights and Trademarks

Regarding copyrights and trademarks, about one-quarter of respondents reported receiving a trademark related to the surveyed project, while less than 10 percent reported receiving a copyright.[37]

Peer-Reviewed Publications

Publications in peer-reviewed journals and conference proceedings are a standard method for disseminating scientific knowledge. As with the first-round assessment by the Academies, several case study respondents noted that publication in peer-reviewed journals was an essential part of the firm's work.[38]

For the purposes of this assessment, peer-reviewed publications are important for two reasons:

- They validate the quality of the research being conducted with program funds.
- They are themselves the primary mechanism through which knowledge is transmitted within the scientific community.

The survey therefore asked about peer-reviewed publications (Table 5-19). Eighty percent of SBIR respondents and 85 percent of STTR respondents indicated that an author at the surveyed company had published at least one related scientific paper. Overall 42 percent reported publishing three or more related papers. The median number of publications for Phase IIB respondents was five.

Links to Universities

The survey asked a number of questions about the use of university staff and facilities on the surveyed project. Overall, about two-thirds of SBIR respondents and essentially all STTR respondents reported a university connection of some kind.

There were substantial differences between SBIR and STTR with regard to the kind of university linkage (Box 5-2). Seventy-eight percent of STTR respondents and 6 percent of SBIR respondents reported that the PI was a university faculty member. STTR respondents were also more likely to report that technology was licensed from the research institution (27 percent vs. 14 percent) and that the technology was originally developed at the research institution by a project team member (37 percent vs. 17 percent) (see Table 5-20).

[37]2014 Survey, Question 38.2 and Question 38.3.

[38]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, Appendix D.

TABLE 5-19 Peer-reviewed Scientific Publications Related to the Surveyed Project

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	20.1	21.1	14.8	16.7
1	19.7	20.8	13.6	4.2
2	17.9	17.6	19.8	12.5
3 or 4	17.1	16.4	21.0	8.3
5 to 9	14.2	14.1	14.8	37.5
10 or more	11.0	10.1	16.0	20.8
1 or more	79.9	78.9	85.2	83.3
Mean	5.7	5.6	6.2	17.8
Median	2	2	3	5
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	508	427	81	24

SOURCE: 2014 Survey, Question 38.4.1.

Respondents were also asked to identify the universities with which they worked in various capacities on this project. Although the type of help varied widely, some universities were mentioned by a number of respondents. Overall, 255 different research institutions were identified from 488 projects. Those mentioned by four or more respondents are listed below in Table 5-21 (see Appendix D for the complete list of university mentions). Many of the names on this list are large state universities, a number of which have in recent years focused on technology transition as well as basic research, although two of the top three universities mentioned are private universities. Although far from a perfect metric, we believe these data provide a preliminary indication of the connections between specific universities, university systems, and the NIH SBIR/STTR programs.

Finally, for 85 percent of companies in the sample, at least one founder had an academic background (see Table 5-22) and for 60 percent of companies at least one founder was most recently employed at a research institution (see Table 5-23).

Conclusions: Knowledge Effects

What emerges from these data is a picture of companies that are dynamic centers of technological innovation, a considerable amount of which is protected

BOX 5-2
Survey Response Rate and Non-Respondent Bias

As noted in the introduction to this report, and described in detail in Appendix A, the committee recognizes the limitations of the survey effort underlying the data presented in this chapter. The 2014 Survey was sent to every principal investigator (PI) who received a Phase II award from NIH during fiscal years 2001-2010. PIs were asked to complete a maximum of two questionnaires. The preliminary population prior to contact was 3,375. Of these, 1,723 PIs could not be contacted at the SBIR or STTR company listed in the NIH awards database. The remaining 1,652 awards constitute the effective population of the survey. Of those 1,652 potential awards, there were 726 responses. This corresponds to a response rate of 21.5 percent of the entire set of awards and a 43.9 percent response rate from the effective population.

The committee acknowledges that because no information was gathered from non-respondents, the data are likely to be biased toward surviving firms. At the same time, the committee notes that successful PIs who left the original firm to start a new venture and successful firms that merged or were bought out by other firms are also excluded from the results. The committee suggests that, where feasible, future assessments of the SBIR program include comparisons of non-awardees, such as in matched samples (Azouley et al., 2014) or regression discontinuity analysis (Howell, 2015).[a] In addition, future assessments should document the root cause of non-responsiveness. For example, determining whether the company is still in business even if the PI is no longer with the firm could provide useful evidence about the effectiveness of the SBIR award.

[a]Azoulay, Pierre, Toby Stuart, and Yanbo Wang, "Matthew: Effect or Fable?" *Management Science,* 60(1), pp. 92-109, 2014. Howell, Sabrina, "DOE SBIR Evaluation: Impact of Small Grants on Subsequent Venture Capital Investment, Patenting, and Achieving Revenue." Paper presented at the National Academy of Sciences, Engineering, and Medicine Workshop on the Economics of Entrepreneurship, June 29, 2015.

through the patent system. About two-thirds of companies reported receipt of at least one patent based on their work under SBIR/STTR contracts, while 53 percent reported receipt of at least one patent related to the surveyed project only specifically.

SBIR/STTR companies participate at a high level in the standard form of technical knowledge dissemination: publishing in peer-reviewed journals. Eighty percent of respondents reported that their company published at least one article based on the SBIR-funded work, and more than 40 percent reported publication of more than three such papers.

Finally, some SBIR/STTR companies are closely connected to the universities. About 70 percent of respondents reported a university connection

TABLE 5-20 Links to Universities

	Percentage of Responses			
	NIH Survey	SBIR Awardees	STTR Awardees	Phase IIB Awardees
The PI for this project was at the time of the project an RI faculty member	17.4	6.1	77.8	3.6
The PI for this project was at the time of the project an RI adjunct faculty member	10.4	12.1	1.1	17.9
Faculty member(s) or adjunct faculty member(s) worked on this project in a role other than PI	38.7	38.2	41.1	35.7
Graduate students worked on this project	22.3	21.3	27.8	21.4
The technology for this project was licensed from an RI	16.0	14.0	26.7	17.9
The technology for this project was originally developed at an RI by one of the participants in this project	20.2	17.1	36.7	17.9
An RI was a subcontractor on this project	37.4	35.5	47.8	53.6
None of the above	29.7	35.1	1.1	32.1
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	569	479	90	28

NOTE: Responses do not sum to 100 percent because respondents could select more than one answer.
SOURCE: 2014 Survey, Question 71.

on the surveyed project, across a number of different kinds of linkages, and 22 universities were specifically mentioned as playing a role in at least five reported projects. This suggests that SBIR and STTR may in some cases play a potentially important role in supporting the practical implementation of university research.

SBIR/STTR AND COMPANIES

SBIR/STTR programs have a range of effects on companies, which affect their ability to operate and grow. Data about companies can help to define the technological space in which the SBIR/STTR programs operate. In addition, a review of the SBIR/STTR share of overall company activities can provide insights into the degree of dependence on SBIR/STTR for individual companies.

TABLE 5-21 University Participants Mentioned by Four or More Respondents

Research Institution	Number of Mentions
University of Michigan	14
Duke University	10
Johns Hopkins University	8
Massachusetts Institute of Technology	7
University of North Carolina Chapel Hill	7
University of Pittsburgh	7
University of Virginia	7
Indiana University	6
Pennsylvania State University	6
University of Florida	6
University of Illinois Chicago	6
University of Massachusetts Medical School	6
University of Utah	6
Vanderbilt University	6
Children's Hospital Boston	5
MD Anderson Cancer Center	5
Medical University of South Carolina	5
Oregon Health & Science University	5
Texas A&M University	5
UC San Francisco	5
University of Arizona	5
University of Kentucky	5
Case Western Reserve University	4
Cornell University	4
Dartmouth College	4
Harvard University	4
Mayo Clinic	4
University of California, Berkeley	4
University of Connecticut	4
University of Louisville	4
University of Minnesota	4
University of New Mexico	4
University of Pennsylvania	4
Washington University of St Louis	4

SOURCE: 2014 Survey, Question 60.

TABLE 5-22 Number of Academic Founders

	Percentage of Company Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	14.7	14.3	16.8	18.2
1	42.3	44.7	30.5	31.1
2	26.7	26.3	28.9	31.6
3	10.2	9.1	15.7	7.7
4	3.7	3.4	5.4	11.5
5 or more	2.3	2.2	2.7	
Mean	1.54	1.5	1.76	1.63
Median	1	1	2	2
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	445	370	74	17

SOURCE: 2014 Survey, Question 5.4.

TABLE 5-23 Previous Employment of Founders

	Percentage of Company Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Research institution	59.4	56.1	75.4	78.9
Other private company	52.7	54.6	43.1	41.1
Government	4.7	4.8	4.6	5.7
FFRDCs or National Labs				
Other	10.3	11.5	4.0	5.7
BASE: TOTAL COMPANIES ANSWERING QUESTION	453	375	77	17

NOTE: Responses do not sum to 100 percent because respondents could select more than one answer.
SOURCE: 2014 Survey, Question 6.

Impact on Company Formation

SBIR/STTR can have a profoundly catalytic impact on company formation. Seventeen percent of respondent companies were founded because of the SBIR/STTR programs, and a further 27 percent were formed in part because of the program (see Table 5-24).

TABLE 5-24 SBIR/STTR Impact on Company Formation

	Percentage of Responding Companies			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Yes	17.3	17.9	14.2	13.4
In part	26.8	27.1	25.4	37.3
No	55.9	54.9	60.3	49.3
BASE: TOTAL COMPANIES ANSWERING QUESTION	464	382	82	17

SOURCE: 2014 Survey, Question 8.

SBIR/STTR Share of R&D Effort

The survey asked respondents to estimate how much of their company's total R&D effort—defined as man-hours of work for scientists and engineers—was devoted to SBIR/STTR-funded projects. Overall, 42 percent of SBIR/STTR respondents indicated that the programs funded 10 percent or less of total effort, while 34 percent indicated that they funded greater than one-half (see Table 5-25).

These data correspond fairly closely to responses from Question 9, which asked what percentage of company revenues during its current year were from SBIR/STTR awards. Thirty-four percent of companies reported zero SBIR/STTR revenues, while 27 percent reported receiving greater than one-half of revenues from SBIR/STTR. Three percent were entirely dependent on SBIR/STTR (see Table 5-26).

Prior Use of the SBIR/STTR Programs

Although a more linear interpretation of the innovation process would imply that ideas are tested in Phase I, prototyped in Phase II, and commercialized in Phase III, actual practice involves multiple iterations, or projects that must restart with an earlier phase, or multiple efforts needed to meet specific problems.

The survey asked respondents to indicate how many of the prior SBIR/STTR Phase I awards received from the NIH and other agencies were related to the project and technology being surveyed. Table 5-27 summarizes the responses. Less than 20 percent of projects received no other related SBIR/STTR awards. Greater than 20 percent received at least three additional related awards. These data strongly support the view that innovative products emerge from clusters of activity, rather than from simple straight line development from Phase I to Phase II to commercialization.

TABLE 5-25 Percentage of R&D Effort Funded by SBIR/STTR

	Percentage of Company Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0%	31.5	32.9	24.4	35.4
1-10%	10.5	10.5	10.4	25.8
11-25%	12.8	13.1	11.2	1.0
26-50%	11.5	11.0	14.2	1.4
51-75%	14.7	14.1	18.1	19.1
76-100%	18.9	18.4	21.7	17.2
Mean	33	32	38	29
Median	18	18	38	5
BASE: TOTAL COMPANIES ANSWERING QUESTION	421	355	66	17

SOURCE: 2014 Survey, Question 10.

TABLE 5-26 Percentage of Company Revenues from SBIR/STTR

	Percentage of Responding Companies			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0%	34.0	35.8	24.4	46.9
1-10%	13.9	14.0	13.2	28.2
11-25%	12.2	11.3	16.5	2.9
26-50%	12.8	13.1	10.9	
51-75%	9.9	8.7	16.0	7.7
76-99%	14.0	14.4	12.2	11.5
100%	3.3	2.6	6.9	2.9
Mean	29.0	28.0	35.0	20.0
Median	18	18	18	5
BASE: TOTAL COMPANIES ANSWERING QUESTION	409	344	66	17

SOURCE: 2014 Survey, Question 9.

TABLE 5-27 Prior SBIR/STTR or STTR Phase I Awards Related to the Surveyed Project

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	18.1	18.4	16.3	11.1
1	43.9	44.0	43.0	44.4
2	16.5	15.4	22.1	22.2
3 or 4	13.9	14.3	11.6	22.2
5 to 9	5.5	5.6	4.7	
10 or more	2.2	2.2	2.3	
1 or more	81.9	81.6	83.7	88.9
Mean	1.92	1.93	1.83	1.59
Median	1	1	1	1
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	547	461	86	27

SOURCE: 2014 Survey, Question 39.1.

Turning to prior Phase II awards, about three-quarters of respondents reported at least one related Phase II award, while 11 percent reported at least three (see Table 5-28).

Long-Term Effects on the Recipient Company

Although SBIR/STTR awards have direct effects on specific projects, they can also have a longer term effect on the trajectory of company development. The survey asked respondents about the impacts directly. The results are summarized in Table 5-29.

These results indicate an overwhelmingly positive impact. Overall, 97 percent of SBIR/STTR respondents reported a positive effect, and 62 percent reported a transformative effect. Two respondents out of 570 reported negative effects.

Respondents were also asked to describe these effects in their own words. Key aspects of their comments are reported below, focused on the ways in which SBIR/STTR and STTR made a profound difference to the company in the long term.

TABLE 5-28 Prior SBIR/STTR or STTR Phase II Awards Related to the Surveyed Project

	Percent of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
0	23.9	25.0	17.9	11.5
1	46.0	43.9	57.1	38.5
2	18.9	19.8	14.3	34.6
3 or 4	8.1	8.3	7.1	15.4
5 to 9	1.9	1.8	2.4	
10 or more	1.1	1.1	1.2	
1 or more	76.1	75.0	82.1	88.5
Mean	1.34	1.35	1.32	1.54
Median	1	1	1	1.5
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	528	444	84	26

SOURCE: 2014 Survey, Question 39.2.

TABLE 5-29 Long-Term Effects on Recipient Companies

	Percentage of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Positive, highly positive, or transformative effect	96.5	96.5	96.7	92.9
Highly positive or transformative effect	61.8	62.7	56.7	71.4
Positive effect	34.7	33.8	40.0	21.4
No effect	3.2	3.1	3.3	7.1
Negative, highly negative, or disastrous effect	0.4	0.4		
Negative effect	0.2	0.2		
Highly negative or disastrous effect	0.2	0.2		
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	570	480	90	28

SOURCE: 2014 Survey, Question 57.

Key Aspects of SBIR-Driven Transformation

It is not easy to summarize the numerous ways in which SBIR/STTR awards from NIH helped to transform recipient companies. What follows is therefore a limited list of impacts.

- Supported company formation
- Provided first dollars
- Funded areas where venture capital and other funders were not interested
- Supported development of critical company infrastructure
- Opened doors to potential partners
- Helped address niche markets too small for major players/funders
- Funded technology development
- Enabled projects with high levels of technical risk and high potential return
- Supported adaptation of technologies to new uses, markets, and industry sectors
- Funded development of core technology
- Diversified expertise, allowed hiring of specialists
- Gave companies immediate credibility
- Funded researchers to enter business full time
- Transformed company culture to become more market driven
- Created new companies and kept companies in business (that would not exist without SBIR/STTR funding)
- Helped increase the company's knowledge base applied to later projects
- Expanded the scope and scale of R&D capabilities
- Supported technology development that led to spin-off companies

From these responses it is clear that small innovative companies are highly sensitive to the impact of outside factors. The sudden withdrawal of a sponsor can crush a company; a single contract can provide funding for 2 or 3 years of growth. Above all, these small companies are highly path dependent: what happens to them at a given moment can dramatically affect long-term outcomes.

In the end, SBIR/STTR can be viewed in many cases as a positive outside factor: one that provides funding, validation, and often market access not otherwise available. Even though it seems tenuous to link one award to the eventual success of a large corporation, that is, in fact, how some very small companies grow into large ones. The evidence from survey respondents suggests that this positive jolt is not an uncommon effect of these awards.

Other Company-Level Information

The survey asked about other potentially significant aspects of the company. Previous analyses of SBIR/STTR did not address a potentially important

intervening variable: industry sector. It is quite possible that commercialization outcomes may be affected by the average cycle time of product development in different sectors. For example, product cycle time is much shorter in software than in materials or medical devices. Overall, 92.3 percent of NIH SBIR/STTR survey recipients worked in the medical technology sector. Table 5-30 shows the distribution of responses by phase and sector.

This question was designed to provide an approximate map of activities by sector. There is considerable overlap between some categories, and respondents would have substantial leeway to define sectors differently, so these finding should be viewed as highly preliminary. A few key points emerge:

- Almost all awards were to companies primarily working in medical technology.
- About one-third of respondent companies were working in medical devices and biotechnology.
- About one-quarter were working on research tools.
- A further 17 percent were working in pharmaceuticals, with the remainder spread across medical information technology and education.
- Responses show that there are no substantial differences between SBIR and STTR respondents.

TABLE 5-30 Distribution of Responses by Sector Phase

	Percent of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Aerospace and Defense	2.6	2.9	1.1	6.9
Aerospace	0.2	0.2		
Defense-specific products and services	2.6	2.9	1.1	6.9
Energy and the Environment	2.5	2.9		
Renewable energy production (solar, wind, geothermal, bio-energy, wave)	0.2	0.2		
Energy storage and distribution	0.7	0.8		
Energy efficiency	0.3	0.4		
Other energy or environmental products and services	1.6	1.9		

continued

TABLE 5-30 Continued

	Percent of Responses			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Engineering	9.5	10.1	6.5	6.9
Engineering services	1.5	1.4	2.2	
Scientific instruments and measuring equipment	5.9	6.8	1.1	3.4
Robotics	1	0.8	2.2	
Sensors	4.1	4.9		3.4
Other engineering	0.3	0.2	1.1	
Information Technology	8.6	7.8	12.9	3.4
Computers and peripheral equipment	2.1	2.3	1.1	
Telecommunications equipment and services	0.2	0.2		
Business and productivity software	1	1	1.1	
Data processing and database software and services	3.1	2.7	5.4	3.4
Media products (including web-, print-, and wireless-delivered content)	3	2.9	3.2	
Other IT	1.3	1.2	2.2	
Materials (including nanotech for materials)	2.8	3.1	1.1	
Medical Technologies	92.3	91.5	96.8	100
Pharmaceuticals	17.3	17.3	17.2	24.1
Medical devices	32.9	34	26.9	58.6
Biotechnology (including therapeutic, diagnostic, combination)	32.9	32.4	35.5	34.5
Health IT (including mobile, big data, training modules)	7.4	7.2	8.6	3.4
Research tools	25.8	25.2	29	10.3
Education materials	8.9	8.5	10.8	
Other medical products and services	3.9	4.3	2.2	
Other (please specify)	6.9	8	1.1	3.4
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	608	515	93	29

NOTE: Responses do not sum to 100 percent because respondents could select more than one answer.
SOURCE: 2014 Survey, Question 20.

COUNTERFACTUALS

It is always difficult to tightly determine the impact of a given SBIR or STTR award. Many factors affect the success and failure of companies and projects, and it is difficult to determine whether a specific factor was a *necessary* condition for success. Worse still, the large number of factors and the multiple paths to success and failure mean that it is unusual to be able to state with confidence that a particular intervention—in this case an SBIR or STTR award—constitutes a *sufficient* condition for a project's success.

Still, it is worth considering what would have occurred absent SBIR or STTR funding from the perspective of those most likely to have detailed knowledge and understanding of their particular projects: the principal investigators. Accordingly, the 2014 Survey asked a series of questions focused on the likely effect of the absence of SBIR or STTR funding. Of course, asking recipients about the impact of funding raises possible conflicts of interest, so results should be interpreted with some caution. However, these awards are some years in the past now, and many recipients no longer apply for SBIR/STTR funding for a variety of reasons.

Project Go-Ahead Absent SBIR/STTR Funding

One approach has been to ask recipients for their own views on the impact of the program on their project or company. In particular, the survey asked Phase II recipients whether the project would have been undertaken absent SBIR/STTR funding and whether the scope and timing would have been affected. Responses are summarized in Table 5-31. About 7 percent of Phase II respondents indicated that the project probably or definitely would have proceeded without program funding. In contrast, almost 75 percent thought the project probably or definitely would not have proceeded absent program funding: 34 percent were definite and 41 percent thought it unlikely.

These data have interesting wider implications for debates about early-stage funding: they suggest a weakness in the "crowding out" hypothesis, because more than 70 percent of respondents (presumably those with the closest knowledge of funding prospects for the project) believed it unlikely that alternative funding would be found.

The small number of respondents (12) who believed the project might have proceeded without SBIR/STTR funding were asked additional questions about the impact on project scope, duration, and timelines. They responded as follows:

- Project scope would have been narrower (67 percent)
- Project would have been substantially delayed (75 percent)
- Project would have taken longer (75 percent)
- Project would not have hit necessary milestones (75 percent)

TABLE 5-31 Project Undertaken in the Absence of this SBIR/STTR Award

Project Go-Ahead Absent Award	Percentage of Responses
Yes	6.7
Definitely yes	1.7
Probably yes	5.0
Uncertain	19.0
Probably not	40.8
Definitely not	33.5
	100.0
N=	179

SOURCE: 2014 Survey, Question 24.

Overall, these views indicate that SBIR/STTR funding was important not only for the go/no-go decision but also for the eventual shape and indeed likely impact of the project. Delay in bringing projects to conclusion—and hence to the point of potential market entry—can have a disastrous effect, because the window for market entry can be a narrow one.

6

Participation of Women and Minorities

One of the four primary congressional objectives for the SBIR program is "to foster and encourage participation by minority and disadvantaged persons in technological innovation."[1] Given the explicit congressional objective, this chapter focuses more on the SBIR program; the STTR program does not have a similar explicit legislative objective, although we believe that greater inclusiveness is a concern for both programs. Within the SBIR program, this congressional objective has been taken to mean that the relevant metric for participation is company ownership, that is, that participation by women or minorities is equivalent to the participation of companies that are majority owned by women and/or minorities. In addition, "minority and disadvantaged persons" has been defined as those who are either women or are members of a specific disadvantaged group as defined and enumerated by the Small Business Administration (SBA).[2]

For the purposes of this analysis—and for determining whether agencies are meeting this objective—neither the metric nor the definition is adequate. In implementing the statute via its Policy Guidance, SBA has transformed "minority and disadvantaged persons" into "socially and economically disadvantaged small businesses (SDBs), and [. . .] women-owned small businesses (WOSBs)."[3] Although this formulation has become traditional among SBIR stakeholders, it has several unintentional consequences:

[1]P.L. 97–219, § 2, July 22, 1982, 96 Stat. 217.

[2]See http://www.sba.gov/content/who-are-socially-disadvantaged-individuals, accessed May 25, 2014.

[3]SBA SBIR/STTR Policy Directive, February 24, 2014, p. 3.

- It focuses attention entirely on company ownership, rather than the "participation" described in the statute. There are many different ways to participate in the program, and only one of them is through ownership.
- It replaces "minority and disadvantaged persons" with "socially and economically disadvantaged small businesses," which aligns the program not with the needs of women and minorities that were at the forefront of congressional objectives, but instead with SBA definitions of socially and economically disadvantaged.

These definitions include in particular Asian Americans. And although in some contexts Asian Americans have been disadvantaged, they are strongly represented in the world of high-tech companies where, for example, 13.4 percent of startups in Silicon Valley were owned by immigrants from India.[4] Wadhwa and colleagues found that between 2006 and 2012, 43 percent of Silicon Valley startups had at least one immigrant as a key founder and, of these, 33 percent had Indian founders and 8 percent Chinese founders.[5]

As a result of the definitions provided by SBA, all participation other than via ownership is disregarded by all agencies; no data are maintained by any agency on female and minority principal investigators (PIs), for example. And as we shall see, SBA definitions of "socially and economically disadvantaged" have the effect of largely obscuring agency performance in meeting congressional objectives to support the participation of African Americans, Hispanic Americans, and Native Americans.

AGENCY DATA

NIH has provided data on the participation of women and minorities (as defined by SBA). These data are discussed in detail in this chapter, following a short summary.

Woman-Owned Small Businesses

For woman-owned small businesses (WOSBs), the share of SBIR Phase I applications increased slightly during the study period to end at 12.8 percent in FY2014. Partly in consequence, the share of awards also increased during the study period (see Figure 6-1).

The growing share of awards to WOSBs is encouraging. However, the share must be considered in the context of the success rate (the rate at which applications turn into awards). For Phase I grants, WOSB applications had a lower suc-

[4]Vivek Wadhwa, AnnaLee Saxenian, F. Daniel Siciliano, *America's New Immigrant Entrepreneurs: Then and Now*, Kauffman Foundation, 2012.

[5]Ibid.

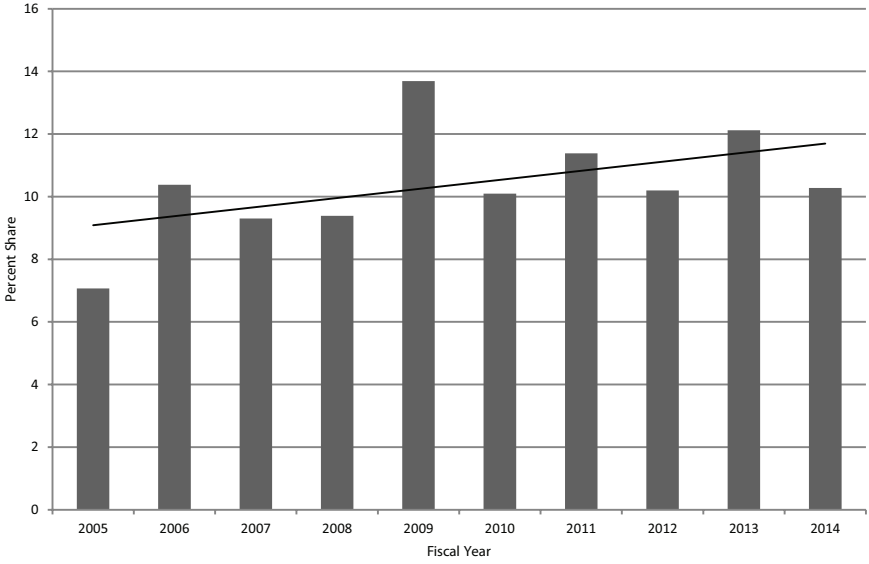

FIGURE 6-1 WOSB share of Phase I awards, FY2005-2014.
SOURCE: Based on NIH RePORTER database, Table 127.

cess rate in every year during the study period: overall, WOSBs accounted for 13 percent of applications and 10.3 percent of awards.

Although the amount of funding for an award is largely determined by the amount applied for by the company, it is also notable that WOSBs consistently receive smaller awards than non-WOSBs (see Annex). In FY2014, on average WOSB awards were $10,000 smaller than non-WOSB awards.

Patterns of Phase II awards are largely driven by Phase I because, prior to FY2015, only Phase I winners could apply for Phase II awards. Overall, WOSBs applied somewhat more frequently than might be expected: they accounted for 10.3 percent of Phase I SBIR awards and 13 percent of Phase II applications.

As with Phase I, the share of Phase II awards to WOSBs was lower than the share of Phase II applications. The WOSB share of awards was lower than the share of applications for 7 of the 10 years covered by the study.

The average Phase I funding levels for WOSBs were consistently lower than those for non-WOSB, in all years except FY2007 and FY2013. On average, the first year of Phase II SBIR funding was almost $27,000 lower, which would normally translate into a difference of more than $50,000 over the life of a standard 2-year Phase II award.

Minority-Owned Small Businesses

The definition of "minority" provided by SBA and used by the agencies does not align with the congressional mandate provided in the authorizing legislation and has the unintended effect of concealing the extremely low rates of participation by African Americans, Hispanic Americans, and Native Americans in the program.

This section focuses on analyzing the data provided by NIH, which uses the SBA definitions for data collection purposes. Accordingly, analysis here uses the same definition: "minority" includes African Americans, Hispanic Americans, Native Americans, and Asian Americans.

Participation by minority-owned small businesses (MOSBs) in NIH SBIR Phase I declined on several key metrics. Both the numbers and shares of MOSB applications declined across the study period, with the latter at 3 percent of all applications in FY2014 (see chapter Annex, Figure 6-11).

The declining application share is exacerbated by low success rates relative to other applications. The Annex shows that success rates for Phase I SBIR applications by MOSBs were lower than those by non-MOSBs in every year of the study period, and in some years were barely one-half. The average success rates for applications by MOSBs and non-MOSBS were 10.1 percent and 18.3 percent, respectively.

As a result of these factors, the MOSB share of awards fell from a peak of 3.5 percent in FY2006 to less than 2 percent in FY2014 (See Figure 6-13). In FY2014, 12 SBIR Phase I awards were made to MOSBs.

The small number of Phase I awards means that the pool of potential Phase II applicants is also small, which is reflected in the low numbers of MOSB Phase II grant applicants (see Figure 6-14). Their share of all applications declined quite sharply starting in FY2010 before rebounding in FY2014. It is possible that recent outreach efforts are starting to pay off (see Chapter 2), but data from FY2015 and later will be needed before conclusions can be drawn.

The small and declining numbers of applications will drive small award numbers and a small share of all awards. However, success rates have generally been lower than those for non-MOSB Phase II applicants. Figure 6-15 shows that in 8 of the 10 study years, success rates of MOSBs were lower than those of others.

The net result of these factors is that MOSBs have accounted for a declining share of SBIR Phase II awards, reaching a low of 1.1 percent in FY2013 before rebounding to 2 percent in FY2014. These figures reflect the very expansive definition of "minority" used by SBA and hence NIH, which includes companies that are owned by Asian Americans.

2014 SURVEY DATA[6]

As noted above, the SBA's interpretation of one of the four congressionally mandated objectives for the SBIR/STTR programs is to "foster and encourage participation in innovation and entrepreneurship by socially and economically disadvantaged persons."[7] This mandate has traditionally been interpreted to mean support for women and members of ethnic minorities listed by SBA.

Previous SBIR/STTR studies have focused largely on company ownership by women and by members of socially and economically disadvantaged groups (SEDGs). In most cases, these studies neither addressed the role of the PI nor disaggregated SEDGs by ethnicity. The 2014 survey expands the analysis in both directions.

Woman-Owned Small Businesses and Female PIs

Women have traditionally been viewed as socially and economically disadvantaged in the context of the SBIR program, and expanding opportunities for women has therefore been considered as one of the congressionally mandated goals of the program since the 1992 reauthorization. In most cases, analysts have focused on the participation of woman-owned firms. However, because exercising the responsibilities of a PI may be a stepping stone toward company ownership, the 2014 Survey also addresses the extent to which SBIR awards went to female PIs.

Fifteen percent of Phase II respondents identified a female PI (although only 3.8 percent of the 28 Phase IIB respondents did so).[8]

Overall, 13.6 percent of respondents reported that the company was woman-owned. Again, Phase IIB respondents reported a lower rate (8.6 percent).

Minority-Owned Small Businesses and Minority PIs[9]

The current Academies[10] surveys of the SBIR/STTR programs are, to our knowledge, the first to probe beneath standard definitions of "socially and economically disadvantaged." That is, previous SBIR surveys from the Academies

[6]The text in this section and accompanying tables 6-1 and 6-2 have been revised since the version presented in the prepublication copy.

[7]SBA: SBIR Mission and Goals, http://www.sbir.gov/about/about-sbir, accessed August 27, 2012. This definition has historically been taken to include women. Detailed SBA definition of "socially and economically disadvantaged" is available at http://www.sbda.com/sba_8 percent28a percent29.htm.

[8]2014 Survey, Question 16. N=605.

[9]Different agencies use different terminologies, which also change over time. "Minority-owned" is a widely used term, but others use "socially disadvantaged."

[10]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council or NRC are used in an historic context identifying programs prior to July 1.

and from other organizations—as well as agency data—have all simply sought to determine whether the company is majority-owned by members of socially and economically disadvantaged groups as defined by SBA.

As with the 2005 Survey, the 2014 survey asked whether the PI for the surveyed project was from a minority population. Seven percent of respondents indicated that this was the case for their project.[11]

The survey also asked respondents to provide details about the PI's ethnic background. Detailed categories were drawn from SBA definitions, with the addition of a category for "other" to ensure that all respondents who wished to claim minority status had an appropriate response category.

About 72 percent of respondents reporting a minority PI indicated that the PI was Asian Pacific or Asian Indian. Only 2 of more than 600 responses indicated that the PI was African American.

It must be understood that we are dealing with small numbers of respondents—only 57 respondents indicated that their PI was minority. Even so, the almost complete absence of Black (African American) and Native American PIs and the limited presence of Hispanic PIs is notable (see Table 6-1).

Turning from the ethnicity of PIs to the ethnicity of the owners of surveyed companies showed that approximately 7 percent of respondents indicated that the company was majority-owned by minorities at the time of the award. Probing more deeply into the ethnic distribution of minority company ownership showed a distribution quite similar to that for minority PIs, in that 68 percent of minority-owned companies reported majority owners of Asian Indian and Asian Pacific ethnicity (see Table 6-2).

The numbers involved here are very small indeed: the survey reported three Phase II awards to African American owned companies.

NIH SBIR/STTR OUTREACH TOWARD POTENTIAL WOMEN AND MINORITY PROGRAM PARTICIPANTS[12]

NIH began more detailed tracking of its SBIR/STTR outreach 3 years ago, as is effectively required by the 2011 SBIR/STTR Reauthorization Act. Today, this effort includes tracking the following data:

- The number of overall attendees at outreach events
- The state of residence of each attendee
- Whether the attendee is from a WOSB and/or a MOSB

[11]See Table 6-1.

[12]This section of the report is based on material provided directly by the NIH SBIR/STTR Program Office and through discussions with agency staff.

TABLE 6-1 Composition of PIs by Gender and Ethnicity, as a Percentage

	NIH Total	SBIR	STTR	Phase IIB
Woman	14.9	15.2	13	3.6
Minority	9.4	10	6.5	7.1
Asian-Indian	1.8	2	1.1	
Asian-Pacific	5.0	5.7	1.1	7.1
Black	0.3	0.2	1.1	
Hispanic	2.0	2.1	1.1	
Native American	0.2		1.1	
Other	0.3	0.2	1.1	
Not a woman nor a minority	76.8	76	81.5	89.3
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	604	512	92	28

SOURCE: 2014 Survey, Question 16.

TABLE 6-2 Minority Company Ownership, by Ethnicity and Program

	Percentage of Respondents			
	NIH Total	SBIR Awardees	STTR Awardees	Phase IIB Awardees
Woman-owned	13.1	13.4	11.2	8.3
Minority-owned	6.9	7.5	3.4	4.2
Asian Indian	1.2	1.3	1.1	
Asian Pacific	3.5	4.0	1.1	4.2
Black	0.5	0.4	1.1	
Hispanic	1.6	1.9		
Native American				
Other	0.2	0.2		
Not woman- or minority-owned	81.8	81.2	85.4	87.5
BASE: TOTAL RESPONDENTS ANSWERING QUESTION	567	478	89	24

SOURCE: 2014 Survey, Question 15.

Overall, NIH spent about $2 million in administrative funds on outreach in FY2014.[13] A review of the activities described in the NIH Annual Report to SBA indicates that numerous other outreach activities appeared to be higher priority

[13]NIH SBIR Report to SBA, FY 2014, p. 10.

than outreach to women and minorities. Of all the activities listed, only one mentions underrepresented groups.[14]

Most NIH outreach activity is conducted through partnerships with other event organizers. The FY2014 report included participation in conferences sponsored by the Advanced Medical Technology Association, the Association of University Technology Managers, and the International Meeting for Autism Research. Because it has only limited influence over their activities, NIH has focused on improving reporting from these partners. NIH now sends each organizer a request form that asks the organizers to track attendance from IDeA states,[15] WOSBs, and MOSBs (although, using SBA terminology, the latter are owned by individuals from socially and economically disadvantaged groups). NIH program managers acknowledge that acquiring accurate data through event organizers is challenging.

NIH and the Department of Health and Human Services (HHS) are also targeting events to reach out specifically to women- and minority-owned small businesses. NIH has held a well-attended WOSB/MOSB workshop within its own Annual Conference in each of the past several years and has begun outreach to professional societies for women- and minority-owned small businesses. The NIH Program Office expects that its staff will attend events from those organizations in the future. The Program Office is also working to reach younger potential entrepreneurs, and its staff will attend the AAAS Minority Fellowship conference in 2016 to present on the agency's SBIR/STTR programs.

Finally, NIH is participating and supporting the SBIR Road Tour, organized by SBA, to reach underrepresented states and women- and minority-owned small businesses. This effort, however, is primarily focused on the states rather than on underrepresented groups.

The Challenge of Improving Diversity[16]

The committee recognizes that small businesses often introduce the radical ideas that can transform industries and markets, and that mobilizing all skilled individuals, regardless of race/ethnicity or gender, strengthens the economy and the nation. To this end, the committee convened a workshop to draw attention to participation of women, minorities, and both older and younger scientists, engineers, and entrepreneurs in the SBIR program and to identify mechanisms for improving their participation rates.[17] The workshop also drew attention to the fact

[14]NIH SBIR Report to SBA, FY 2014, pp. 10-11.

[15]NIH established the Institutional Development Award (IDeA) program in 1993. IDeA—the largest of the EPSCoR-like programs—is designed to broaden the geographic distribution of NIH funding for biomedical research.

[16]National Academies of Sciences, Engineering, and Medicine. 2015. *Innovation, Diversity, and the SBIR/STTR Programs: Summary of a Workshop.* Washington, DC: The National Academies Press.

[17]Ibid, p. 5.

that improving the participation of women and minorities in the SBIR program is a part of a broader national challenge. See Box 6-1.

Participants in the workshop examined broad demographic trends in the science and engineering workforce and statistical measures from the SBIR program for women and minorities, and searched for pragmatic solutions to boost SBIR awards to women and minorities. The workshop highlighted the fact that women comprise 51 percent of the U.S. population and 27 per cent of STEM graduates, but woman-owned companies have received only about 6 percent of SBIR awards. Hispanics, African Americans, Asian Americans, and Native Americans together comprise 36 percent of the U.S. population and 26 percent of STEM graduates, but less than 10 percent of all SBIR awards. Beyond NIH's SBIR program, the current participation of women and minorities was found to be low and decreasing, and participation of African-Americans and Hispanics is particularly low.

Steps identified by participants to stimulate participation by under-represented populations included steps to expand the applicant pool, eliminate barriers in grant applications and selection, and provide greater education and support for entrepreneurship training and commercialization efforts. Participants also saw the need to

BOX 6-1
Expanding Participation of Women and Minorities in STEM

The 2011 publication by the National Research Council, *Expanding Underrepresented Minority Participation: America's Science and Technology Talent at a Crossroads*, notes that underrepresented minorities, defined here as Hispanics, African Americans, Native Americans/Alaska Natives, comprise a small percentage at each step of the science, technology, engineering, and mathematics (STEM) education process.[a] The percentage of African American and Hispanic undergraduate majors interested in STEM is similar to that of white and Asian Americans, but their completion rates are much lower. At the graduate school level for science and engineering, underrepresented minorities receive only 14.6 percent of master's degrees and 5.4 percent of doctoral degrees. Data from the National Science Board indicates that women earn roughly half of S&E degrees at the bachelor's, master's, and Ph.D. levels, but they earn "fewer than one-third of the doctorates awarded in physical sciences, mathematics and computer sciences, and engineering" and less than a quarter of engineering master's degrees.

[a] National Research Council, *Expanding Underrepresented Minority Participation: America's Science and Technology Talent at a Crossroads,* Washington DC: The National Academies Press, 2011.

align and leverage resources and programs at the state level that aim at providing access and support to woman- and minority-owned businesses; and to team with other federal and state/local programs which are addressing this issue.

Speaking at the workshop, Matthew Portnoy, SBIR/STTR program coordinator at the National Institutes of Health, said that the NIH has diversity supplement programs to support under-represented groups on SBIR and STTR awards.[18] In this regard, he noted that NIH is targeting outreach to women-owned and socially and economically disadvantaged businesses. NIH is also coordinating its SBIR/STTR programs with the NIH Institutional Development Award (IDeA) program to target underrepresented states. The NIH's annual IDeA Symposium includes sessions on the SBIR/STTR program and the NIH Annual SBIR/STTR Program includes a session on the IDeA program.

Over time, discussions regarding possible underlying causes of the underrepresentation of women and minorities in the SBIR/STTR program have been broadened. While the workshop on diversity convened by the committee focused, for example, on upstream barriers in the STEM pipeline leading to SBIR/STTR application, recent studies have extended the look to potential downstream barriers in the pipeline leading to the successful commercialization of SBIR/STTR-funded innovations. Box 6-2 lists a selection of recent publications that examine barriers to women and minority SBIR/STTR participation rates in the broader context of an extended pipeline. It remains for further investigation to more fully explain causation and to arrive at practical solutions leading to higher participation rates of women and minorities in SBIR/STTR.

SUMMARY: WOMAN AND MINORITY PARTICIPANTS IN THE NIH SBIR/STTR PROGRAM

Although participation of WOSBs in the NIH SBIR program appears to be improving, there are areas of continuing concern. Their share of applications is still relatively low, despite the high percentage of female PhDs in the life sciences. The fact that success rates for WOSBs for both Phase I and Phase II were persistently lower than those for non-WOSBs requires further analysis by NIH. Although the amounts involved are not very large (perhaps 5 percent of award size), it is important to determine why WOSB award sizes are consistently lower than those for non-WOSBs.

The review of the data reveals that NIH experiences serious difficulties in attracting MOSBs to the SBIR program. Using the SBA definition, award shares to MOSBs have declined and now account for only 2 percent of Phase II awards. Success rates for MOSB applicants are persistently lower than for non-MOSB applicants, for both Phase I and Phase II.

[18]National Academies of Sciences, Engineering, and Medicine. 2015. *Innovation, Diversity, and the SBIR/STTR Programs: Summary of a Workshop.* Washington, DC: The National Academies Press, p. 41.

BOX 6-2
Extending Perspectives on Diversity

Recent inquiries by the Academies and others to examine the participation of women and minorities in the SBIR/STTR programs and in other STEM activities seek to gain a better understanding of the scope and nature of the problem. In particular, to what extent are the low participation rates by women and minorities a failure of the NIH SBIR/STTR program, and to what extent is this a problem that comes out of the communities served by and interfacing with the NIH program. These are the communities of academic and industrial life-sciences that spawn the populations of existing and potential small businesses that could benefit from the NIH SBIR/STTR program.

More recent studies examine the possibility that significant barriers may lie beyond the interface of the SBIR/STTR with the life-sciences community (as witnessed by efforts at universities to encourage and support women in science, and the availability of opportunities for research support provided by the NIH SBIR/STTR program). These studies point to institutional and cultural impediments to women- and minority-owned entrepreneurial businesses that exist downstream of SBIR/STTR, in financial markets and business communities that are critical to the commercialization of innovation resulting from research. The committee's own workshop report, cited below, sheds light on upstream issues of participation for women and minorities, and the several listed afterwards, point to downstream issues:

National Academies of Sciences, Engineering, and Medicine, Innovation, Diversity, and the SBIR/STTR Programs: Summary of a Workshop, Washington, DC: National Academies Press, 2015.

The workshop and the workshop summary examined broad demographic trends in the science and engineering workforce, the experiences of SBIR/STTR staff and participants, and ideas and pragmatic approaches put forward by participants to boost the participation of women and minorities.

Gicheva, Dora, and Albert Link, "The Gender Gap in Federal and Private Support for Entrepreneurship, "Working Papers 15-05, University of North Carolina at Greensboro, Department of Economics, 2015, and Dora Gicheva and Albert Link, "Leveraging Entrepreneurship through Private Investments: Does Gender Matter?," Small Business Economics, Vol. 40, No. 2 (February 2013), pp. 199-210).

These papers use SBIR data collected by the Academies 2005 survey for NIH to explore gender differences in access to investment funds when attempting to develop a new technology. A finding is that female-owned firms are disadvantaged in their access to private investment funding, especially in the West and Northeast regions of the United States. The lower probability that a female-owned firm will receive follow-on private investment funding to help commercialize an SBIR-funded technology can be expected to have a negative impact of the long-run outcome.

continued

BOX 6-2 Continued

Scott, John T. and Troy J. Scott, "The Entrepreneur's Idea and Outside Finance: Theory and Evidence about Entrepreneurial Roles," European Economic Review, September 2015.

This paper investigates the problem faced by the entrepreneur seeking outside support for commercialization of a successful technological innovation resulting from research and development. Using the Academies 1999 SBIR data for DoD, results suggest that difficulty in getting outside third-party finance then makes it more difficult to secure other forms of agreements with other firms that would help with the commercialization effort—a finding with direct, negative implications for women- and minority-owned innovative companies participating in the SBIR program.

Link, Albert N., Christopher J. Ruhm, and Donald S. Siegel, "Private Equity and the Innovation Strategies of Entrepreneurial Firms: Empirical Evidence from the Small Business Innovation Research Program," Managerial and Decision Economics, Vol. 35 (2014), pp. 103-113.

This paper further examines the role of public and private investment on long-term innovation performance. It finds that SBIR firms attracting private equity investments are significantly more likely to license and sell their technology rights and engage in collaborative research and development agreements.

Low participation rates are even more apparent when African American and Hispanic American participation is considered, both as PIs and through company ownership. Here the numbers are extremely small: 2014 Survey respondents reported 2 African American and 12 Hispanic American PIs. It is therefore concluded that NIH is finding minimal success in attracting MOSB participants into the SBIR/STTR programs. Furthermore, declining participation trends are a matter of concern.

The Committee considered the question of whether woman- and minority-owned firms could be assigned a percentage of awards as a way to enhance program diversity. It concluded that the size of the applicant pool of women- and minority-owned businesses is so small that setting quotas would not be as effective as increasing the size of the applicant pool through some of the long-term initiatives that were suggested by speakers in the committee's workshop.

NIH is aware of this issue and understands the need to improve outreach toward women- and minority-owned businesses as part of its overall outreach efforts.

ANNEX 6-A: ANALYSIS OF NIH DATA RELATING TO THE PARTICIPATION OF WOMAN- AND MINORITY-OWNED BUSINESSES

Woman-Owned Small Businesses

WOSB SBIR Phase I

Across the study period, applications from WOSBs remained relatively flat, averaging 483 annually. The overall decline in SBIR Phase I applications in recent years was mirrored but to a lesser degree for WOSBs (see Figure 6-2).

As a result, the WOSB share of applications increased slightly during the study period, reaching 15.5 percent in FY2013 (see Figure 6-3).

Across the same time period, the success rates for WOSB applicants were consistently lower than those for non-WOSB applicants (see Figure 6-4). They were lower in every year of the study period, and across the period they averaged 14 percent while the non-WOSB success rate averaged 18 percent.

Thus while the share of applications grew, the number of awards made to WOSBs remained essentially flat across the study period, averaging about 66 annually, with a high of 89 in FY2007 (an outlier) and a low of 55 in FY2005. In FY2014, WOSBs received 67 awards.

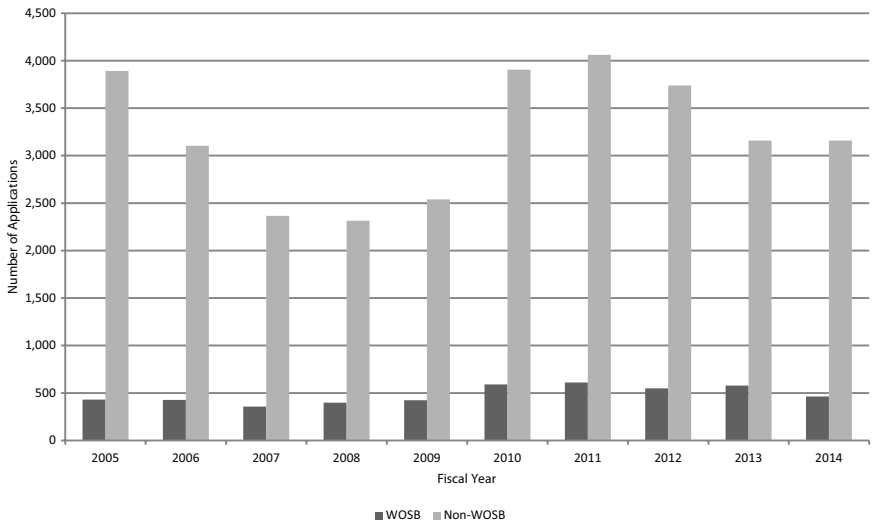

FIGURE 6-2 NIH SBIR Phase I applications from WOSBs and non-WOSBs, FY2005-2014.
SOURCE: Based on NIH RePORTER database, Table T127.

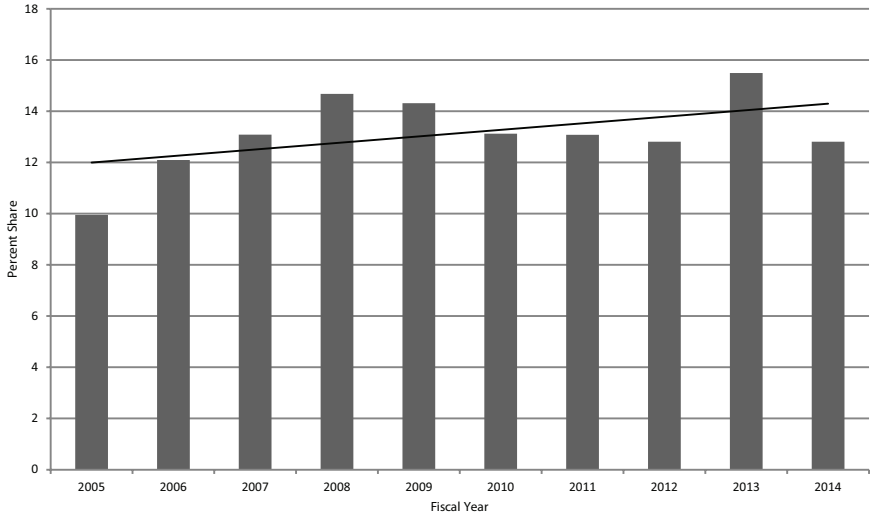

FIGURE 6-3 WOSB percentage share of NIH Phase I SBIR applications, FY2005-2014.
SOURCE: Based on NIH RePORTER database, Table T127.

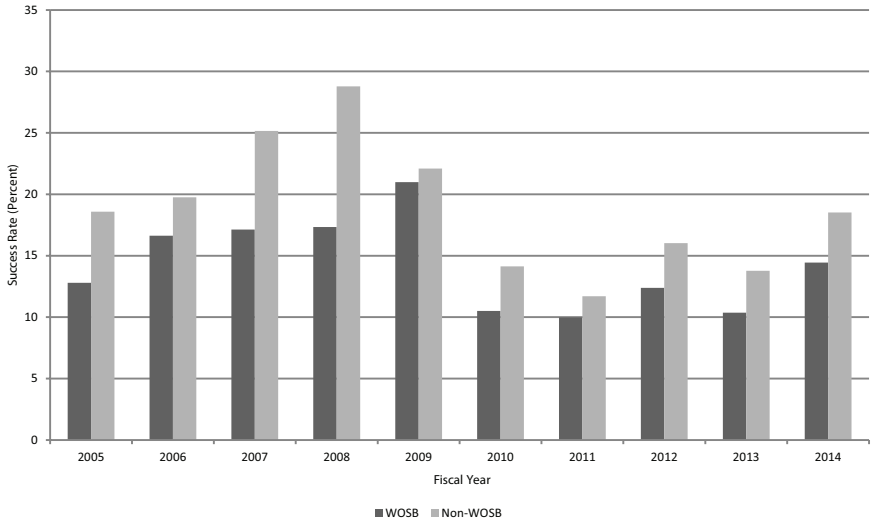

FIGURE 6-4 Success rates for NIH SBIR WOSB and non-WOSB applications, FY2005-2014.
SOURCE: Based on NIH RePORTER database, Table T127.

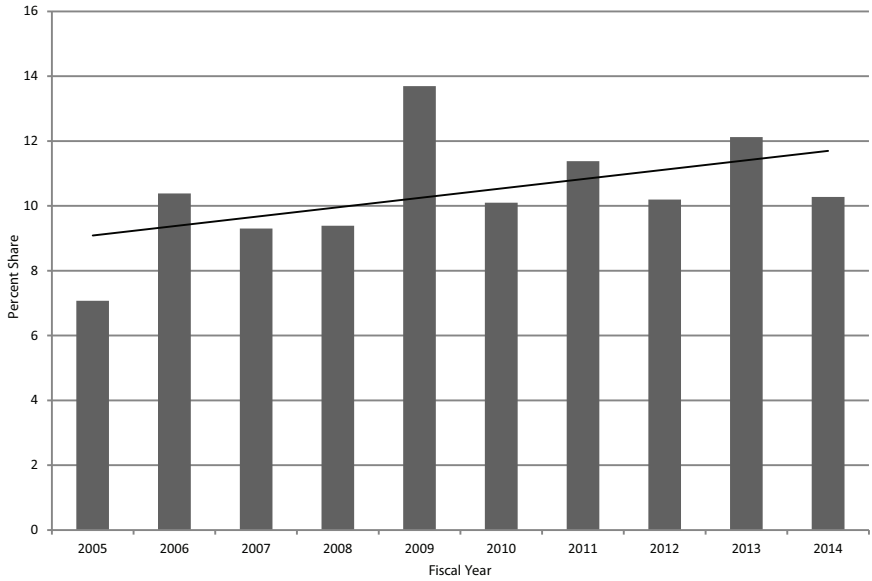

FIGURE 6-5 WOSB share of NIH SBIR Phase I awards, FY2005-2014.
SOURCE: Based on NIH RePORTER database, Table T127.

Overall, the number of Phase I awards declined in recent years, so the percentage of awards made to WOSBs increased slightly (see Figure 6-5). But the share of awards was consistently lower than the share of applications in every year across the study period. Overall, WOSBs accounted for 13 percent of applications and 10 percent of awards.

Finally, NIH awards differ in size. Phase I awards to WOSBs were consistently smaller on average than those to non-WOSBs (see Figure 6-6). WOSBs received smaller awards on average in every year except FY2007. Because the amount applied for is largely at the discretion of the company, explanations for this difference are not obvious. Furthermore, the difference neared or exceeded 10 percent of the average award size in only 3 years. This is a metric that NIH needs to watch closely in coming years.

WOSB SBIR Phase II

Levels of Phase II applications from WOSBs for each year are somewhat higher than the share of relevant Phase I awards (for the previous year) almost without exception. Although the lags between Phase I and Phase II at NIH vary, there is no simple explanation for this pattern. It may simply be that WOSBs have less access to other sources of funding, but that reasoning is speculative. Across

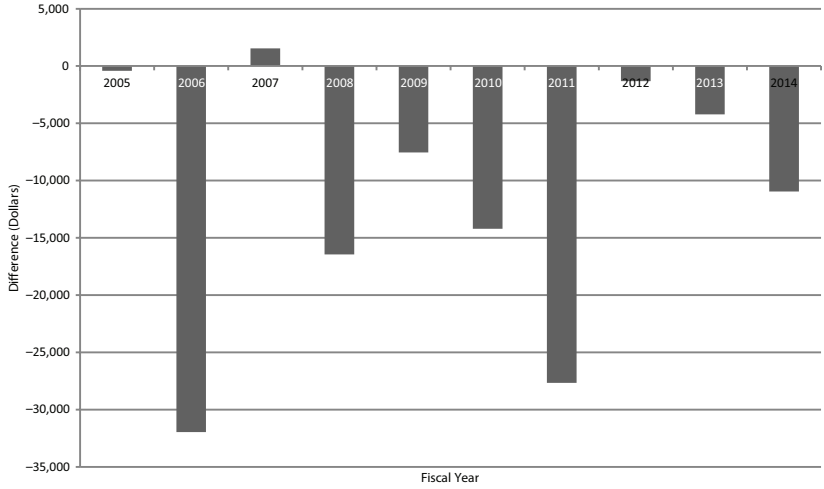

FIGURE 6-6 Difference in size of awards between WOSB and non-WOSB NIH Phase I SBIR awards (dollars), FY2005-2014.
SOURCE: Based on NIH RePORTER database, Table T127.

the study period as a whole, WOSBs accounted for 10.3 percent of Phase I awards and 13.3 percent of Phase II applications. They accounted for 11.9 percent of Phase II awards. (See Figure 6-7.)

As with Phase I, Phase II WOSB success rates were persistently lower than those for non-WOSBs (see Figure 6-8). They were lower in 7 of the 10 years of the study period, on average by 5 percentage points. Also, as with Phase I, the Phase II WOSB share of awards was lower than the share of applications (see Figure 6-9). WOSB shares of awards were lower than the shares of applications for 7 of the 10 years covered by the study.

Average Phase I funding levels for WOSBs are consistently lower than those for non-WOSBs, being lower in all years except FY2007 and FY2013. On average, the first year of Phase II funding was almost $27,000 lower, which would normally translate into a difference of more than $50,000 over the life of a standard 2-year Phase II award (see Figure 6-10).

Minority-Owned Small Businesses

MOSB SBIR Phase I

Figure 6-11 illustrates the number and share of MOSB Phase I applications across the study period. The number and share of applications declined. The latter fell from a high of about 6 percent in FY2006 to 3 percent in FY2014.

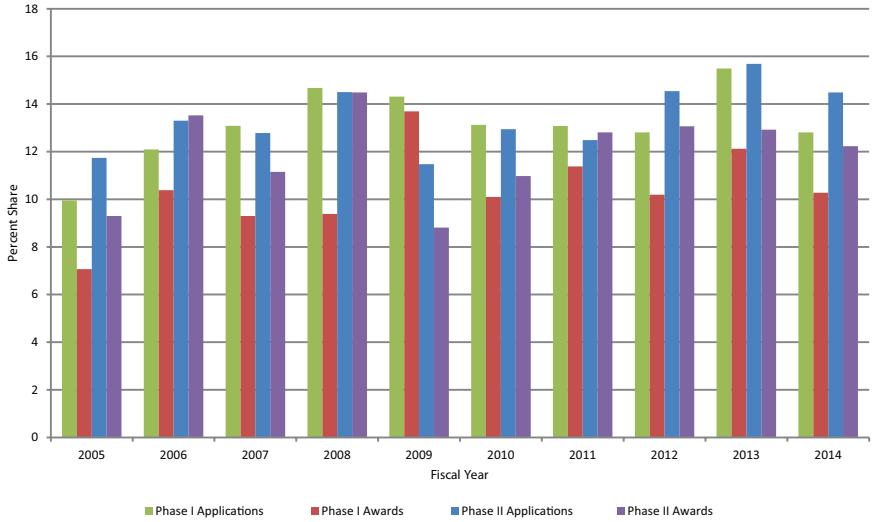

FIGURE 6-7 Patterns of access: WOSB Phase I applications, Phase I awards, Phase II applications, and Phase II awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

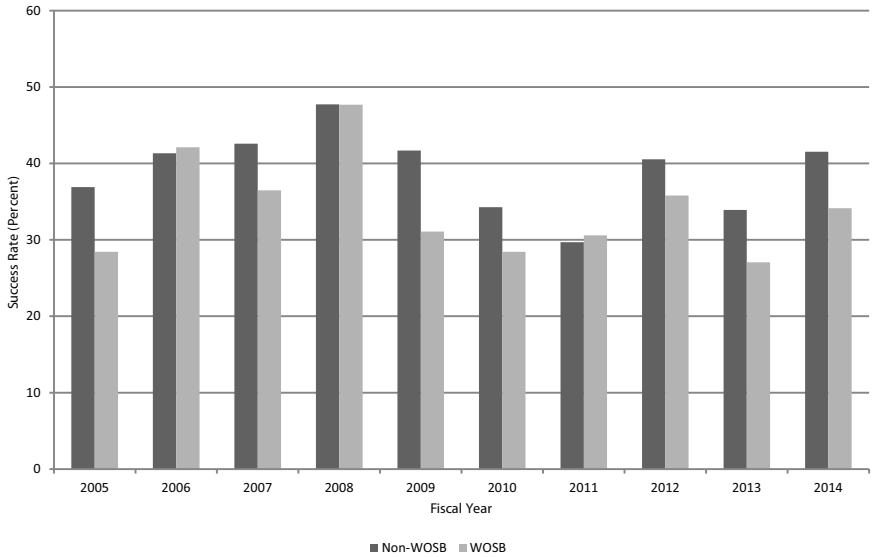

FIGURE 6-8 Success rates for WOSB and non-WOSB NIH Phase II SBIR applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

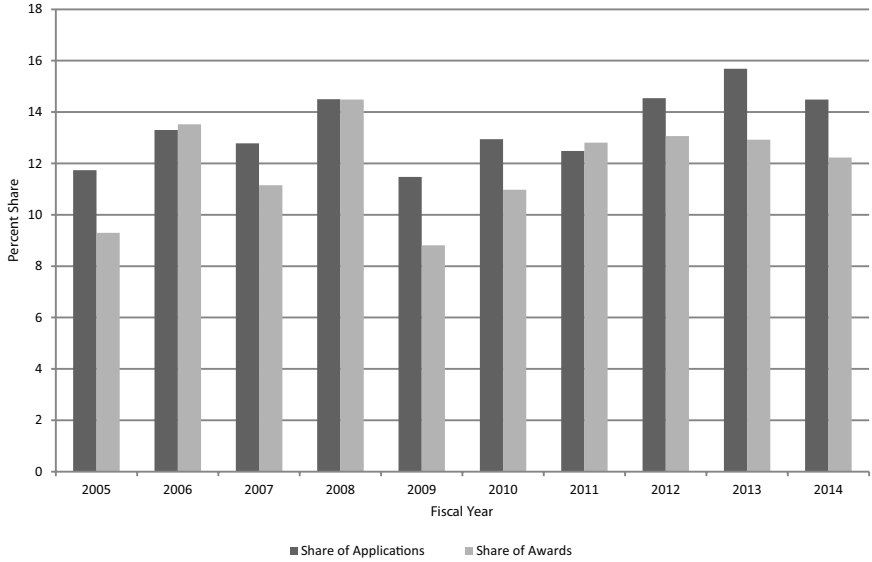

FIGURE 6-9 WOSB percentage shares of NIH Phase II awards and applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

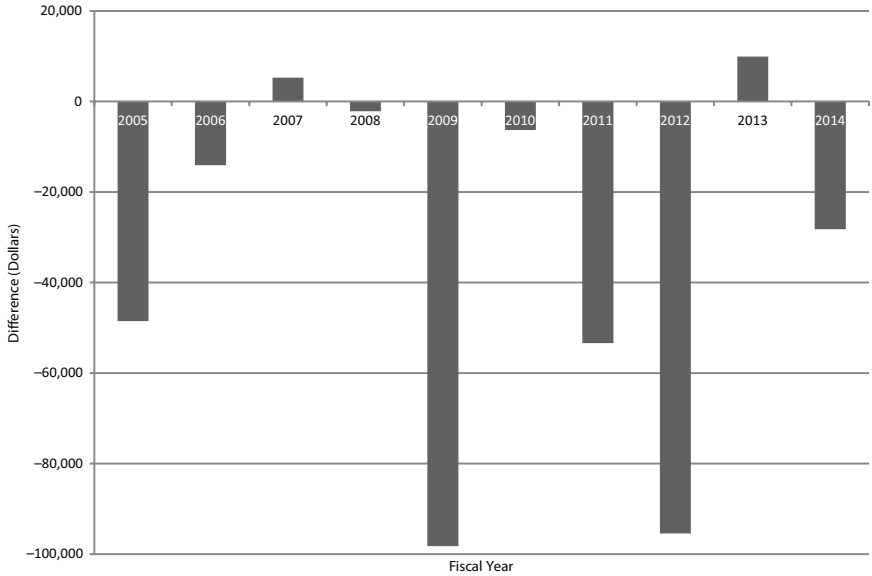

FIGURE 6-10 Average size of first-year Phase II SBIR grants to WOSB and non-WOSB applicants, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

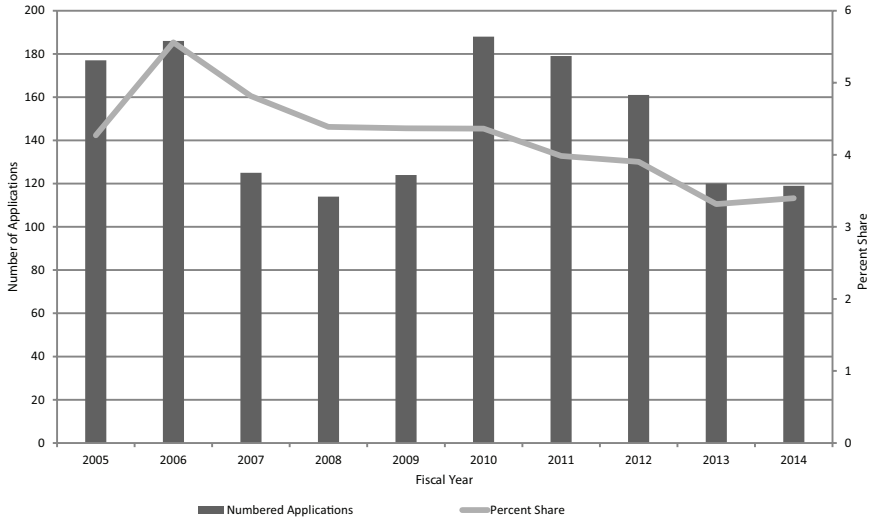

FIGURE 6-11 Number of MOSB Phase I SBIR grant applications and percentage share of all applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

Declining application rates are reinforced by relatively low success rates. Phase I success rates for MOSBs were lower than those for non-MOSBs in every year of the study period, and in some years were barely half. The average success rate for MOSB applications was 11.5 percent, while that of non-MOSB applications was almost 18 percent (see Figure 6-12).

As a result the number and share of MOSB awards declined across the period. The number of Phase I awards to MOSBs decreased from 24 in FY 2005 and FY2006 to 11 in FY2013 and 12 in FY2014. The share of awards fell from a peak of 3.5 percent in FY2006 to less than 2 percent in FY2014 (see Figure 6-13).

MOSB Phase II SBIR Awards

The small number of Phase I awards made to MOSBs means that the pool of potential applicants is also small, which is reflected in the low numbers of SBIR Phase II grant applicants (see Figure 6-14). However, the MOSB percentage of all Phase II applications rebounded in FY2014 after several years of steady declines. In recent years MOSB Phase II applicants accounted for a higher percentage of the total applicants than they did for Phase I awards. This suggests either that MOSB firms are more committed to the SBIR program or that their projects are more successful at Phase I, permitting relatively more to apply for Phase II.

Success rates for MOSB Phase II applicants are lower than those for non-MOSB Phase II applicants. Figure 6-15 shows the gap: MOSB rates are lower in

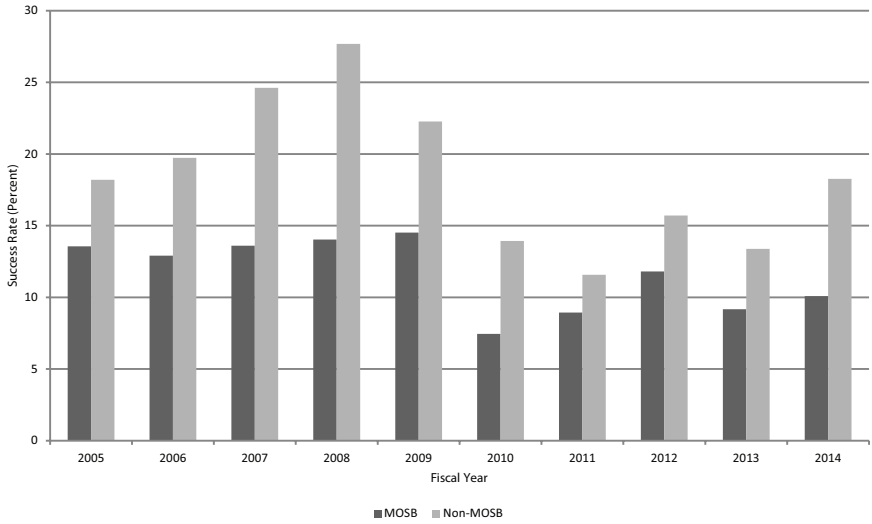

FIGURE 6-12 Success rates for MOSB and non-MOSB NIH Phase I SBIR applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

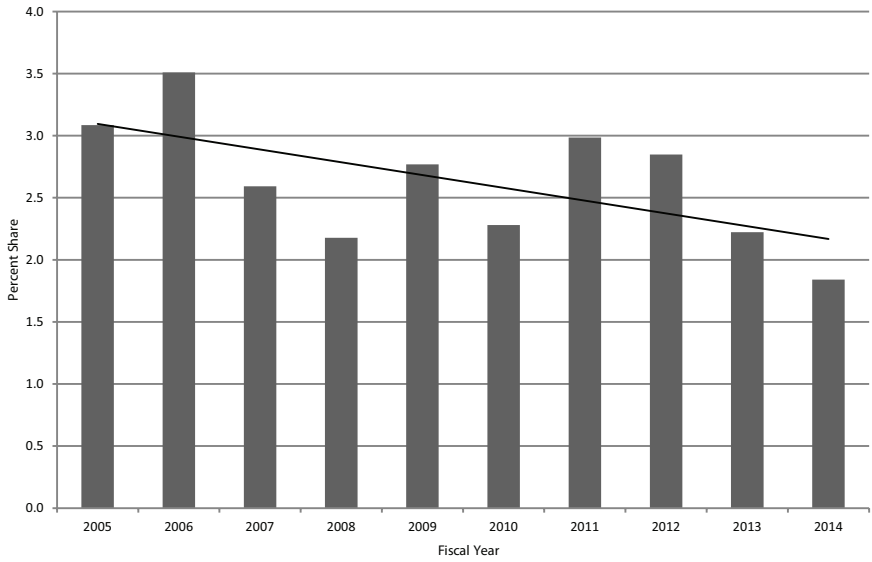

FIGURE 6-13 MOSB percentage share of Phase I SBIR awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

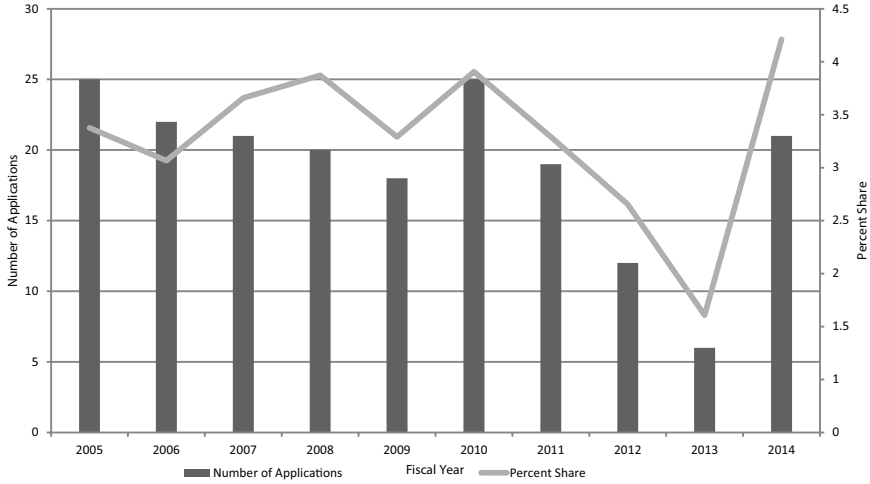

FIGURE 6-14 MOSB applications and percent share of all SBIR Phase II applications, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

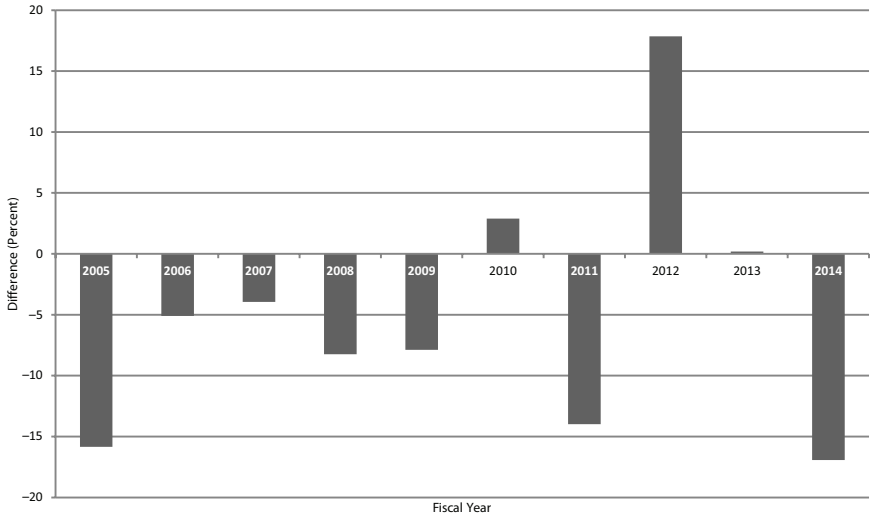

FIGURE 6-15 Difference between success rates of MOSB and non-MOSB SBIR Phase II applicants, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

every year except FY2012 and FY2010 and are on average 6 percentage points lower, at 32 percent for MOSB compared to 38 percent for non-MOSBs.

As a result of the small applicant pool for Phase II and the lower success rates, MOSBs won only a handful of Phase II SBIR awards at NIH—receiving a maximum of nine grants in any year of the study period. The share of awards dipped to a low of 1 percent in FY2013 before rebounding to 2 percent in FY2014 (see Figure 6-16). These figures all reflect the expansive definition of "minority" provided by SBA, which includes Asian-owned firms. The numbers of African Americans, Hispanic Americans, and Native Americans would all likely be lower (as we found through the 2014 Survey, whose findings are discussed above).

MOSB award sizes were also considerably lower than those for non-MOSBs, being on average almost $70,000 smaller in the first year, which translates into a gap of about $140,000 over the life of a standard 2-year award. Figure 6-17 shows a gap in award size in every year except FY2009; the substantial variations year to year are in part explained by the low number of awardees (less than 10 per year).

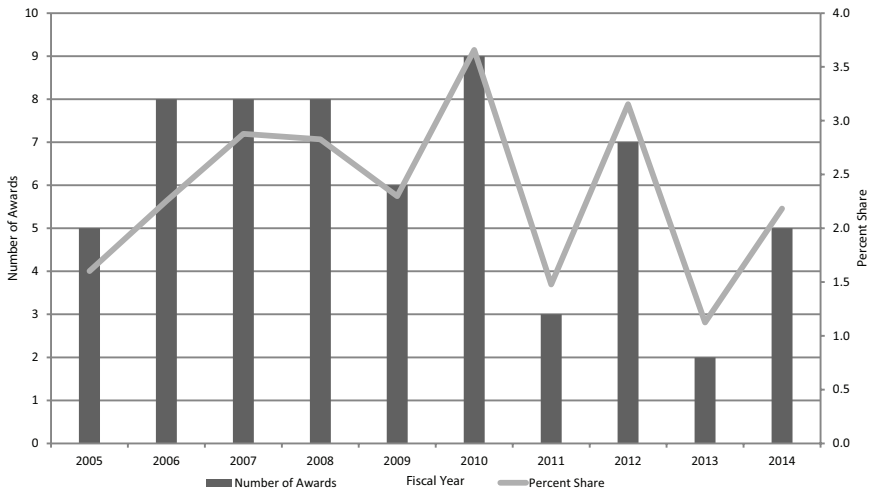

FIGURE 6-16 MOSB SBIR Phase II awards and percent share of all such awards, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

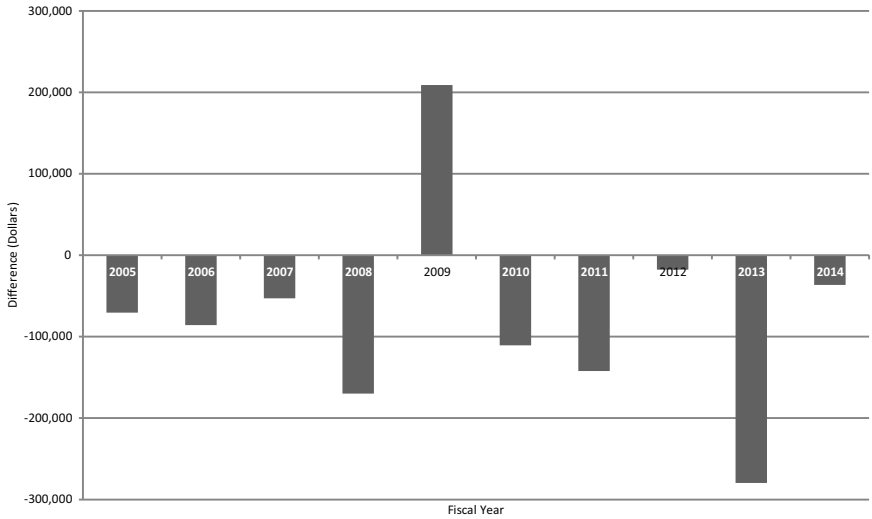

FIGURE 6-17 Difference in first-year award size for MOSB and non-MOSB SBIR Phase II awardees, FY2005-2014.
SOURCE: NIH Division of Statistical Analysis and Reporting, Table 127.

7

Insights from Case Studies and Survey Responses

This chapter addresses a range of impacts as described by executives from case study companies (see Box 7-1) and as provided in textual responses to open-ended questions from the 2014 Survey fielded by the Academies. Highlighting some of the details of program operation and the various roles that the SBIR/STTR program play in the development of small innovative firms, the case studies and survey comments enable a broader qualitative understanding of the program, particularly from the user's perspective, and are thus an essential part of the information gathered by the committee to assess whether the NIH SBIR/STTR programs are meeting their legislative goals.

ROLE OF CASE STUDIES

Case studies are an important part of data collection for this assessment, in conjunction with other sources such as agency data, the survey, meetings with agency staff and other experts, and workshops on selected topics. The impact of SBIR/STTR funding is complex and often multifaceted, and although these other data sources provide important insights, case studies allow for an understanding of the narrative and history of recipient firms—in essence, providing context for the data collected elsewhere.

A wide range of companies were studied: They varied in size from fewer than 10 to more than 500 employees and included firms owned by women and minorities. They operated in a wide range of technical disciplines and sectors. Overall, this portfolio of 15 case studies was designed to capture many of the types of companies that participate in the NIH SBIR/STTR programs.

BOX 7-1
NIH Company Case Studies

Case studies are included in this volume as Appendix E.[a]

23andMe
Advantagene, Inc.
ArmaGen Technologies
Auritec Pharmaceuticals
Avanti Polar Lipids, Inc.
Avaxia Biologics, Inc.
Conversion Energy Enterprises
Danya International, Inc.
GMSBiotech
Lpath Therapeutics, Inc.
NOVA Research Company
Sanaria, Inc.
Stratatech Corporation
Targeson, Inc.
TissueTech, Inc.

[a] Two draft case studies included provisionally in the prepublication version of this report have been deleted from the final version, at the request of the companies.

Given the multiple variables at play, the case studies are not presented as any kind of quantitative record. Rather, they provide qualitative evidence about the individual companies selected, which are, within the limited resources available, as representative as possible of the different components of the awardee population. Given the multiple variables at play, and their small number, it is not possible to draw statistical inferences from the case studies. The case studies are presented in full in Appendix E of this report and highlighted in this chapter. The featured companies have verified the case studies and have explicitly permitted their use and identification in this report.

This chapter is organized in terms of the broad types of impacts of the NIH SBIR/STTR programs:

- Company impacts
- Support for agency mission
- Program management and company recommendations

Together, these sections provide the first wide-ranging publicly available feedback of the NIH SBIR and STTR programs from program recipients. We conclude this chapter with some views on the STTR program from recipients.

COMPANY IMPACTS

For many small companies—especially those that receive SBIR or STTR funding early in their history—receiving an award (especially Phase II) can be a highly positive or transformative experience. One-third of the respondents to the Academies' 2014 survey indicated that program funding had indeed had a transformative effect on the company. Appendix E shows in detail how SBIR/STTR funding affected the trajectory of development for each of the 15 companies studied. This section describes some of these impacts.

General Comments

In general terms, the 15 companies that participated in this analysis are strong supporters of the SBIR/STTR programs. Comments from selected meetings include the following:

- "I love the SBIR program—I would still review and support it even if I never got another SBIR. It is critical to innovation in this country; without SBIR lots of innovation would die on the vine." Dr. Robert Sabbadini, Lpath
- "SBIR is the lifeblood of the company. SBIR funding is the only conceivable way in which the company could have been founded and the technology perfected to the point of successful clinical trials." Dr. Stephen Hoffman, Sanaria
- "The SBIR/STTR program at NIH has provided absolutely critical funding for Stratatech. I have no doubt that Stratatech and its associated products would not be in existence without SBIR/STTR funding." Dr. Barbara Allen-Hoffman, Stratatech
- "ArmaGen has traversed the valley of death and our horse was SBIR." Dr. William Pardridge, ArmaGen

The Valley of Death refers to the early stages of a startup, before a new product or service brings in revenue.

Company Formation

In a number of cases, the decision to form a company was driven in part or entirely by access to SBIR/STTR funding. This seems—at least at NIH—to have been particularly important for helping academics navigate the transition from the university to the private sector.

Dr. Allen-Hoffman at Stratatech said that an STTR award was instrumental in creating Stratatech to pursue technologies developed at her lab at the University of Wisconsin. Mr. DiFranco at Targeson noted that the founder's original PhD dissertation research was directly picked up through an NIH SBIR Phase I

BOX 7-2
The 2014 Survey—Comments on Company Formation

"The company would not have started and would not have survived without SBIR funding to get off the ground. . . . We are now financially independent of the SBIR program."

"SBIR funding has sustained the company since its inception. . . . The road to commercialization has included a clinical trial, peer-reviewed publications and navigation of the Medicare coding/coverage/payment process. This effort has taken many years; without SBIR support, the company would not have survived."

"Company was founded using SBIR/STTR to commercialize technology discovered in an academic laboratory. Would not have been founded otherwise (as an academic I had no prior interest in founding a company, but learned the process by serving on a panel review)."

"I would not have started this company without SBIR funding."

"The experience that I gained from starting [this company] led me to founding another company, which has two FDA [U.S. Food and Drug Administration] approved products and employs some 40 employees plus many contractors."

award. At ArmaGen, which commercialized research from Dr. Pardridge's lab at the University of California, Los Angeles, SBIR funding was central from company formation until the first round of venture capital funding 10 years later (see Box 7-2).

Funding for Small Innovative Businesses

Providing seed funding for company formation is an especially important program function because other sources of such funding have become more difficult to find. This difficulty reflects the increasing preference of venture capital firms for supporting more established companies and technologies. The case studies (and survey responses) underscored the many types of project for which alternative funding sources are scarce.

Companies noted that in general there have been two shifts in the funding landscape in recent years: first, venture capital retreated downstream toward projects that are closer to the market and hence both more expensive but less risky. Therefore, funding for seed-stage companies is increasingly difficult to attract. Second, strategic partnerships with large biomedical companies are difficult to find and to sustain. At Lpath, for example, a project with Pfizer was well advanced when the company simply decided to leave the sector, with minimal warning. Funding dried up as a result. It may also be that larger companies are also becoming more risk averse and hence require more evidence of likely success (e.g., completion of Phase II or Phase III clinical trials).

Companies also pointed out that the SBIR program has a special role to play in funding projects that do not fit well with commercial imperatives facing some large markets and the need for relatively quick returns. Advantagene, for example, noted that larger companies are not especially interested in addressing prostate cancer because the market is not large enough. This obstacle is more prevalent in even smaller markets: for example, ArmaGen is developing enzyme replacement therapies that can cross the blood-brain barrier for a pair of lysosomal storage diseases called Hurler syndrome and Hunter syndrome. Fewer than 10,000 people have these diseases in the United States.

Many of the research projects described in the case studies require many years of research. Dr. Swift at Auritec has spent the past 20 years working on extended-release drug delivery. Dr. Pardridge at ArmaGen has been working on the blood-brain barrier since the 1970s and the enzyme replacement therapies he has developed are only now reaching the end of clinical trials. Dr. Sabbadini founded Lpath in 1997. These high-risk projects with a long and uncertain path to market depend on SBIR funding to reach a stage where other investors may become interested.

These comments are further supported by evidence from the responses to the 2014 Survey: more than three-fourths of the respondents did not expect to find alternative funding for a project if their SBIR application had been rejected.

Company Existence

Dozens of companies providing comments in the 2014 Survey stated quite bluntly that they would not be in existence without the SBIR program. As expected, these companies include many very small firms that had limited access to alternative funding both at the time and now. However, they also include companies that had successfully moved far beyond the SBIR program. Some of the companies are now publicly listed with market capitalizations in excess of $1 billion, and others have made major contributions to public health. Box 7-3 provides broad views on the SBIR program from survey respondents.

Profiles of individual companies provide a more nuanced view and illustrate both the difficulties of raising very early funding and the critical role of the SBIR program in filling this gap. For many biomedical companies, the road to a successful product is long and expensive. Private investors are often reluctant to assume the risks involved, which can be substantial even for companies that raise significant outside funding. One company, for example, raised about $300 million in private investment funding (along with a substantial investment from NIH through the SBIR program), only for its lead candidate to fail in Phase 3 clinical trials. In few industries is such an enormous and risky investment required before the product's functionality is fully validated.

BOX 7-3
2014 Survey Responses—Company Existence

"The SBIR program is possibly the only source of funding that is available to support an idea that is not already supported with a prototype and a lot of validating data. . . . For an independent small company the SBIR program is the difference between existence and potential success and extinction."

"We could not have done any development without the SBIR awards[.] There is literally no other funding available that a small company can realistically hope to receive on their own."

"We wouldn't have a company without the SBIR program. If we did have a company, its goals in innovation and technology development would be much less ambitious."

"Without SBIR funding the company would not have survived its first year. Now we have been commercially active for nearly 30 years."

"Funding enabled us to develop all products and services; recruit skilled employees; attract investment capital. The company would not exist if the program didn't."

"Without SBIR funding our company would not exist. The result of the company and innovation has been screening of over 100,000 children for autism thus far."

Filling Funding Gaps

Many of the case study companies and a considerable number of survey respondents described major difficulties in raising funding before the end of clinical trials. The SBIR/STTR programs were designed to fill some of this gap, by providing funding that could be used for preclinical work, Phase 1 clinical trials, and in some cases work on Phase 2 trials.

Dr. Pardridge (ArmaGen) noted that, working with a well-connected lawyer, he initially approached 25 venture capital firms for funding and received one interview and no further responses. In 2010, ArmaGen again sought funding, armed this time with numerous papers explaining and validating its approach, as well as a growing record of research funded by the NIH SBIR program. However, none of the venture capital firms showed any interest. Eventually funding was raised from strategic investors, but throughout this process, the SBIR program provided irreplaceable funding.

Dr. Tseng said that for TissueTech, which has since become a highly successful $40 million/year company, NIH SBIR funding was especially important during the early 2000s when the company was still small and had very limited resources. At the time, SBIR funding paid for almost all of the development costs for TissueTech products.

Dr. Hoffman observed that absent SBIR program there was no possible source of funding for Sanaria's work: the private sector would never fund high-risk investments in areas where potential rewards were uncertain and likely to be much lower than those for chronic diseases.

Validation Effects

The NIH SBIR program provides sufficient funding for product development in only limited circumstances. However, both case studies and survey responses illuminate the ways in which SBIR/STTR awards can provide the technological and commercial validation that underpins acquisition of funds from other sources (see Box 7-4). In particular, companies stressed that the SBIR program can provide the necessary confidence that peer review brings, while the provision of non-dilutive funding sets the stage for successful efforts to raise funds in the private sector.

It is apparent from both case study meetings and survey responses that the NIH peer-review system plays an important role in validating SBIR/STTR for investors. The peer review provides a technical assessment that even a well-established venture capital firm would be hard pressed to match and that lowers risks for investors.

Among the case studies, Ms. Wojcicki (23andMe) said that SBIR funding had a powerful validating effect for the company, underscoring its efforts to

BOX 7-4
2014 Survey Responses—Validation

"The SBIR program is critical to funding early stage technology that has been both scientifically and business-wise vetted by highly skilled individuals. The benefit to the individual companies and the society at large cannot be overstated."

"Essential for our ability to attract private venture capital. It gave the company enhanced credibility. This is essential in pharmaceuticals given the current climate for VC funding."

"NIH funding in the form of SBIR/STTR programs gave us the credibility that we needed as an early stage biotech company... [It] gave private investors some comfort that the science has been vetted by peers and experts in the field."

"NIH funding is a critical indicator of the scientific value for a project, since applications are peer-reviewed by experts in the field. This helps reduce the perceived risk for potential investors."

"SBIR truly cultivates innovations. Personally, the NIH peer review process is the best mechanism to nourish the best innovations. Companies and investigators do work hard when the awards are given primarily on merit judged by peer reviewers."

present itself as a serious medical research organization as well as a direct-to-consumer genomics company. Dr. Sabbadini (Lpath) noted that the peer review undergone by SBIR projects and their eventual funding from NIH provided important validation when seeking other investments.

Staffing

Retention of high-quality technical staff is a perennial challenge for small innovative businesses. These businesses, particularly those in biotechnological fields, are challenged by the long periods encountered between the start of research and the eventual deployment of a product in the market. The need for approval by the U.S. Food and Drug Administration (FDA) in many cases adds many years to this timeline. In addition, because non-revenue status means that additional funding must somehow be acquired throughout that period, these small companies are constantly at risk of losing key staff simply through bumps in the funding timeline; a long gap can mean the elimination of key staff who may therefore not be available even if funding resumes.

The SBIR/STTR programs improve the certainty of funding over a period of at least 2 years (for Phase II), which provides small businesses with the confidence and means to hire and retain staff. (See comments on staffing in Box 7-5.)

BOX 7-5
2014 Survey—Comments on Staffing

"Our company has had 5 Phase I and 3 Phase II grants from different agencies since 1998. . . . They allow us to maintain R&D staff that were successful in producing both funded and other products."

"SBIR funding . . . allows for employment of post-doctoral fellows, research scientists and research assistants and facilitate training of interns in the field of vaccinology."

"Our company was also able to hire quality help to progress our company where additional technology can be developed, licensed, patented, and eventually commercialized."

"For a small company that is providing a specialized technical service, it is a constant challenge to balance staffing with demand for services. Having a body of strategic research and development work that is funded . . . that can be accelerated or slowed, really helps . . . it reduces the risk associated with hiring good staff because there is a large pool of work that can be done at a (relatively) flexible pace."

"Number of employees increased from 1 (founder/PI) to 5 with additional part-time consultants and university students as interns."

AGENCY MISSION

The NIH mission is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." Within that very broad framework, essentially all SBIR-funded activities can be included—indeed, it is difficult to see how SBIR projects would not contribute in some way to that mission.

That said, it is worth highlighting some of the ways in which SBIR/STTR projects have made and could make a difference. This section draws in particular on the case studies undertaken for this report. Other examples of high-impact research can be found in the survey responses and in the success stories highlighted on the NIH SBIR/STTR website.[1]

The companies listed below are addressing major high-priority diseases or needs. If successful, then their work will be transformative and will illustrate the long-term effect of NIH funding on health and welfare.

- Stratatech has developed a substitute for human skin for use in grafts to treat burn victims and others with major skin requirements. Its Stratagraft™ technology is absorbed into the body over a period of weeks, and photographs comparing standard autograft and Stratagraft treatments (see Appendix E, Stratatech case study) clearly show the potential importance of this work. The company recently received a contract from the Biomedical Advanced Research and Development Authority (BARDA) to scale up its ability to address a mass casualty event.
- TissueTech has developed ground-breaking technology (CryoTek™) to solve ocular surface problems and to develop an ocular transplantation graft, a glaucoma shunt tube graft, and a range of corneal bandage devices. The company now generates $40 million in revenues.
- ArmaGen is working on overcoming the blood-brain barrier to deliver therapeutic molecules into the brain. Dr. Pardridge notes that this issue represents a huge and rapidly growing societal challenge: he estimates the cost of caring for Alzheimer's disease and stroke victims at more than $500 billion by 2025, because the 65 and older population will grow by 50 percent during that period.
- 23andMe has made groundbreaking steps toward delivering low-cost ($100) genetic testing direct to individuals. The company had 700,000 individual customers as of October 2014. And even though it is still resolving regulatory issues with the Food and Drug Administration (as of April 2015), making such tests available has changed the way that individuals look at genetic testing.
- Conversion Energy has developed a biological adhesive system based on laser light curing of a biological compound fabricated from collagen as a

[1] See https://sbir.nih.gov/statistics/success-stories.

biological adhesive for wounds and surgeries. Such biological adhesives reduce infection by eliminating foreign matter at the wound site. They also accelerate wound repair and reduce scarring of the healed tissue.

Other NIH SBIR/STTR awardees are working on some of the most difficult and challenging areas of the life sciences. Sanaria now has in clinical trials the first malaria vaccine. Avaxia has a contract with BARDA to deliver anthrax vaccine for first responders nationwide. Avanti Polar Lipids has a new treatment for cystic fibrosis in clinical trials.

Innovative Technologies and Product Development

For the majority of SBIR/STTR recipients, the program supports work on the company's core technology. At least initially, few companies are large enough to advance multiple technologies, although in a number of cases companies are working on platform technologies that can then be further developed into a number of products that share a core technology. Over time, companies may grow to the point that they can support multiple projects, but are still small enough to qualify for SBIR funding, which can then be used more selectively.

For smaller SBIR/STTR companies in particular, funding for core technologies that are not yet proven is extremely difficult to acquire outside the SBIR/STTR programs. As noted elsewhere, the number of seed-stage venture capital investments has declined steadily over the past decade. In the fourth quarter of 2014, there were a total of 39 seed-stage deals in all industries. Overall, biotech accounted for 14 percent of all deals.[2] And according to the Center for Venture Research 2013 report on angel funding, 11 percent of deals were in biotech, funding about 8,000 companies with an average amount of about $350,000.[3]

Many of the companies responding to the survey noted that the SBIR/STTR programs have provided critical support in developing core innovations and platform technologies (see Box 7-6). This was also the case for many of the case studies (see below).

Attracting Venture Capital

Although there are important advantages to an infusion of venture capital (VC) funding for small innovative businesses, there are costs as well. The need to relinquish equity and, in many cases, control is well known. However there are other potential costs. Dr. Aguilar-Cordova (Advantagene) noted that VC funding requires both a tight focus on a specific product and a specific timeline to a funding event that will allow for an exit. The SBIR program permitted his company

[2]PWC MoneyTree™ Report, https://www.pwcmoneytree.com/, accessed April 24, 2015.

[3]Jeffrey Sohl, "The Angel Investor Market in 2013: A Return to Seed Investing," Center for Venture Research, April 30, 2014.

BOX 7-6
2014 Survey—Comments on Core Technologies

"We made a brain monitor that has been shown to improve patient outcomes. Without the SBIR funding, we won't be able to accomplish that."

"This STTR grant supplied the resources for us to build prototype live cell . . . tools . . . which resulted in the sale of our first instrument and . . . services we've sold to pharmaceutical and biotechnology companies."

"The technology developed under this program served as the cornerstone for development of [our] industrial metrology business . . . now responsible for about $5 million [in annual revenues.]"

"SBIR [funded] a novel ground-breaking platform technology that was used to develop a portfolio [of technologies] with high commercial value [which could] significantly reduce casualties in combat (KIA) and reduce mortality in emergency medicine following trauma."

"SBIR funding has been critical in supporting the company's vaccine research and development programs. . . . The SBIR program is vital for innovation in this field and should be expanded for its own value without sacrificing other federal research programs."

to work on a platform technology that could have applications to several different kinds of cancer, and he observed that this profile did not match the requirements of venture capital firms.

Other companies reported similar challenges in attracting VC financing to develop platform technologies and highlighted the importance of SBIR/STTR funding in this regard. The case study of ArmaGen shows that the company's technology to cross the blood-brain barrier can lead to a number of applications in high-priority areas such as caring for Alzheimer's disease and stroke patients. Another company, Auritec Pharmaceuticals, owns two technologies for extended-release drug delivery and has tested them to improve treatment for a broad range of medical indications.

Niche and Small Commercial Markets

Innovation companies, especially small innovation companies, are often driven at least initially by the passion of the founders to make a difference. What they often find is a substantial gap between technical success and commercial success, and between meeting the needs of the technology users and creating a sustainable or successful business.

Niche Markets

This is especially true when the market being served is small either in numbers or resources. Outside investors are often less interested in investing where markets are small and lower revenues make it less economically possible to complete the necessary clinical trials. FDA has recognized this reality by permitting the registration of products targeted at rare diseases. Some of these circumstances are discussed in the case studies of SBIR/STTR companies and highlighted below.

- ArmaGen is developing enzyme replacement therapies that can cross the blood-brain barrier for a pair of lysosomal storage diseases called Hurler syndrome and Hunter syndrome; fewer than 10,000 people have these diseases in the United States. If successful, ArmaGen plans to apply its technology to other diseases with larger markets.
- Advantagene uses SBIR funding to support research in smaller or less remunerative markets, for example cervical cancer, which is a problem for some developing countries.

Serving the Research Community

Many SBIR/STTR companies do not work directly on patient diseases or dysfunctions. Instead, they serve the research community. The products and services they deliver are therefore rarely of the scale needed to deliver very large commercial successes. Nonetheless they are of enormous importance to the biomedical ecosystem as whole: they provide the tools that others use to address large-scale problems.

- GMS Biotech has developed a technology that turns high resolution DNA analysis into a benchtop test that can be performed with simple equipment and little training. The company believes this technology can in the medium term be a key facilitator for personalized medicine. It is currently targeted at the 4,000 ASHI-certified labs worldwide.
- NOVA Research provides its SBIR-funded QDS (Questionnaire Development System) for data collection and management to researchers worldwide. QDS is currently used by 13,000 researchers.

These are usually small and highly technical markets, although they can in some cases become very substantial: Illumina, an SBIR-funded company described in the 2009 assessment by the National Research Council[4] of the NIH

[4]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council are used in an historic context identifying programs prior to July 1.

SBIR program, now has a market cap of more than $30 billion, from providing genetic testing services.[5]

Long Cycle Research

One of the challenges for biomedical research is that it takes a long time to reach the market. Several of the founders of the case study companies have been working on their projects for more than 20 years, and still have to reach the market.

This is challenging because of the very long period before revenue starts and because the core funders of biomedical research aside from the government (strategic partners, usually from large pharmaceutical companies, and venture capital investors) are increasingly reluctant to fund projects that are not well along the path to market.

The NIH SBIR/STTR programs therefore play a particular role in funding the early development of technologies that may have enormous social or even commercial value downstream, but which are too far from the market to be funded by other sources. (See Box 7-7 for survey respondent comments.)

Connections to Research Organizations

Although the STTR program is specifically designed to connect small companies to research organizations, this is also accomplished to a considerable degree by the SBIR program. Data from the survey is provided in Chapter 5, but case study meetings and survey comments underscored the closeness of the connection for many companies. (See Box 7-8 for comments on collaboration.)

- Advantagene has relationships with a number of universities and research organizations, such as Johns Hopkins University, the University of Pennsylvania, Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Lurie Children's Hospital (Chicago).
- Stratatech is commercializing technology spun out of the University of Wisconsin lab managed by its founder, Dr. Barbara Allen-Hoffman.
- ArmaGen's innovative solutions to the blood-brain barrier derive directly from the 3 decades of funding received by Dr. Pardridge at the University of California, Los Angeles.

For small companies, the capacity to attract the right collaborators is often a critical part of the process from initial idea to eventual product. Companies may need access to expensive equipment, often located in a university. They may

[5]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, Washington, DC: The National Academies Press, 2009, Appendix D.

BOX 7-7
2014 Survey—Comments on Long Cycle Research

"SBBIR/STTR has allowed our company to pursue R&D of valuable technologies and products that are higher risk or take longer to generate a return on investment."

"The funding allowed us to pursue high risk software development that had a fairly long time to market and market adoption."

"All founders spent significant life time [and] effort to develop and de-risk, translate the technology for industry partners and commercial markets."

"[SBIR] allows for obtaining funds for development of innovative technologies with the pace that is not artificially skewed by short-term commercial interests."

"This program allowed our core technology to incubate for a period of time that allowed us to advance the technology to the point where strategic partners became interested. Without SBIR funding we could not have gotten the technology to this point and the company would have likely failed."

BOX 7-8
2014 Survey—Comments on Collaboration

"We would never have been able to develop this product, conduct the necessary clinical trials, solidify a strategic partnership, and get it to commercialization without SBIR funding."

"The timeliness of the [SBIR] funding allowed us to form a partnership with the American Academy of Surgeons, which was extremely important for the content, credibility, and fidelity of the simulator."

"The NCI SBIR funding allow us to bridge the "Valley of Death" resulting in a significant corporate partnership and other fundraising efforts. . . . We have nearly completed enrollment in the Phase 2 [clinical] trial."

"SBIR funding bridged the 'Valley of Death' and allowed us to partner with our corporate partner as we received a Bridge Span award that . . . allowed us to obtain a partnership for the Phase 2 clinical trials."

"Without these awards, we would not have reached our milestones, and would not have been able to partner 2 of our 3 drug candidates with a major pharma company."

need technical help from experts. They may need help with funding and especially organizing clinical trials. In particular, they may need help with marketing their products and services. For NIH companies, links to universities and other research organizations may be especially important.

Yet meeting all of these needs requires that the small business overcome some substantial barriers. Some are simply financial—the SBIR/STTR programs

may provide the funding needed to access tools and equipment, or to hire the right consultants. But often, the SBIR/STTR programs provide a unique mix of validation and funding for the acquisition of preliminary data needed to persuade potential partners that the technology has value, that the management team is competent, and that the company is sufficiently stable to be worth partnering with.

The case study companies described not only partnerships with a considerable number of research organizations and commercial partners, but also partnerships to meet a number of different needs and objectives:

- Auritec partners with numerous research organizations, including the University of Southern California, Albert Einstein College of Medicine, Oak Crest Institute of Science, International Partnership for Microbicides (IPM), CONRAD, Centers for Disease Control and Prevention (CDC), The University of North Carolina, University of California, Irvine, Emory University, North Carolina State University, and The University of Massachusetts. Each provides different capabilities to Auritec. For example, Auritec looks to the Albert Einstein College of Medicine for expertise on HIV, The University of North Carolina for expertise in HSV, and the University of Southern California for expertise in pharmacokinetics.
- TissueTech maintains research relationships with organizations such as Bascom Palmer Eye Institute, the New York Eye and Ear Institute, Walter Reed National Medical Center, and Columbia University.
- Sanaria is undertaking clinical trials with a wide range of partners in the United States, Africa, Asia, and Europe, including a number of different stakeholders: African governments, Marathon Oil, nonprofit foundations, universities and research labs, and private companies. Sanaria recently signed a path-breaking agreement with Marathon Oil and the government of Equatorial Guinea to completely fund clinical trials through Phase III through $48 million in support. (Box 7-8 captures some of the survey response comments focused on collaboration.)

PROGRAM MANAGEMENT

Feedback from case study executives and the survey respondents indicate that issues related to project (or proposal) selection and review are of considerable concern. Many of the case study meetings were with scientists who also served on NIH study sections, so they could provide perspectives both as a reviewer and an applicant.

Innovation, Novelty, and the Challenge of Assessing Commercialization Potential

Executives of companies participating in the case studies were more concerned about review-related issues than any other aspect of the program, other than the limited funding available to support clinical trials. They were especially concerned about the preponderance of academic scientists in review panels and its effect on review outcomes.

Dr. Allen-Hoffman (Stratatech) noted that the alignment between topics and awards has changed significantly over the past 10 years. During her early years with the program, she was confident that a strong project would receive consideration and perhaps funding regardless of its connection to a topic described in the Omnibus Solicitation. That has changed, and Stratatech now only applies for awards where there was a clear alignment between the topic and the proposal. In her view this is not a positive development.

Dr. Aguilar-Cordova (Advantagene), who has held academic positions for nearly two decades at Harvard Medical School and Baylor College of Medicine, said that his experience as a reviewer had changed his perspective. Reviews used to be conducted primarily in person, with one primary reviewer per project, one secondary reviewer, and one reader. The group as a whole would listen to the discussion between the reviewers. The process is now conducted primarily via asynchronous review through the internet. Reviewers only see the comments of the primary and secondary reviewers, followed by a vote in which the group almost always follows the primary and secondary reviewer. He also observed that while the SBIR program provides funding for small business, the majority of reviewers are academics. This results sometimes in a misunderstanding of research and development (R&D) as conducted in the private sector. For example, a recent Advantagene proposal was criticized because "two key people were from the same company"—a comment not relevant to private-sector research.

Ms. Soltz (CEE) observed that the heavy preponderance of academic reviewers tends to tilt the playing field toward university-based applicants (her most recent panel had two small business participants out of a total of eight). Not only did these researchers have notable advantages through access to the huge base of university resources (including low cost labor in the form of graduate students, facilities, and sometimes university intellectual property), but also they were in her opinion less prepared to turn good ideas into commercially successful projects.

Several executives noted confusion in the review process between innovation and novelty. The former requires path-breaking research. The latter involves the long process of refining results to the point that a commercially sustainable innovation can be marketed. More widely, SBIR reviewers often misunderstand the relationship between innovation and novelty, and between novelty and product development.

Dr. Aguilar-Cordova (Advantagene) said that the long process of product development is sometimes criticized by academic reviewers as insufficiently

innovative. The entire project may be an innovative solution, but the grind of proving the concepts may not look much like innovative research. Another CEO contacted in the course of this study observed that the predominance of academics on study sections is unfortunate, in particular because they tend to take a narrow view when defining innovation. They tend to lower scores of projects that they see as insufficiently innovative, perhaps as compared with viewing them as an NIH Research Project Grant Program (RO1) application.

Dr. Swift (Auritec) focused on the role of Scientific Research Officers (SROs) who manage study sections. He noted that in general they subscribe to and support the focus on novelty. He identified a number of cases in which potentially important innovations were rejected by study sections on the grounds that they were insufficiently novel. He urged NIH to refocus the role of SROs so that they become defenders of innovation. In his opinion, this could be accomplished relatively easily once NIH decides that this shift would be appropriate. SROs could provide detailed instruction on the definition of innovation at the start of the study section and could also provide ongoing direction to ensure instructions are followed.

Dr. Hoffman (Danya) observed that, at the same time that SBIR has become more competitive and selective, the selection process has tilted further toward science rather than commerce. Commercialization reviews at NIH are "fairly generic," that is, not a careful analysis of a product's return on investment.

One CEO suggested that NIH ensure that the chair of the study section is a person with product development experience. He also said that more rotation of study section members, including in particular section chairs, would be a positive step toward ensuring that appropriate selections are made.

Box 7-9 provides some of the detailed comments on review offered by survey respondents.

Dr. Hoffman (Sanaria) said that proposal review panels largely include majorities of mediocre academic scientists who have little understanding of translational research. On the other hand, some of these scientists are also potential competitors, and Sanaria has in several instances asked for specific reviewers to be removed from panels addressing its proposals. Overall, the quality of reviews—especially of business reviews—was relatively poor.

Improving the Process

Rebuttal and a More Iterative Application Process

A number of executives from the case study companies shared their frustration with the inability to rectify minor problems with applications upon first submission, which forces them into resubmission and hence into lengthy delays. Several executives suggested different ways in which the connection between applicant and study section review panel could be improved.

BOX 7-9
2014 Survey—Comments on the Review Process

"Often review panels do not understand the FDA process and difficulties getting clearance or approval from the FDA. . . . Review panel members should be educated on the purpose of Phase IIBs before the review panel and proposal reviews take place."

"Give proposal reviewer fewer proposals to review so they can do a better job. Insist that reviewers who do not understand what is proposed recuse themselves from being one of the three primary reviewers."

"Most SBIR study sections are made up of academic investigators with little to no understanding of the FDA or the commercialization process. SBIR grants are handled as if they were R01 or R21 proposals."

"(The) majority of the reviewers for SBIR/STTR are professors, who have no commercialization backgrounds or experiences. Good research proposal[s[and idea[s] may not lead to good products to fit the market. I think the reviewer committee should add some reviewers with more marketing and product development background to evaluate the proposals in addition to the scientific reviews."

"Stay transparent and fund grants based on a payline so that the scientific reviewers choose the grants to be funded based on the strength of the technology and the need it serves."

"The NIH review process for SBIR/STTR has become more and more frustrating to all device companies. The funding repeatedly rewards proposals including complex biochemical research devoted to a new test or therapy that will be of little direct benefit to patients."

Dr. Aguilar-Cordova (Advantagene) called for selection to be an iterative process. Reviews are already uploaded into the system a week or two in advance of the review panel meeting. It would require minimal additional effort to permit companies to read preliminary reviews and to offer additional information (perhaps only a page) for the record. This would be a "fantastic way to improve things," according to Dr. Aguilar-Cordova, and would make the review process more like the peer-review process for scholarly publications.

Dr. Swift (Auritec) noted that a brief rebuttal process could accelerate review, reducing costs for companies and improving the efficiency of the review process for NIH. A response of less than one page could easily be generated before a study section meets, or indeed during the meeting itself. Dr. Swift also noted that this kind of interactive approach was standard at the FDA, where IND applications are generally subject to a number of rounds of correction and improvement.

Dr. Pardridge (ArmaGen) considered the idea of the ability to respond to initial reviewer comments to be promising, but he was concerned that it might not be practical.

White Papers

Dr. Swift observed that, in his experience, a majority of applications are very poor quality and that a white paper process in which applicants are required to submit a brief summary for review by program officers could lead to a sharp reduction in the number of eventual applications, which would reduce the workload for both companies and reviewers. He cautioned, however, that this process should not be used as a hard filter and that projects receiving negative responses to the white paper should still be permitted to apply.

Dr. Hogan (GMS) suggested that NIH explore the adoption of a white paper approach that could draw on the experiences at the National Science Foundation (NSF) and the Department of Energy (DoE). This approach reflects his strong belief that "study section should not be king—they should be viewed as important high level consultants, not decision-makers."

Funding Gaps and Timelines

Many company executives indicated that funding gaps are a major concern. Ann Wojcicki (23andMe) argued that the slow pace of the application and award cycles made the SBIR program essentially untenable as a funding source in fast-paced sectors such as genetic testing.

Dr. Aguilar-Cordova (Advantagene) said that that SBIR awards process at NIH is very slow, especially in comparison with industry, even if resubmission is not required. An application made in May might eventually be funded in May of the following year. Resubmission currently causes a 2-year delay because comments are returned too late to meet the next submission cycle. Speeding up the delivery of comments by just a few weeks would save companies a year of time and expenses.

Dr. Swift noted that pink sheets, which provide the basis for resubmission, are delivered too late for the next submission deadline, imposing an 8-month delay on applicants. He observed that this was not the case for HIV/AIDS proposals and suggested that NIH work to make this more rapid process available to all applicants; for small companies, this kind of delay could be very serious.

Survey respondents raised a number of general concerns about timelines, which are summarized in Box 7-10.

Alongside the general concerns noted above, survey respondents had particular concerns about the gap between Phase I and Phase II. This gap is also addressed in Chapter 5, where survey data reveals it as a persistent problem. Box 7-11 summarizes some of the survey respondent comments on this issue.

BOX 7-10
2014 Survey—Comments on Timelines and Funding Delays

"Reduce delay between application and award decision and actual award (can stretch to 12 months or longer). Reduce administrative delays for non-competitive renewals (delays of several months are often encountered). Better communication, particularly in regard to F&A cost negotiation. Reduce delays in F&A negotiation. We experienced 12+ month delays in processing proposals."

"Reduce time between application and award decision. This has taken more than 12 months in our case. Reduce administrative delays in funding release each year during phase II. This has taken greater than 4 months in our case. That is we have at times experienced a four month delay between years of Phase II."

"Overall, the process of submission, review, & funding was fair, but agonizingly slow. One must start the Phase II proposal process almost as soon as Phase-1 funding is received in order to avoid funding gaps. Combined Phase-1&2 awards with clear milestones, prompt and rigorous review, and realistic deliverables would be a more efficient system."

"Shortening the time between Phase I and Phase II, (re)balancing awards and the award process so that most of the Phase I's awardees receive Phase II funding."

"Faster review cycles. Currently it takes approximately 1 year between conception of a research project and funding. . . . Review feedback within a month or two after submission would be very helpful even if the actual funding comes later."

BOX 7-11
2014 Survey—Comments on the Phase I-Phase II Gap

"Improved access to gap funding and/or ways to reduce the gap between Phases 1 and 2, since the odds of winning a fast-track NIH grant are close to zero."

"The funding gap between Phase I and II is difficult. Some thought needs to be given to gap funding. A reduction of time between Phase I and II would be very helpful."

"Address the Gap between Phase I and Phase II. Create review cycles that allow for earlier re-submit of un-funded grant applications."

"Opportunities for gap funding (with suitable milestones met) would help to retain valuable/trained staff used on the Phase I and would help to assure a smooth transition to Phase II."

"Reducing the gap time between Phase I and Phase II would be most helpful, or providing some Phase I to Phase II interim funding, as this being an IT technology, others were filling the gap for the product while [our company] was waiting on the Phase II award."

Innovative Funding Mechanisms

Phase IIB

Dr. Aguilar-Cordova (Advantagene) applied for a Phase IIB award from the NCI Bridge program, but found that the company's proposed match of extensive in-kind contributions (in the form of expensive cancer-treating drugs, which would be provided free to the clinical trials conducted by a large pharmaceutical company) did not meet National Cancer Institute (NCI) requirements for matching funds. Ironically, if the pharmaceutical company donated cash to Advantagene, which then used the cash to pay the company for the drugs, NCI's match would be satisfied. But the drug company did not have procedures in place to permit such a transaction.

Dr. Hogan (GNS) said that the Phase IIB program is an excellent idea. He noted that the valley of death is a large and growing problem and that such a program is critical given the absence of other NIH funding and declining interest in early-stage investments from venture capital firms and large pharmaceutical companies. In the current environment, he believes it is extremely difficult to attract outside funding if the company does not have a product ready to sell: it is not necessary to have substantial sales, but some sales have to be at least imminent. Dr. Hogan also noted that the timeframe of the Phase IIB program is somewhat unrealistic: moving from the end of Phase II to marketing a product (as a medical device or a drug) in 3 years is an extremely fast track to market.

At Lpath, Dr. Sabbadini, who sits as reviewer on Bridge awards, believes that other Institutes would be well served to follow NCI's example with regard to Bridge awards.

Mr. DiFranco (Targeson) said that the NCI Bridge program is important given the difficulties in funding clinical trials but that it could be improved. In his experience, neither venture capital firms nor strategic investors believe that the program met their needs. It requires matching funds up front, while it provides money only on an annual basis ($1 million annually), and requires that the funding be fully committed before the award is made. It does not recognize contributions other than cash investments. As a result, potential investors are reluctant to commit before the award is made. Take-up of these opportunities has, as a result of these difficulties, been slow, and Mr. DiFranco urged NIH to find a way to make a preliminary commitment pending the completion of matching fund arrangements.

Dr. Hogan (GMS) also observed that Phase IIB does not provide sufficient funding to complete FDA review. Although $3 million is not insignificant, it is still considerably less than required to meet the program's goals (he estimated that completion of FDA review would cost his company $6-9 million). Currently, Phase IIB provides enough money to enter the regulatory structure, hire consultants, put quality systems in place, and begin to pay for the start of studies. He therefore suggested that the maximum size of Phase IIB awards be increased to

$5 million and permit funding of business personnel to perform functions mandated by the required business plan. Dr. Rose (Auritec) also urged that Congress consider increasing the size of awards at NIH so that they could be used to fund Stage 1 and Stage 2 clinical trials. He believes that fewer but larger awards would be appropriate. In particular, he suggested increasing the size of Phase IIB awards to $1.4 million for 3 years.

Fast Track

Dr. Allen-Hoffman said that Stratatech participated in the Fast Track program in the early 2000s when working on developing cell-based clones. The company feared that the Phase I-Phase II gap would kill the project. Fast Track worked perfectly from the company's perspective. It provided a seamless transition from Phase I to Phase II, allowing the company to retain key people. Continuity of staffing remains a key issue for small companies.

Direct to Phase II

Dr. Swift (Auritec) approved of the recent NIH decision to pilot a direct approach to Phase II awards: he noted that many companies already have feasibility data for projects and could therefore move forward without Phase I. This pilot will also have the effect of substantially accelerating the overall project by providing more funding more quickly. Dr. Swift noted, however, that this might squeeze out startups that rely on Phase I funding for early data.

Case Study and Survey Respondents Comments on Other Issues

The Relative Decline of Investigator-Initiated Proposals

In the view of some stakeholders, the rapid switch away from grants toward contracts at NCI reflects a wider shift toward tighter direction of funding by the Institutes themselves. Funding also now flows more through tightly-specified Funding Opportunity Announcements and correspondingly less through the standard omnibus solicitation. Dr. Aguilar-Cordova (Advantagene) suggested that NIH continue to support investigator-initiated proposals, which is a hallmark of the NIH program but is being steadily eroded by a push toward programs defined in advance by the Centers.

Support for Working with the Food and Drug Administration

Many survey respondents highlighted their difficulties in working with FDA to receive approval for required clinical trials. The following possible solutions were offered:

- Hiring and making available FDA consultants (as is the case with the National Heart, Lung, and Blood Institute)
- Better education for applicants starting at a relatively early stage through NIH-sponsored webinars and workshops
- Improved training and better processes for study section panelists, where there appears to be a an information gap related to FDA requirements
- Strategic review by NIH and FDA of NIH vision for innovation and FDA caution
- Advocacy for NIH projects at FDA
- Survey responses related to FDA approvals are summarized in Box 7-12.

Allowable Costs

Under current regulations, SBIR/STTR funding may only be used for research, and published guidelines define what expenditures are acceptable. Many awardees profiled in the case studies argued for more flexibility, particularly with regard to patenting costs and the need to spend on commercialization.

BOX 7-12
2014 Survey—Comments on FDA Approvals

"Small businesses are often inadequately informed about the requirements and process for obtaining FDA approval for products they envision. Efforts by the NIH to 1) educate and encourage small businesses to appropriately approach the FDA for regulatory approval and 2) encourage the FDA to work with and facilitate the regulatory process for medical devices arising from NIH-funded small business and academic grants would be enormously helpful."

"There is a huge disconnect between NIH and FDA. FDA is looking for more simple solutions to problems (i.e. one drug delivery) and NIH reviewers are typically looking at extremely innovative solutions, which FDA does not look favorably upon. There needs to be a better connection between the two."

"FDA process is very uncertain and heavily dependent on the particular reviewers assigned to the application. Any help with respect to helping small business to receive from the FDA more clear guidance with respect to the Agency's expectations regarding the supporting clinical data needed would be of a huge significance and help avoid small companies going out of business due to uncertainty and long lead time associated with the FDA process."

"It would be great if the NIH hosted a web site, webinar, handouts, etc. explaining more clearly how to approach and work with the FDA; these materials should be oriented to small firms with no prior FDA experience."

"Small businesses are uneducated and intimidated by the requirements for obtaining FDA approval. NIH could assist by (1) facilitating appropriate timely communication between the small business and the FDA and (2) encouraging the FDA to reach out in a user-friendly way to small businesses."

Dr. Pardridge (ArmaGen) said that patent costs represented part of the outcome from the grants and that protecting IP was likely to generate better commercial outcomes. It is therefore in the interests of the taxpayer to permit some use of SBIR funding for patent costs.

Dr. Hogan (GMS) noted that Phase IIB does not fund any commercial or marketing personnel, but these are absolutely necessary for a commercial venture capital, which is what Phase IIB is designed to help fund. He suggested that either NIH or Congress should consider changing these limitations to permit a more realistic approach, in which a limited percentage of Phase IIB funding (perhaps 30 percent) be used for commercial activities. He thought this could be a transformative change for Phase IIB companies: Phase IIB would not only provide funding for FDA review, but also would more broadly help fund the shift toward commercial activities.

Dr. Hoffman (Danya) said that even a great product needs marketing: Danya's autism products are highly reviewed, but an extensive outreach campaign, for example through Google, would cost $100,000, and would be unallowable under SBIR awards.

Contracting Concerns

Dr. Allen-Hoffman (Stratatech) said that contracting has become more difficult at NIH because there is no longer an ability to develop a relationship with specific financial management officers. As a result, the advice received is more uneven, which matters in particular in relation to indirect costs, for which approved rates are published only 2 years or so after the costs are incurred, and hence good advice is especially important to a small firm trying to budget accurately.

Commercialization: Competition from Free Sources of Information

A closer focus on outcomes tracking and analysis would help NIH to fund projects, which would provide the best return on the investment (considering all aspects of "return"). The comments below from Danya illustrate how such an analysis could help guide NIH away from funding projects that are technically strong and address a clear need but nonetheless will never generate either commercial returns or even take-up and use.

Dr. Hoffman (Danya) believes that there are fundamental difficulties that essentially preclude commercialization of educational and support materials in the health care sector: competition from free sources is simply too great, particularly as other parts of the government (for example, the Centers for Disease Control and Prevention) continue to publish high-quality resources that are available at no

cost to the user. The Substance Abuse and Mental Health Services Administration (SAMSA) is another major federal source of free materials.[6]

Overall, Dr. Hoffman concluded that even generating substantial take-up when materials are free is a problem. Unless a product is adopted by a large organization, it is simply not feasible to expect that it will generate traction among users.

STTR

Dr. Allen-Hoffman (Stratatech) said that the STTR program was particularly important for her company. Once Stratatech was established as a functioning company, and the basic research was completed, other sources of funding became more available. But some of the initial work—such as work on genetically enhanced tissues—had to be completed in the university lab because the necessary equipment was not available elsewhere.

She believes that academic organizations continue to view STTR more favorably than SBIR, particularly with regard to issues related to the allegiance of faculty. University departments take a different view of projects where more of the work and most of the PI's time is committed to the university as opposed to the private sector. Dr. Allen-Hoffman observed that despite some changes, tenure decision committees are still very conservative about the activities of junior faculty outside academia, and STTR provides a modestly useful mechanism for helping to resolve that tension.

[6]See http://www.samhsa.gov/.

8

Findings and Recommendations

The findings and recommendations in this chapter reflect the performance of the NIH SBIR/STTR programs against the broad congressional objectives for the SBIR and STTR programs.[1]

For SBIR, these objectives were reiterated in the 2011 program reauthorization and elaborated in the subsequent policy directive of the Small Business Administration.[2] Section 1c of the Small Business Administration (SBA) SBIR Directive states program objectives as follows:

> *The statutory purpose of the SBIR Program is to strengthen the role of innovative small business concerns (SBCs) in Federally-funded research or research and development (R/R&D). Specific program purposes are to:*
>
> *(1) Stimulate technological innovation;*
> *(2) use small business to meet Federal R/R&D needs;*
> *(3) foster and encourage participation by socially and economically disadvantaged small businesses (SDBs), and by women-owned small businesses (WOSBs), in technological innovation; and*
> *(4) increase private sector commercialization of innovations derived from Federal R/R&D, thereby increasing competition, productivity and economic growth.*[3]

The parallel language from the SBA's STTR Policy Directive is as follows:

[1] See Box 1-2 and the discussion of the Committee's task in Chapter 1 (Introduction).
[2] SBA SBIR/STTR Policy Directive, October 18, 2012.
[3] Ibid., 3.

> *"(c) The statutory purpose of the STTR Program is to stimulate a partnership of ideas and technologies between innovative small business concerns (SBCs) and Research Institutions through Federally-funded research or research and development (R/R&D). By providing awards to SBCs for cooperative R/R&D efforts with Research Institutions, the STTR Program assists the small business and research communities by commercializing innovative technologies."*[4]

The findings below review the extent to which each of these program objectives is being addressed at NIH, as well as examine some specific aspects of NIH's management of the program.

FINDINGS

The Small Business Innovation Research (SBIR) program at the National Institutes of Health is having a positive overall impact. It is meeting three of the four legislative objectives of the program with regard to stimulating technological innovation, using small businesses to meet federal research and development (R&D) needs, and increasing private-sector commercialization of innovations derived from federal R&D. However, we find that more needs to be done to "foster and encourage participation by socially and economically disadvantaged small businesses (SDBs), and by women-owned small businesses (WOSBs), in technological innovation." The Small Business Technology Transfer (STTR) program at the National Institutes of Health is meeting the program's statutory objectives, defined above.

The order in which the findings below are presented reflects the committee's relative emphasis. The first set of findings focus on the commercialization of SBIR/STTR funded projects. This is followed by findings concerning the participation of women and minorities in the program. The third and fourth sets of findings address how well the NIH SBIR/STTR programs are stimulating technological innovation and fostering innovative companies. The final set of findings concern the management of the programs at NIH.

Sources of Findings

The committee's findings are based on a complement of quantitative and qualitative tools including a survey, case studies of award recipients, agency data, public workshops, and agency meetings. The methodology is described in Chapter 1 and Appendix A of this report. In reviewing the findings below, it is important to note that the Academies' 2014 Survey—hereafter referred to as the 2014 Survey—was sent to every principal investigator (PI) who received a Phase II award from NIH, FY2001-2010. PIs were asked to complete a maximum

[4]Small Business Administration, Office of Investment and Innovation, "Small Business Technology Transfer (STTR) Program—Policy Guidance," updated February 24, 2014.

of two questionnaires. The preliminary population prior to contact was 3,375. Of these, 1,723 were determined to be not contactable at the SBIR/STTR company listed in the NIH awards database. The remaining 1,652 awards constitute the effective population for this study. We received 726 responses, for a preliminary population response rate of 21.5 percent and an effective population response rate of 43.9 percent.

I. Commercialization

The focus at NIH has primarily been on the commercialization of SBIR/STTR funded projects and on the development of technologies that help to meet the agency's mission (discussed separately below). The committee recognizes that issue of commercialization is complex.[5] For NIH, these objectives are primarily met when projects are commercially successful in private-sector markets. Keeping in mind the low response rate for the 2014 survey, the key findings are as follows:

A. SBIR/STTR projects at NIH commercialize at a substantial rate.[6]

1. Sales are reported by a substantial fraction of the survey respondents: Forty-nine percent of SBIR and STTR respondents reported some sales or licensing revenues at the time of the survey, and a further 25 percent expected sales in the future, according to the 2014 Survey.[7] This is similar to the rates reported in the 2005 Survey (46 percent and 19 percent, respectively) as reported in the Academies' 2009 report on the NIH SBIR program.[8]
2. Sales anticipated: These rates inevitably undercount the eventual share of projects that generate sales, and an additional 25 percent of Phase II respondents reported that they anticipate future sales.[9]
3. There is room for improvement: The large number of companies with small-scale revenues suggests that while many companies reach the market, fewer can be described as successful in commercial terms.[10] Despite the high percentage of SBIR/STTR projects with sales, the amount of sales was often small: of those with some sales, 39 percent had sales less than $100,000. Six percent had sales over $10 million.[11]

[5]See the discussion on Defining "Commercialization" in Chapter 5.

[6]NIH does not yet have in place internal capacity to track project outcomes.

[7]See Table 5-7.

[8]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health,* Washington, DC: The National Academies Press, 2009, Figure 4-4, p. 88.

[9]See Table 5-7.

[10]See Table 5-8.

[11]See Table 5-8.

B. NIH SBIR/STTR projects are primarily commercializing in the domestic private sector.

1. According to the 2014 Survey, 57 percent of responses with sales reported revenues from domestic private-sector customers.[12]
2. Seventeen percent reported export customers.[13]
3. Eleven percent of responses identified customers in the public sector (primarily state and local governments or other federal agencies).[14]

C. Further investment in NIH SBIR/STTR projects is additional evidence of commercial activity. Subsequent investment in NIH SBIR/STTR projects is an indicator that they are expected to generate substantial commercial value even if they have not yet reached the market. The 2014 Survey shows that:

1. About 80 percent of 2014 Survey respondents reported additional investment funding.[15]
2. The most likely source of additional funding (other than their own company and personal funds) was the U.S. private sector (44 percent of responses). This included funding from strategic investors (21 percent), angel investors (14 percent), and venture capital (10 percent).[16]

D. NIH SBIR/STTR awards are not overall associated with substantial direct job growth, but some awardees grew rapidly.

1. The 2014 Survey indicates, based on responses received, that the median size of firms with NIH awards remained flat on average at seven employees between the time of award and late 2014. Other things being equal, larger employment gains are more typically associated with the long-term commercialization phase of the resulting innovation, rather than with the research phase.
2. Some firms grew rapidly, however, as mean employment grew from 19 at the time of award to 88 employees on average at the time of survey.[17]

E. For small innovative firms, SBIR/STTR funding makes an important difference to project outcomes. SBIR/STTR funding makes a substantial

[12]See Table 5-9.
[13]See Table 5-9.
[14]See Table 5-9.
[15]2014 Survey, Question 30. N=572.
[16]See Table 5-13.
[17]See Tables 5-10 and 5-11.

difference in determining project initiation, scope, and timing. The 2014 Survey data show that:

1. Seventy-four percent of respondents reported that the project probably or definitely would not have proceeded without SBIR/STTR funding.[18]
2. Fifty-seven percent of those who would likely have proceeded anyway reported that the project would have been narrower in scope.[19]
3. About one-third of those who would likely have proceeded anyway reported that the project would have been delayed by at least 1 year.[20]

F. Venture capital funding plays only a modest role for NIH SBIR/STTR firms.

1. Venture capital funding plays an instrumental role in the eventual commercialization of many medical therapeutics and devices. The 2011 reauthorization permitted NIH to use up to 25 percent of its SBIR/STTR funding for projects submitted by companies that are majority owned by venture capitalists.
2. However, while 80 percent of respondents surveyed reported that they raised additional investment funds, only 10 percent reported that the funding included funds from venture capitalists (VCs).[21] Most NIH SBIR/STTR projects do not meet the narrow criteria set by VC firms, including timeline to market exit, size of opportunity, amount of funding required, capabilities of the management team, and industry sector.

G. NIH SBIR/STTR firms face challenges particular to the commercialization of biomedical technologies.

1. A large proportion of NIH SBIR/STTR projects must receive approval from the Food and Drug Administration (FDA) before they can reach the market. Responses to the 2014 Survey indicated that 45 percent of funded SBIR and STTR Phase II project products required FDA approval.[22]
2. The FDA regulatory process is often a barrier for SBIR/STTR companies. While costs vary, the overall cost of a Phase 3 clinical trial is normally much more than is available through SBIR/STTR, even with additional funding through Phase IIB. Funding in the tens of millions of

[18]See Table 5-31.
[19]2014 Survey, Question 26A.
[20]2014 Survey, Question 26A.
[21]See Table 5-2.
[22]See section on "Survey Data about FDA Approval" in Chapter 2 (Program Management).

dollars is not exceptional.[23] SBIR/STTR companies often do not have sufficient expertise in dealing with the FDA.[24]

3. Extensive evidence from open-ended survey responses solicited in the 2014 Survey and from case studies indicates that small innovative companies do not have a straightforward pathway to funding for clinical trials. As a result, about one-half of the NIH SBIR/STTR awardees face a major funding challenge before they can reach the market.

    - NIH has no dedicated mechanism to fund clinical trials.
    - 15 percent of respondents who were engaged in clinical trials mentioned venture funding.
    - Less than 10 percent of respondents mentioned "other company" funding, which in this case would include large pharmaceutical companies.

II. Fostering the Participation of Women and Other Underserved Groups in the SBIR/STTR Programs

A. Current outcomes data show that the objective of fostering the participation of women and underserved minorities has not been met by the NIH SBIR/STTR programs.

1. Levels of participation by underserved groups are low and declining.

    - Data from NIH indicate that the share of Phase I awards made to SBIR/STTR Minority-Owned Small Businesses (MOSBs) has declined from a peak of 3.5 percent in 2006 to less than 2 percent in 2014.[25] The pattern for Phase II awards is more variable, but the trend there too is downward.[26]
    - MOSBs also show lower success rates for both Phase I and Phase II applications than non-MOSB applicants. The success for Phase I MOSB applicants was lower in every year, and averaged 10.1 percent across the period, while the rate for non-MOSB applications was 18.3 percent.
    - The success rate of Phase II MOSBs averaged 6 percentage points lower over the period, and was lower for every year except 2010 and

[23]For example, Sanaria recently announced an agreement for clinical trial funding for $48.5 million. See Sanaria case study in Appendix E.

[24]See Chapter 2 (Program Management).

[25]See Figure 6-13.

[26]See Figure 6-16.

2012.[27] NIH does not maintain data on woman and minority Principal Investigators (PIs). Data from the 2014 Survey indicate that these numbers were also low. The survey indicated that 15 percent of PIs were female.[28]

2. Participation by Black, Hispanic, and Native Americans in NIH SBIR/STTRs program is low.

   - The 2014 Survey indicates that Black-owned small businesses accounted for only 0.7 percent of all respondents; Hispanic-owned small businesses, about 1.7 percent.[29]
   - Seven percent of survey respondents indicated that the Principal Investigator on the surveyed project was from a minority. However, more detailed analysis indicates that 0.5 percent were Black American, 1.6 percent Hispanic, and 0.2 percent American Indian.[30]

3. Levels of participation by women are also low.

   NIH data show that 10 percent of SBIR/STTR Phase I awards were to WOSBs and that these firms receive 12 percent of Phase II awards.[31] However WOSB success rates were persistently lower than those for non-WOSBs for both Phase I and Phase II.[32]

B. NIH efforts to "foster and encourage" the participation of women-owned and minority-owned small businesses are not adequate.[33]

1. NIH outreach efforts have focused more heavily on efforts to attract participation from low-award states than from women-owned and minority-owned small businesses.

   - The SBA-sponsored Road Show is a primary outreach activity and is targeted at low award states.

[27]See Figure 6-12 for Phase I MOSB comparative success rates for applications receiving awards, and Figure 6-16 for Phase II MOSB comparative success rates.

[28]2014 Survey, Question 16.

[29]See Table 6-2.

[30]See Table 6-1.

[31]See Figure 6-4 for percentages of SBIR/STTR Phase I awards going to WOSBs, and Figure 6-8 for percentage of SBIR/STTR Phase II awards going to WOSBs.

[32]See Figures 6-4 and 6-8.

[33]Information in this section is based on the "Outreach" section in Chapter 6 (Participation of Women and Minorities).

- The NIH Annual Report to SBA for FY 2014 mentions a considerable catalog of outreach activities—but mentions under-represented groups only as a part of one activity.
- Most NIH Program outreach is conducted in conjunction with other partners. This means that NIH has limited capacity to attune these events to its own needs. NIH is now working to improve reporting on outreach activities with these partners, especially in relation to women and minorities.

2. NIH is developing outreach activities focused on women and minorities.

   - NIH now holds a well-attended workshop focused on women and minorities at its regular annual SBIR/STTR conference.
   - NIH is planning to work more closely with woman and minority professional societies in the life sciences and science and engineering more generally.

C. NIH's efforts to understand the patterns of woman and minority participation in the SBIR program are not adequate. Concerted analytic effort is needed to determine what practical steps can be taken to improve participation and hence both meet congressional objectives for the program and expand the pool of qualified applicants and capabilities.[34]

1. NIH maintains no separate data on African American-, Hispanic-, or Native American-owned small businesses.
2. NIH has not followed up with a review of application and award patterns for women and minorities. These patterns would show differences between woman/minority applications and other applications on a variety of metrics.[35]
3. NIH has not sought to contextualize observed patterns against larger patterns of participation in life sciences. Participation rates are low especially for minorities. NIH needs to determine whether this is a function of the life sciences sector, of the SBIR/STTR programs, of the financial and business communities, or of a combination of these factors. Furthermore, trends are an especially important indicator: declining participation rates are especially a matter of concern.[36]

[34]A discussion of women and minority participation and NIH's limited efforts to address the issue is provided in more detail in the section, "Summary: Woman and Minority Participants in the NIH SBIR/STTR Program," in Chapter 6.

[35]See Figures 6-8 and 6-9.

[36]See Figure 6-14.

III. Stimulating Technological Innovation and Meeting Agency Mission Needs

NIH's agency mission is to "seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."[37] Thus the twin objectives of using small business to meet federal agency needs and to stimulate technological innovation are closely intertwined and are therefore discussed together in this section.

A. The SBIR/STTR programs at NIH support the development and adoption of technological innovations that advance the agency's mission.[38]

1. NIH topics focus on new research and technological opportunities. Some SBIR/STTR topics are generated by program officers and are then approved by the NIH's Institutes and Centers (IC) and some are applicant-generated. The former are funded via proposals resulting in contract arrangements; the latter via applications resulting in awards. Because the agency does not typically buy or use the outputs from SBIR/STTR research, the topics for contract research are likely to be driven by the research priorities of the agency.[39]
2. Awards are not limited to problems and technologies described in the NIH solicitations. Under the terms of the solicitation, non-matching applications can also be accepted, in an effort to ensure that potentially important innovations are not excluded by the topic structure. However, with both the recent shift toward more targeted contracts at the National Cancer Institute (NCI) and the general increase in more targeted funding opportunities, this hitherto central characteristic of the NIH program may be eroding. NIH does not track whether applications match the solicitation topics, so assessing the actual impact of these shifts on SBIR/STTR applicants is difficult.[40]
3. NIH scoring selects for novelty.

    - Selection scoring for individual projects utilizes the standard NIH scoring criteria, which are heavily weighted toward the novelty of the proposed project.[41]

[37]National Institutes of Health, "Mission," http://www.nih.gov/about/mission.htm, accessed July 9, 2015.

[38]See Chapter 2 (Program Management) for a discussion of NIH topic selection and funding selection procedures.

[39]See Chapter 2 (Program Management).

[40]See Chapter 2 (Program Management).

[41]See Chapter 2 (Program Management).

- Qualitative research conducted for this study confirms that in practice, SBIR/STTR review panelists focus heavily on the novelty of proposals.

B. The NIH SBIR/STTR programs continue to connect companies to universities and research institutions.

1. Faculty and student participation: For the SBIR program alone, 63 percent of survey respondents reported a link to some kind to a research institution. In 39 percent of responses, faculty worked on the project (not as a PI); 22 percent employed graduate students; and 37 percent used universities and research institutions as subcontractors.[42] These figures are in all cases up from those reported from the 2005 Survey.[43]
2. Project partners: 255 different universities were identified by survey respondents as project partners; 34 were mentioned by more than four respondents.[44]
3. Academic founders: Eighty-five percent of SBIR/STTR companies responding to the 2014 Survey reported at least one academic founder, and 59 percent reported that the most recent prior employment of the founder was at a university.[45]

C. NIH SBIR/STTR projects generate substantial knowledge-based outputs such as patents and peer-reviewed publications.

1. Patents: Patenting remains an important component of knowledge diffusion (and protection).

    - About two-thirds of companies overall (and more than 80 percent of Phase IIB recipients) responding to the 2014 Survey claimed to have been awarded at least one patent related to any SBIR/STTR-funded technology.[46]
    - Fifty-three percent of SBIR respondents reported receiving at least one patent related to the surveyed technology. Nine percent reported receiving 5 or more related patents, and 4 percent reported 10 or more. STTR awardees were not more likely to report receiving

[42]See Table 5-20.
[43]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 259.
[44]See Table 5-21.
[45]See Tables 5-22 and 5-23.
[46]See Table 5-17.

patents. These figures are down slightly from those reported in the 2005 Survey, where 57 percent reported at least one patent.[47,48]

2. Peer-reviewed publications: Publication of peer-reviewed articles remains the primary currency of scientific discourse, and despite the need to protect ideas in the commercial environment of small businesses, the 2014 Survey shows that SBIR/STTR firms continue to pursue and achieve scientific publication.

   - Seventy-nine percent of SBIR respondents and 85 percent of STTR respondents indicated that an author at the surveyed company had published at least one related scientific paper.[49]
   - Forty-two percent reported publishing three or more related papers.[50] Many of the companies interviewed for case studies made a point of indicating that they take a great deal of pride in the number of peer-reviewed publications developed by their scientists and engineers, both within and outside of the SBIR/STTR programs.[51]

D. The NIH SBIR/STTR programs fund projects with social benefits that may not be attractive to commercial sources of funding.[52] The NIH SBIR/STTR programs fund some projects that are high risk, socially desirable, and market oriented but that are unlikely to generate the high returns needed to attract venture-type funding. Companies working on projects with these characteristics are often not attractive to commercial investors:

1. Small markets. The FDA orphan drug designation recognizes that some markets are not commercially attractive. Companies like ArmaGen are seeking to develop therapies for small populations.[53]
2. Long cycle research. NIH SBIR/STTR help support the development of innovations that will take many years to reach the market. While these projects may hold great potential for positive impact, the time taken to get to market can be a major barrier for commercial investors.[54]

[47]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, 265.

[48]See Table 5-18.

[49]See Table 5-19.

[50]See Table 5-19.

[51]See Chapter 5 (Outcomes).

[52]See section on "Funding Otherwise Un-fundable Projects" in Chapter 5 (Outcomes).

[53]See ArmaGen case study in Appendix E.

[54]For example, Dr. Pardridge (Armagen) has been working on the blood-brain barriers for more than 30 years. Dr. Sabbadini founded Lpath in 1997. See section on "Long Cycle Research" and Box 7-7 in Chapter 7 (Insights).

E. SBIR/STTR funds the development of research tools that leverage its impact many times. Case studies show that the impact of awards can be multiplied if SBIR/STTR technologies are used to develop innovative tools and services for biomedical researchers working in partnership with larger pharmaceutical companies to dramatically reduce the cost and increase the success rate of clinical trials. Avanti Lipids has become a core provider of lipids to the research market.[55] Another company, Invitrogen, has now become the world's largest provider of genetic testing to the research community.[56]

IV. Fostering Innovative Companies

A. The NIH SBIR/STTR programs support the foundation of new innovative firms: Many of the survey respondents reported that SBIR/STTR funding was instrumental in the founding of the company. The formation of new innovative companies is a positive outcome for the program.

1. Forty-four percent of survey respondents said that the company was founded entirely or in part because of the SBIR/STTR programs.[57]
2. For some companies included among the case studies, SBIR/STTR funding permitted the shift from an exploratory to a professional operation.[58] And for some STTR companies in particular, funding permitted university faculty to retain their positions while initially building the company.[59]

B. **Funding provided by the NIH SBIR/STTR programs reduces the risk for subsequent investors:** Leveraging of SBIR/STTR funding helps small innovative firms lower their risks while retaining the power of markets to make final decisions about funding.

1. Early stage: Many respondents to the 2014 Survey and a number of companies contacted for case studies said that NIH SBIR/STTR funding was provided at a stage when the project was simply too risky for commercial sources of funding. Once the project proceeded further, risk was lower and additional funding could be acquired.[60]

[55]See Avanti Lipids case study in Appendix E.

[56]See Invitrogen case study in National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*.

[57]See Table 5-24.

[58]See section on "Validation Effects" and Box 7-4 in Chapter 7 (Insights).

[59]See, for example, Stratatech case study in Appendix E.

[60]See section on "Company Formation and Very Early Stage Funding" and Box 7-2 in Chapter 7 (Insights).

2. Support for core technology development: NIH SBIR/STTR funding supports technology development, which can be supported through commercial funding further downstream. SBIR/STTR is particularly important for funding proof of concept for new technologies, as described in several case studies (Appendix E) as well as in survey responses.[61]
3. Validation: NIH SBIR/STTR funding has itself been important validation for companies seeking further investments, according to discussions with representatives of case study companies and survey responses. The strength of the selection process and growing understanding of SBIR/STTR among both equity and strategic investors may be strengthening this effect.[62]
4. Exploit technology platforms: In some cases, companies use SBIR/STTR funding to build off existing platform technologies specifically to enter new markets. This platform-driven approach is used by a number of the companies highlighted in the case studies. (See Chapter 7.)
5. Strategic corrections: Innovative companies must often make mid-course corrections to their business strategy. NIH funding has—according to respondents to the 2014 Survey—helped a number of companies successfully make what are often difficult changes that are hard to fund.

C. The NIH SBIR/STTR programs have supported the development of small innovative companies in the United States.

1. The 2014 Survey provided SBIR/STTR companies with the opportunity both to report the overall impact of SBIR/STTR on the company and to identify specific kinds of impacts. Sixty-two percent of Phase II winning recipients indicated that the NIH SBIR/STTR programs had a "highly positive or transformative" effect on their company. Another 35 percent said that it had a "substantial positive long term effect."[63]
2. The 393 detailed comments received in the 2014 Survey offered widely differing kinds of impacts, as summarized in Box 8-1.[64]

D. Company dependence on the NIH SBIR/STTR programs is limited: SBIR/STTR is not designed to provide permanent life support for companies. Congress has—through changes under the 2011 reauthorization—indicated that it expects companies to use SBIR/STTR to move on to a commercialization phase that is not funded by SBIR/STTR. And NIH is, according to discussions with representatives of case study companies as well as com-

[61]See section "Innovative Technologies and Product Development" and Box 7-6 in Chapter 7 (Insights).
[62]See section on "Validation Effects" and Box 7-4 in Chapter 7 (Insights).
[63]See Table 5-29.
[64]See section on "Key Aspects of SBIR-Driven Transformation"" in Chapter 5 (Outcomes), as well as Chapter 7 (Insights) and Appendix E (Case Studies).

BOX 8-1
Different Ways in Which SBIR/STTR Awards Helped to Transform Companies

Unique Source of Seed Funding
- Provided first dollars
- Funded areas where venture capital and other funders were not interested
- Provided funding during downturns in the business cycle
- Created new companies and kept companies in business that would not exist without SBIR/STTR funding
- Supported projects with longer time horizons/long sales cycles

Introduced New Stakeholders
- Opened doors to many potential stakeholders in specific technologies, including agencies, prime contractors, investors, suppliers, subcontractors, and universities
- Stimulated international collaboration
- Gave companies added credibility because SBIR/STTR research is peer reviewed

Opened New Markets
- Helped address niche markets too small for major players/funders
- Supported adaptation of technologies to new uses, markets, and industry sectors

Funded New Technologies
- Funded technology development
- Funded disruptive technologies
- Funded proof of concept
- Supported feasibility testing for high-risk/high-payoff projects
- Drove researchers to focus on technology transition

Reduced Risk and Costs
- Enabled projects with high levels of technical risk
- Reduced technological risk
- Helped address needs that require high tech at low volume and relatively low cost

Allowed Job Growth and Firm Expansion
- Diversified expertise and allowed hiring of specialists
- Attracted and developed young researchers
- Redirected company activities to new opportunities
- Funded researchers to enter business full time
- Transformed company culture to become more market driven
- Provided the basis for spin-off companies
- Encouraged R&D companies to transition into manufacturing
- Provided significant mentoring especially for new businesses

SOURCE: Analysis of company responses to the 2014 Survey. For each bullet multiple responses indicated its existence and importance for surveyed projects and firms.

ments from several survey respondents, now tightening its requirements, to the point that some respondents indicated that they no longer seek awards because their commercialization record is not strong enough.

1. No formal limits on multiple awards. NIH does not limit either the number of awards or the number of applications from a company. This practice contrasts with that of the National Science Foundation (NSF) SBIR/STTR programs.
2. Awards are spread widely across the applicant pool. At NIH, the most prolific winners account for a relatively low percentage of all awards (compared to SBIR/STTR programs at other agencies). The most prolific winners received 24 Phase II awards over the 10-year study period, and the top 21 winners (top 20 plus ties) received 9.9 percent of Phase II SBIR/STTR awards and 8 percent of funding during this period.
3. The company's commercialization track record is of growing importance. While there are no formal metrics or benchmarks, companies believe that NIH is increasingly focused on outcomes and that companies without commercialization from previous awards will find it harder to garner new ones.[65]
4. Most NIH firms are not dependent on SBIR/STTR awards. Only 27 percent of companies responding to the 2014 Survey report that SBIR/STTR accounts for more than half of current revenues.[66] However, a considerable number of surveyed firms reported in textual responses that SBIR/STTR has been the most important source of funding prior to reaching the market.[67]
5. NIH SBIR/STTR innovation is non-linear. Most projects at most companies do not proceed directly from Phase I to Phase II to commercialization.[68]

    - About 80 percent of Phase II survey respondents reported at least one additional SBIR/STTR Phase II award related to the surveyed project.[69]
    - About one-third reported at least two additional related Phase II awards.[70]
    - As noted above, more than 60 percent of Phase II respondents reported additional investment funding related to the project subsequent to the SBIR/STTR award.[71]

[65]See Chapter 7 (Insights from Case Studies and Survey Responses).
[66]See Table 5-26.
[67]See Chapter 7 (Insights) and Appendix E (Case Studies).
[68]See section on "Prior Use of the SBIR/STTR Program" in Chapter 5 (Outcomes).
[69]See Table 5-27.
[70]See Table 5-28.
[71]See Chapter 5.

V. Program Management

A. The NIH SBIR/STTR programs are managed in a flexible way in terms of application topics, dates, and funding.[72]

1. Focus is on investigator-initiated research: NIH makes clear that topics listed in the Omnibus Solicitation are guides for applicants, not boundaries. And while targeted solicitations have become more common, research conducted under SBIR/STTR at NIH is still largely investigator driven.
2. Multiple applications dates: NIH offers three submission dates annually, which provides investigators with a much reduced timeline to funding.
3. Significant funding flexibility:

    - Funding amounts. Amounts are not pre-set, and selection panels do not compare funding requests among applications. NIH has in many cases, and with appropriate SBA waivers, provided funding that goes beyond the standard SBA guidelines.
    - Supplementary funding. NIH provides small amounts of supplementary funding in cases where the completion of research plans can be accomplished with a minor increase in support.
    - No-cost extensions. NIH will normally extend the timeline for an award.
    - Multiple support mechanisms. The introduction of Phase IIB and direct to Phase II indicates that NIH continues to seek ways to match available funding with the needs of companies and investigators.

4. Resubmission of applications: The ability to resubmit applications after addressing flaws identified by selection panels is a unique feature of the NIH SBIR/STTR programs and, while highly commendable, can be further improved.

B. The NIH application review system can be improved: Case studies, survey responses, and discussions with agency managers all indicate that although the NIH application review system is highly regarded and has many positive characteristics, it is not serving the SBIR/STTR community as well as it could.[73]

1. NIH's commercialization review is overly weighted toward the views of academic reviewers.

    - Based on information gathered through case study and agency discussions and survey responses, a large majority of reviewers appear

[72]See section on "Program Flexibility" in Chapter 2 (Program Management).
[73]See section on "The Peer Review Process" in Chapter 2 (Program Management).

to be academics. (NIH does not track the composition of review panels.)
- NIH's Center for Scientific Review counts as "commercially experienced" all reviewers working in the private sector. This is not appropriate because most industry scientists have no more knowledge of commercialization than academic scientists. Recently issued guidelines are insufficient to ensure that each application is assessed by at least one reviewer with commercialization expertise. This is a minimal requirement for effective review.
- Academic reviewers are permitted to review commercial potential, for which they may have no valid expertise.
- Selection of awards is based on standard NIH criteria, which do not include commercial potential. Thus, commercial potential is not part of the formal scoring system.
- Scientific Review Officers, assigned to SBIR/STTR panels, are not usually specialists in SBIR/STTR.

2. Reviewers may have a weak or misinformed view of innovation in the context of SBIR/STTR.

    - Grants at NIH are reviewed against standard NIH criteria including innovation, defined as "novel theoretical concepts, approaches or methodologies, instrumentation, or interventions."[74] However, "novelty" in the context of an academic grant application is not the same as "innovation" for SBIR/STTR. The latter includes all of the steps necessary to reach the market, many of which have no "novelty" in academic terms.[75]
    - The result is that the SBIR/STTR Phase II applications may be subject to misapplied innovation criteria.

3. Timelines for NIH review cause unnecessary and expensive delays for small businesses.

    - There are three NIH deadlines for submission annually. This is a positive feature of the NIH program, especially compared to agencies that provide a single annual deadline. However, NIH debriefings for rejected applications are usually delivered too late for resubmission at the next deadline, effectively imposing a minimum 4-month additional delay on applicants.

[74]See section on "Peer Review Process" in Chapter 2 (Program Management).
[75]See Chapter 7 (Insights).

- Delays can be a major challenge for small companies—especially startups—who must often use up their own limited capital to stay in business until they can receive funding and begin their SBIR/STTR project, which may eventually lead to revenue generation and a growing self-sufficiency for the company.
- Case studies show that projects that are rejected based on minor defects and misunderstandings, and then allowed to be revised and resubmitted, may in fact impose heavy penalties on small innovative firms if the wait time for resubmission is too long.[76]

4. NIH does not employ methods used by other agencies to help reduce the number of poor-quality applications.[77]

   - Discouraging the submission of poor-quality proposals can improve program efficiency and may allow reviewers to focus more carefully on a smaller number of better proposals.

     For example: NSF limits the number of applications that a given firm can submit, ensuring that firms put forward only what they consider their most promising projects. The Department of Energy (DoE) requires the submission of a white paper before application and provides applicants with rapid feedback on their chances of success. Some agencies use pre-review screenings as triage to remove obviously fatally flawed and highly deficient proposals.

C. Survey data shows that the NIH Phase IIB program supports the accelerated commercialization of SBIR-funded research through the provision of funding for clinical trials.

1. About 45 percent of those responding to the 2014 Survey indicated that their project will require FDA approval; the costs of clinical trials pose a large barrier to commercialization of SBIR/STTR technologies.

   - Full completion of clinical trials' costs range widely, but they now account for approximately 40 percent of drug development costs.
   - The size, scope, and complexity of required clinical trials have increased sharply.[78]

[76]See Chapter 7 (Insights).

[77]See Chapter 2 (Program Management).

[78]See Table 1 and Table 2 in S. Avik and A. Roy, "Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials," Manhattan Institute of Policy Research, April 2012.

2. Survey data indicate that Phase IIB funding is associated with improved outcomes in relation to clinical trials.

    - Twenty-one percent of Phase IIB projects report having completed clinical trials, compared with 9 percent for other SBIR and STTR Phase II awards.
    - Conversely, only 5 percent of Phase IIB projects report having abandoned the clinical trials process, compared to 36 percent of other Phase II SBIR/STTR projects.[79]

3. The National Cancer Institute (NCI) has been an active proponent of Phase IIB awards, and its Bridge program offers a potential new model for Phase IIB at NIH.

    - The NCI Bridge program is based on the NSF Phase IIB matching funds model.
    - It differs from NSF's Phase IIB, in that it is focused—as with other Phase IIB programs at NIH—on providing support for clinical trials.

4. Both case-study companies and survey respondents had positive views of the impact of Phase IIB funding on their projects and their companies as a whole.

    - Three-quarters of the 21 Phase IIB respondents indicated that the funding had made a "tremendous difference to the project." The case studies conducted for this assessment support this view.[80]
    - Phase IIB had a positive long-term impact on the company. Nearly two-thirds stated that the program had a substantial positive impact, and nearly 1 in 10 responded that the Phase IIB program had a "transformative effect" on the company.[81]
    - Comments from respondents indicate that Phase IIB supports a wide range of activities tied to a considerable variety of commercialization strategies and approaches.[82]

5. Other aspects of the Phase IIB program.

    - Current policies on matching funds may exclude worthy projects from Phase IIB funding.

[79]See Table 5-3.
[80]See Appendix E (Case Studies).
[81]See Table 5-29.
[82]See section on "Phase IIB" in Chapter 7 (Insights).

- NIH Phase IIB funding provides qualifying companies $1 million per year for 3 years. This level of funding may not be appropriate for all projects, because the amount required to complete Phase 2 clinical trials varies widely and not all projects go through clinical trials.[83]
- Despite positive preliminary outcomes (and 10 years of experience) the number of Phase IIB awards has not increased.[84]

D. The flexibility of award patterns at NIH helps address the diverse needs of small innovative companies in the biomedical sector.

1. NIH continues to make extra-large awards. These awards conform to recent changes stipulating maximum award size, and in particular the new requirement that SBA apply waivers to specific topics.

   - NIH began to make extra-large Phase II awards in FY 2003, when 20 were made totaling $69 million.[85] The number of extra-large Phase II awards remained flat until 2009, when it grew to 30, and then to more than 40 in 2011-2012.[86]
   - Phase II awards above $1.5 million accounted for $647 million in funding from FY2001-2014, equivalent to 430 additional awards at $1.5 million each. The cost of these awards grew as a share of total Phase II awards across the study period until the impact of 2011 SBIR reauthorization limits was felt in FY2013. The share peaked at 26 percent in 2012.[87]
   - Respondents with larger awards account for more positive outcomes, based on preliminary data from the 2014 Survey. And a higher percentage of companies with large awards report large positive sales outcomes ($20 million or more).[88] These conclusions are based on small samples and should be viewed cautiously.

2. New entrants account for a substantial portion of awards at NIH, and the share of awards made to multiple award winners does not seem excessive.

   - New participants: New companies have accounted for more than 30 percent of companies applying for Phase I funding in almost all

[83]See section on "Phase IIB" in Chapter 2 (Program Management).
[84]See section on "Phase IIB" in Chapter 2 (Program Management).
[85]See Table 3-5.
[86]See Table 3-5.
[87]See Table 3-4.
[88]See Figure 3-9.

years of the study period.[89] New companies account for between 20-25 percent of awards and 25-30 percent of successful FY2005-2013 applications during the study period. The access provided for new entrants to the program is appropriate.

- Multiple award winners: The top 20 awards winners at NIH account for 7.7 percent of Phase I SBIR/STTR awards and 8.1 percent of Phase I funding.[90] They account for 9.6 percent of awards and 8.1 percent of funding for SBIR/STTR Phase II awards. This level of concentration is lower than that for other agencies. For example, at the Department of Defense (DoD) the top 20 winners account for 14.4 percent of awards and 14.3 percent of Phase I SBIR funding.[91]

3. Fast Track awards. NIH is increasing the number of Fast Track awards (combined Phase I and Phase II).

    - The number of Fast Track awards has grown steadily and in FY 2014 reached 70 awards.[92]
    - The share of Fast Track awards as percentage of all regular Phase II + Fast Track awards has increased from 8 percent in 2005 to 24 percent in 2014.[93]

4. Use of contracts is expanding at the National Cancer Institute (the largest IC). NCI has made a substantial shift from grants—the traditional funding mechanism—to contracts.

    - Approximately one-third of NCI SBIR/STTR funding is now awarded as contracts.
    - Aside from NCI there has been little change in contracting patterns across NIH over the study period.
    - NCI is focused on contracts in part because this mechanism leaves control of selection entirely with NCI. (NIH's Center for Scientific Review [CSR] is not involved in selection.) Contracting by NCI also offers tighter control of the project itself, where payments can be linked to agreed milestones.[94]

[89]See Figure 4-2.
[90]See Table 4-3.
[91]National Research Council, *SBIR at the Department of Defense*, Washington, DC: The National Academies Press, 2014, Table 2-3.
[92]See Figure 4-23.
[93]See Figure 4-24.
[94]See section on "SBIR Phase I Contracts" in Chapter 4 (Awards).

E. NIH Institutes and Centers are pioneering new models of program management (e.g., the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI)).

The SBIR/STTR programs at NIH are implemented by the ICs. Therefore, they have leeway to experiment with different ways of managing the program. Under the prevailing model at NIH, ICs simply add SBIR/STTR responsibilities to the other responsibilities of NIH technical staff, but NCI and NHLBI have developed new approaches.

1. The NHLBI model—professionalized consulting support and support across the entire SBIR/STTR timeline.

   The NHLBI model is based on the detailed recommendations of an assessment team that reported to the Institute Director in 2007. Implementation of the model is too recent to determine impacts. Key features include:[95]

   - Dedicated full-time consulting and advisory staff for SBIR/STTR applicants and winners, and for NHLBI program staff.
   - New pre-SBIR activities aimed at improving and expanding the pool of applicants through new accelerators/hubs located at universities and through innovative use of social media for outreach.
   - Improving the effectiveness of Phase I/Phase II in meeting agency priorities especially through more targeted Funding Opportunity Announcements (FOAs).
   - Better training and support for awardees, including participation in I-Corps.
   - Two post-Phase II award programs: Bridge awards (like NCI, see below) and Small Market awards targeted at socially beneficial but less commercial technologies.
   - NHLBI has also commissioned the Research Triangle Institute (RTI) to support data collection and analysis for outcomes research.

2. The NCI model—replacement of part-time program officers with SBIR/STTR staff.

   The NCI model is closer in concept to the NSF model, in that it replaces NCI technical staff rather than providing them with consulting and support services. Key features include:[96]

[95]See section on "The NHLBI Model" in Chapter 3 (Program Initiatives).

[96]See section on "The NCI Model: Building on the NSF Management Model" in Chapter 3 (Program Initiatives).

- Staff at the NCI SBIR Development Center run the SBIR/STTR programs. They develop solicitations, to a considerable extent manage the selection process (more so than for most ICs), and make funding decisions.
- Staff are hired because they have a combination of scientific and entrepreneurial skills.
- Bridge awards, though comprising a small share of the budget thus far, are a focus—a variant on Phase IIB, which highly recommends (though does not formally require) an investor match.
- Bridge awards generated approximately a 2:1 match for NCI investments, as of November 2014.[97]
- NCI has also pioneered the introduction of the I-Corp executive training program at NIH. This is a promising program in use at NSF that provides a coherent framework and program for entrepreneurs. Initial results are positive, and expansion is planned.[98]

3. The new management models at NCI and NHLBI are encouraging but require data tracking and analysis.[99]

   NIH and the participating Institutes should be commended for experimenting with promising new ways to manage the SBIR/STTR programs. The NCI and NHLBI models have different strengths and weaknesses—as does the standard model.

   - The new models are too recent to permit quantitative analysis.
   - NHLBI's commitment to better data collection and outcomes research is commendable.
   - NCI's existing data collection is helpful but also illustrates pitfalls (see above). Two-thirds of the additional investment reported from a reportedly successful 2010 investor forum may not finally eventuate.
   - Building on the 2014 Survey, additional data collection can be specifically tailored to provide comparisons of the program officer model of program management with the newer forms that have been recently introduced.

F. NIH is seeking to improve its data collection and tracking.

1. Data collection and tracking is necessary for effective program management.

[97]See Figure 3-2.
[98]See section on "I-Corps" in Chapter 3 (Initiatives).
[99]See section on "New Management Models" in Chapter 3 (Initiatives).

- NIH faces broad challenges in tracking commercialization, at both the company and project levels. Companies move in and out of the program, and tracking is harder once companies have left. More generally, commercialization may come years after an award, and may involve multiple awards plus considerable additional funding. All this makes it difficult to assert that any specific outcome "results from" an SBIR/STTR award, particularly if developments are tracked for only a limited time.
- Longer term tracking of outcomes is essential for effective program management: without outcomes data and analysis it is impossible to determine what is working and what is not. The previous report by the Academies (2009) recommended that NIH improve its tracking and evaluation of SBIR awards and in particular their outcomes.[100]

2. Data collection at NIH is still limited.

   - Only outcomes from participants in the CAP are currently captured in the NIH Performance Outcome Data System.[101]
   - Tracking of CAP participants is limited in duration (18 months).
   - Tracking does not currently capture some important characteristics of company activities, such as interactions with FDA, clinical trials, and relationships with the Centers for Medicare & Medicaid Services (CMS).
   - Tracking addresses only commercialization outcomes. Other program objectives are not tracked.

3. NIH is taking steps to improve outcomes tracking and analysis.[102]

   - NIH is working with SBA to utilize the anticipated commercialization database being developed by SBA. The new database will require that companies provide updated information on all awards whenever they apply for new funding, and also that they voluntarily report for 5 years after the end of the award.
   - NIH is also improving its own Performance Outcome Data System (PODS) to capture data on all awards, for areas not covered by the SBA database such as outcomes from clinical trials.
   - NHLBI is also focused on improved tracking as a prerequisite for better program management decisions. It has engaged RTI to provide further recommendations.[103]

[100] See section on "Data Collection, Tracking, and Analysis" in Chapter 2 (Program Management).
[101] See section on "Data Collection, Tracking, and Analysis" in Chapter 2 (Program Management).
[102] See section on "Data Collection, Tracking, and Analysis" in Chapter 2 (Program Management).
[103] See section on "NHLBI" in Chapter 3 (Program Initiatives).

G. NIH is seeking to gauge the effectiveness of its commercialization support initiatives.

1. NIH provides considerable commercialization support and training to its awardees.

    - NIH was among the first SBIR agencies to provide commercialization training and support to awardees.
    - The Commercialization Assistance Program has been operated by a third-party provider, LARTA, since its inception 10 years ago. It provides support to selected Phase II awardees.[104] According to the 2014 Survey about one-third of respondents reported that they had been through commercialization training.[105]
    - The NICHE program, operated by a different third-party provider (Foresight), provides market research to a limited number of Phase I awardees. Providing early support for commercialization is an unusual feature of the NIH program and should be commended.[106]

2. The effectiveness of this support is not yet established.

    - Data provided by NIH regarding outcomes from the CAP are not sufficient to determine its value. NIH is now moving to bring assessment of the program in-house, having relied on LARTA for analysis in the past.
    - Opinion on training was mixed. Thirty-eight percent of STTR respondents reported that it was valuable or very valuable; 26 percent that it was not at all or not very valuable.[107]

H. A substantial gap remains between the end of Phase I and the beginning of funding for Phase II.

1. Sixty-eight percent of STTR respondents to the 2014 Survey indicated that they had experienced a gap.[108]
2. The funding gap reportedly had a significant effect on company work on the funded project.

[104]See section on "The Commercialization Assistance Program (CAP)" in Chapter 2 (Program Management).

[105]See section on "Commercialization Training and Marketing" in Chapter 5 (Outcomes).

[106]See section on "Niche Program for Phase I Participants" in Chapter 2 (Program Management).

[107]See Table 5-15.

[108]See section on "Funding Gaps and Award Timelines" in Chapter 2 (Program Management).

- Thirty-one percent of STTR respondents indicated that they had stopped work altogether.
- A further 57 percent reported that they had slowed their work.

3. Concerns about funding gaps are among the most frequently highlighted issues in the open-ended responses solicited in the 2014 Survey.[109]
4. While NIH does permit companies to "work at their own risk" between SBIR/STTR Phase I and II, this is insufficient to address the challenges facing many small companies:

    - Small companies may not have the resources to pay their staff well in advance of NIH payments.
    - Some survey respondents did not know about this opportunity, as indicated by the fact that they asked for policy changes to provide this in the future.

5. NIH does not have a gap funding program, such as those offered by some components at the DoD.[110]
6. NIH is funding more Fast Track awards, which can solve the issue for those projects.[111]

VI. STTR

A. STTR is meeting the program objectives defined in the Small Business Administration's Policy Guidance for STTR.

1. STTR is stimulating technological innovation, as evidenced by the substantial knowledge effects identified in Chapter 5 and the relevant case studies referenced in Chapter 7.
2. STTR fosters cooperative R&D between universities and other research organizations and industry.

    - Seventy-eight percent of STTR survey respondents report that the PI was a faculty member of the partnering research institution.[112]
    - Only 1 percent of STTR awards had no research institution linkage, compared to 35 percent for SBIR respondents.[113]

[109] See section on "Funding Gaps and Award Timelines" in Chapter 2 (Program Management).
[110] National Research Council, *SBIR at the Department of Defense*, Washington, DC: The National Academies Press, 2014, p. 180.
[111] See section on "Fast Track" in Chapter 4 (Awards).
[112] See Table 5-20.
[113] See Table 5-20.

- Case-study companies indicated that STTR had helped to bridge the gap between research labs and commercial activities (e.g., Stratatech).

3. STTR is meeting the objective of supporting the commercialization of federally funded technologies.
4. STTR survey respondents report an identical rate of reaching the market with their products compared to SBIR, at 49 percent of responding projects,[114]
5. Fewer STTR respondents report no additional investment in the technology aside from program funds (11 percent against 19 percent for SBIR).[115]
6. STTR projects report receiving additional investment from venture firms at essentially the same rate as SBIR respondents.[116]

B. The STTR program at NIH is administered as an adjunct to the much larger SBIR program.

1. NIH staff discussions confirm that the agency runs both SBIR and STTR as a single program, with minor differences in participation rules.
2. Solicitations for STTR and SBIR are announced jointly.

C. Outcomes from STTR are broadly similar to those from SBIR.

1. Participation rates for research institution staff are broadly similar for SBIR and STTR (with one important exception discussed below).[117]
2. Outcomes for commercialization and for knowledge effects show minimal differences between SBIR and STTR.[118]

D. Companies in some cases do utilize STTR differently from SBIR.

1. STTR rules permit PIs to work less than 51 percent time on the funded project. SBIR does not. As a result, PIs who wish to retain a half-time position or more at a research institution find STTR a helpful option.
2. STTR also permits a larger share of the award to be subcontracted to the research institution. Companies sometimes find this useful when they need to utilize specialized equipment or skill sets.

[114]See Table 5-7.
[115]See Table 5-12.
[116]See Table 5-13.
[117]See Table 5-20.
[118]See "Commercialization" and "Knowledge Effect" sections in Chapter 5 (Outcomes).

RECOMMENDATIONS

Although the NIH SBIR/STTR programs generate substantially positive outcomes, the committee has identified a series of recommendations to improve its processes and outcomes. The order of these recommendations reflects the relative emphasis of the committee. The first set of recommendations address the challenge of drawing more women- and minority-owned companies into the SBIR and STTR programs. The second set of recommendations focuses on ways to improve the commercialization of SBIR/STTR projects. The final three sets of recommendations address how NIH can improve the operation of their SBIR and STTR programs. They examine the Phase IIB and other funding mechanisms beyond Phase I/I; ways to improve the monitoring, assessment and reporting on the programs; and overall changes in management practices to improve program operations.

I. Addressing Underserved Populations

NIH should immediately examine past and current efforts to address the Congressional mandate to foster the participation of underserved populations in the SBIR/STTR programs, examine and report on best practices, develop an outreach and education program aimed at expanding participation of under-served populations, create benchmarks and metrics to relate the impact of such activities.

A. Quotas are not recommended. It is not recommended that NIH develop quotas for inclusion of selected populations into the SBIR/STTR programs, because of the potential problems that this might entail, such as raising issues of fairness and lack of transparencies with the selection process. At the same time, it is important that steps be taken to improve the current situation.[119]

B. NIH should develop new benchmarks and metrics.[120]

1. Improve participation metrics: The SBIR/STTR Program Office should work to improve metrics for benchmarking the participation of under-served populations, developing and publishing benchmarks based on a defensible analysis of existing data.
2. Disaggregate benchmarks: Measures of the participation of socially disadvantaged groups must be disaggregated by race or ethnicity, and attention focused on the congressional intent to support "minority" participation. The current SBA definition of "socially and economically disadvantaged" is not sufficient to meet this objective.

[119]See Chapter 6.
[120]See Finding II-A.

3. Customize benchmarks: Points of reference should be developed separately (though perhaps drawing on a shared methodology) for women and minorities. Benchmarks should address key questions that would include the following metrics, all of which should include both absolute levels and trends over time:

    - Shares of applications from companies owned by women and minorities.
    - Shares of applications with woman and minority principal investigators.
    - Shares of Phase I awards to companies owned by women and minorities.
    - Shares of Phase I awards with woman and minority principal investigators.
    - Shares of Phase II awards to companies owned by women and minorities.
    - Shares of Phase II awards with woman and minority principal investigators. The field of degree or other STEM area classification of the principal investigator.
    - The participation rates of women and minorities on review panels, reflecting the fact that panel participation has been cited by some as a path that led them to company formation and further SBIR involvement including application to the program.

4. Track related program operations: Metrics should also track related program operations including outreach efforts (See below).

C. NIH should develop an outreach and education program focused on expanding participation of underserved populations.[121]

1. This will require the provision of agency resources and senior staff time and should be a high priority for the program, because the existing efforts are not sufficient. NIH will need to make concerted efforts in this area.
2. Develop enhanced outreach strategy: NIH should develop a coherent and systematic outreach strategy that provides for cost-effective approaches to enhance recruitment of woman- and minority-owned companies, as well as female and minority PIs, developed in conjunction with other stakeholders and with experts in the field. Outreach efforts should aim to expand SBIR/STTR awareness among potential applicants from underserved demographics.

[121] See Finding II-B.

3. Establish a graduate intern program for qualified women and minorities with the goal of providing the interns with first-hand experience in applying to SBIR/STTR. The internship could operate with salaries paid for by NIH, with their participation allowed in CAP and other business training, and with the interns potentially provided as additional resources available to awardees who make the best case.
4. Provide management resources: NIH should provide significant management resources, because improving participation is likely to be both difficult and a long-term effort.
5. Designated staff: NIH should consider designating a senior staffer to work exclusively on improving women and minority participation in order to improve reporting and the deployment of new initiatives in this regard.
6. Add-ons to existing outreach activities are not sufficient. There is no evidence that a panel at the National SBIR conference or at AdvaMed has attracted significant numbers of new participants into the program. Focused and extensive outreach activities will be needed.

D. NIH should review selection procedures and remove any identified biases in the selection process.[122]

1. Review selection processes: NIH should review internal award and selection data and processes to address questions arising from disparities between Phase I and Phase II awards, and divergent success rates, for selected populations. The goal is to ensure that there are no biases in the selection process that are adversely affecting the selection of women and minorities.
2. Monitor selection processes: NIH should ensure that patterns of applications, awards, and success rates are monitored going forward and are reported out annually.

II. Improving Commercialization Outcomes

The NIH SBIR/STTR programs are focused on commercialization, and findings of this report indicate that it is doing so with considerable success despite the substantial barriers facing the commercialization of biomedical research. However, it is worth considering possible improvements.

[122] See Finding II-A.

A. NIH should continue to address challenges that conducting clinical trials pose for the commercialization of SBIR/STTR technologies.[123]

NIH should provide improved support for awardees in meeting the challenges in funding clinical trials:

1. NIH should consider options for supporting companies in their approach to clinical trials more effectively. While preliminary evidence suggests that Phase IIB is working to support companies through clinical trials, NIH should consider whether adjustments are warranted.[124]
2. NIH should provide improved support for awardees in dealing with the FDA.[125]

    - NIH should seek to provide ongoing expert consulting to awardees in relation to FDA requirements.
    - NIH should provide more and better detailed briefings on FDA requirements on the NIH SBIR/STTR website.
    - NIH should explore ways in which the NIH SBIR/STTR programs could create better linkages directly to FDA that would benefit awardees.
    - NIH should consider whether a standard briefing on the FDA process should become part of the SBIR/STTR programs for all new awardees.

3. NIH should help awardees to find strategic partners.

    - NIH can leverage its substantial convening power as the premier biomedical research organization worldwide in this effort. The NCI Investor Conferences are a promising initiative that could be expanded to other biomedical subsectors, could be more frequent, and could provide more systematic connection beyond simple conference attendance.
    - NIH should review DoD efforts to build searchable databases of awardees and their activities, for possible adoption. Providing more frequent and better information to potential investors may help to increase the pipeline of projects with funding for clinical trials.
    - NIH should in part refocus its commercialization strategy toward strategic partners: The limited funding for seed and startup projects from U.S. venture capital in general, and the low numbers of NIH firms that report venture capital funding, suggests that NIH should not

[123] See Finding I-G.
[124] See also Recommendations III on Phase IIB.
[125] See Finding V-G.

focus too tightly on commercialization models that rest on venture capital funding. Many alternatives exist, and a VC-focused commercialization model narrows the program by limiting the timeframe viewed as appropriate for commercialization, and also by anticipating certain levels of commercial scale needed to attract VC-type funding.

- NIH should look beyond the VC model: NIH and its ICs should review its conceptual approach to commercialization with a view to ensuring that different paths to commercial success are fully included, such as angel funding, strategic investments by other companies, and foundation funding as well as venture philanthropy. NIH commercialization support should explore ways to improve connections to these funding sources.

B. NIH should review the effectiveness of its commercialization support and training initiatives.[126] NIH should be commended for providing commercialization support on a regular basis to both Phase I and Phase II SBIR/STTR awardees. NIH was one of the first agencies to provide this support, and it has been a feature of the program for more than 10 years. Building on this:

1. NIH should consider whether current commercialization support is effective: Evidence for outcomes provided by LARTA is inconclusive. Evidence from participants is mixed. It seems plausible that LARTA is effective in some cases, and that NIH should determine where this program is effective and where it is not.
2. NIH should look to ICs to identify best practices. NIH should view the management initiatives at NCI, NHLBI, and other ICs as offering potential insights into best practices.
3. The NIH Program Office should review initiatives undertaken by ICs regularly to identify apparent successes (such as the I-Corps program) for potential replication and to learn from failures. ICs can be laboratories for NIH as whole, if they are supported, monitored, and evaluated effectively.

III. Phase IIB and Other Funding Mechanisms Beyond Phase I/II

A. NIH should continue to operate the Phase IIB program and consider expanding its size within the context of a more flexible approach.[127]

1. Preliminary data suggest that the Phase IIB program has had a positive impact on the commercialization of SBIR/STTR-funded research.

[126] See Finding V-G.
[127] See Finding V-C.

2. Respondents to the 2014 Survey support retention of the program.
3. Relatively few projects currently benefit from the program because of its limited use**.** NIH might therefore consider whether additional funds should be made available for an expansion of Phase IIB support.
4. But Phase IIB should not come to dominate the program financially. Given the costs involved ($3 million per award), NIH should be cautious about the impact of expansion on the availability of funding for other aspects of the SBIR/STTR programs.

B. NIH should consider a more flexible approach to funding Phase IIB awards.[128]

1. A more flexible approach would avoid a "one-size fits all" funding approach.

    - It could also provide more effective support for more demanding projects.
    - As the cost of clinical trials varies substantially by project, it seems unnecessary to constrain support to an exact amount.

C. NCI and NHLBI should consider modifying the criteria that define an acceptable third-party match for Phase IIB purposes. (V-E)

1. Explore use of in-kind contributions: NCI/NHLBI may wish to explore allowing the limited use of some specified in-kind contributions (e.g., the cost of drugs used in the trial) as part of the matching funds.
2. Review other types of matching commitment: The original Phase IIB program was developed at NSF. However, the NSF program is much more flexible with regard to matching funds: for example, sales and company revenues can be counted. NCI/NHLBI should review projects that have been excluded from the program to determine whether different matching criteria would be a better fit.

IV. Improving Monitoring, Evaluation, and Assessment

The development of more careful monitoring and more sophisticated analysis of key variables is necessary to improve program outcomes. Although NIH recognizes the need for better data and is working to develop improved tracking mechanisms, more remains to be done in this area.

[128] Ibid.

A. NIH should improve current data collection approaches and methodologies.[129]

Data collected through the current process are a good start but are far from sufficient to underpin a data-driven program.

1. NIH should improve data collection and organization:

    - NIH should collect outcomes data and improve program evaluation, management, and outcomes. This data collection effort should address the entire range of congressionally mandated outcomes, not only commercialization, and should be extended to other aspects of the program, including demographic data for applicants and awardees.
    - Data should also be collected about other aspects of the program. For example, NIH should know the extent to which proposals are in reality constrained by topic boundaries. There are no current data on this.
    - Further, NIH should know the frequency with which review panel funding advice is being overruled in different areas; they should know the composition of review panels; they should know the success rates of applicants at the level of gender and ethnicity; they should know the rates of resubmissions and their success rates.
    - NIH should develop a dataset that can provide a basis for longitudinal analysis.

2. NIH should expand tracking of commercialization outcomes:

    - NIH should track commercialization outcomes in ways similar to the now widely accepted methodology developed for the SBIR studies by the Academies.[130] This approach focuses on multiple metrics in order to provide a deeper and more nuanced basis for analysis.[131]
    - Although NIH tracks outcomes for the participants of its Commercialization Assistance Program, this tracking excludes a significant number of projects, and ends well before significant positive outcomes are likely to occur.
    - The data collection effort now under way at SBA may help NIH build a tracking and analysis capability. And NIH is already aware that NIH-specific metrics will need to be captured separately.

[129] See Finding V-F.

[130] National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology*, Washington, DC: The National Academies Press, 2004.

[131] See Chapter 1 (Introduction) and Appendix A (Methodology).

3. NIH should collect enhanced demographic data.

    - NIH should take immediate steps to improve its collection of demographic data about applicants and awardees.
    - NIH should extend its collection of the demographics of company ownership to show which of SBA's socially and economically disadvantaged categories an applicant belongs to. In addition, applicants should be asked the same demographic questions about the principal investigator.

4. NIH should also develop and adopt a more systematic and critical approach to the use of detailed case studies and success stories.

    - Case studies—written by NIH staff or third parties—can describe the roles played by SBIR/STTR awards, the challenges faced by small businesses, insights into needed improvements in process, lessons learned, and other important information not available elsewhere about program impacts.
    - Success stories—provided by the companies—can provide inspiration and promote interest in the program, but should not be regarded as sole evidence of program effectiveness.

5. NIH should take advantage of modern information management and data visualization tools both in its data collection effects, for communication with companies about program activities and operations, and to facilitate networking of program participants.

    - NIH should explore ways to use new technology such as social media to collect more current data. SBIR/STTR companies—like "customers" in other markets—are an important source of information about program strengths and weaknesses. This knowledge is currently not systematically included in internal program evaluation by NIH's SBIR/STTR programs.
    - NHLBI efforts to use social media may provide a worthwhile template for expanding activities already under way through the NIH Program Office.

6. NIH should develop feedback tools: NIH should develop pathways to provide ongoing feedback from companies about program activities and operations. These should include various electronic communication tools.
7. NIH should improve networking: Similarly, NIH should consider developing mechanisms (like electronic tools) through which recipients can share information about their SBIR/STTR projects, helping them both

to find technical, marketing, or investment partners and to navigate the often-complex regulatory and technical environment of NIH programs.

B. NIH should improve the utilization of outcomes data. As NIH starts to collect effective outcomes data, it should ensure that these data are systematically employed to guide program management.

1. NIH should develop a plan for data analysis: NIH should seek to develop a more sophisticated approach to analyzing and applying the data that are already collected.
2. NIH should evaluate data to identify factors that tend to encourage successful transitions between Phases, into Phase IIB, and then into full-scale commercialization. Such an approach could identify key issues for program management.
3. NIH should develop metrics to gauge how well it is meeting the congressionally mandated objectives for the SBIR/STTR programs.
4. NIH should undertake regular analysis of data. By collecting more and better data on outcomes and participation, NIH will be positioned to undertake regular analysis—either internally or with third-party help—on key program management issues, such as:

    - What is the long-term impact of commercialization training, partnership programs, and other commercialization supports?
    - Is Phase IIB simply picking successful companies or is it at least, in part, causing companies to be successful?
    - How well do NIH selection processes predict eventual successful projects?
    - How effectively do initiatives like direct to Phase II, I-Corps, and the NCI/NHLBI management models improve outcomes?

5. NIH should recognize the impacts of data collection and analysis. In some cases, simply measuring something more closely can provoke needed action. Closely tracking the participation of women and minorities could help assure a fair process and surface problem issues early, when they can be most easily corrected.

C. NIH should prepare an SBIR/STTR Annual Report to the NIH Director and Congress.

1. New annual report: Imposing new reporting burdens on the NIH SBIR/STTR programs is not without cost, but an annual report to Congress could improve transparency and provide a coherent point of discussion for stakeholders.

2. Although the precise details should be left to the agency, NIH should consider including the following areas of program operations:

    - Program Inputs: This relates to budget and related resources put into the program's front end.
    - Program Outputs: This includes initiatives developed, outreach activities, competitions/solicitations held, applications/proposals received, awards and contracts made.
    - Program Results:

        - Early outcomes: This includes progress measures such as attraction of additional funding by funded companies, formation of partnerships, early sales, patents, publications, and licensing agreements.
        - Intermediate outcomes. This includes resulting company growth in sales, employment, and knowledge benefits through the citation of patents and publication.
        - Long-term impacts. This includes measures of the economic return on investment, improvements in national innovation capacity, gains in strength of small businesses attributed to the programs, and growth in the numbers and percentage of women and minority businesses comprising the SBIR/STTR client base.

    - Qualitative review, based on improved use of case studies, as well as success and failure stories and social media.
    - Impact assessment, focused on the extent to which NIH meets congressional objectives for the program.
    - Summary conclusions, including prospective views on program activities and improvements for the coming year.

3. The new Annual Report should replace all existing reporting required from the program.

V. Improving Program Management

The following recommendations are designed to improve program operations in ways that should enhance the program's ability to address some or all of its objectives.

A. NIH should improve its application review system.[132]

Case studies, survey responses, and discussions with agency managers all indicate that although the NIH application review system has many positive characteristics, it is not serving the SBIR/STTR community as well as it could. The Center for Scientific Review currently provides relatively minor adjustments to standard academic grant review procedures to accommodate the needs of SBIR/STTR. This does not address SBIR/STTR needs effectively.

1. In consultation with an expert in this process, NIH should convene a high-level task force to improve the consideration of commercial potential in the selection process for SBIR/STTR applications.

    - The task force should include the Director of CSR, other CSR staff, the SBIR/STTR Program Manager, the Director of the Office of Extramural Research (OER), and selected staff from ICs recommended by the SBIR/STTR Program Manager.
    - The task force should provide a report within 6 months to the Director of NIH with an assessment of the SBIR/STTR review process and recommendations for improvement.

2. Some of the changes that should be considered by the task force include:

    - Guarantee of commercial expertise for all SBIR/STTR proposal reviews (especially Phase II). Every reviewed proposal should receive expert commercialization assessment. Commercialization reviews should be made based on published selection criteria that are designed to draw out the applicant companies' commercial thinking and planning. The effect of contracting on commercialization and company growth should also be analyzed.
    - More agile approaches to review that would streamline the process sufficiently to provide timely debriefs for resubmission at the next deadline.
    - Better pre-review briefing for all panelists to ensure that they fully understand the SBIR/STTR programs. In particular, to ensure that they understand that the full commercialization pathway is considered part of "innovation" by NIH.
    - Exploring opportunities for a more interactive process whereby companies have an opportunity to provide a brief further explanation or rebuttal to reviewer comments during the process. If feasible,

[132] See Finding V-A.

this would reduce resubmission, thus reducing the burden both on companies and on NIH staff and reviewers. (V-A)

- Developing an expert capacity in commercialization review, while leaving the existing system to do what it does best—scientific review. This could potentially be through the addition of consultants to panels or the development of separate commercialization review panels.
- Implementing a pre-application white paper similar to those in use at NSF and DoE. Reducing the number of applications with limited potential for success could help companies, reduce demand on the review process, and permit better linkage between NIH and the wider applicant community.

B. NIH should address the funding gap between Phase I and II awards.[133] Despite some efforts, it is apparent from the case studies and survey responses that funding gaps between the NIH Phase I and Phase II awards are a problem for small businesses. Although recognizing that some delays are unavoidable—for example, Congress has at times not provided definitive budgets until well into the fiscal year—NIH should take steps to support a smooth transition.

1. NIH should address the funding gap between Phase I and Phase II awards. Although data from the NIH Annual Report to SBA are not definitive on this point, there is evidence to suggest that significant improvements could be made.
2. NIH should improve awareness of the "work at own risk" process. Some survey respondents recommended that something similar be implemented, suggesting that they do not know how this works at NIH.
3. NIH should streamline review so that debriefs can be provided more rapidly. NIH is aware of this problem and is working to address it, but insufficient progress has been made to date.
4. NIH should encourage more firms to apply for Fast Track. Some survey respondents indicated that they thought success in applying for Fast Track was essentially impossible, but the awards data suggest otherwise.
5. NIH should make it clear that firms are able to resubmit for Phase I if they fail to get a Fast Track.
6. NIH should also consider additional ways to provide financial support during funding gaps. Such support might for example be available to top scoring Phase II proposals as a supplement to their Phase I award.

[133] See Finding V-H.

C. NIH should track and evaluate new program management initiatives.

1. Use of contracts:[134] The shift toward contracts at NCI reflects the new management approach adopted there. Although understandable, we believe that the NIH SBIR/STTR programs should remain primarily grants-based (i.e., investigator initiated) and that the use of contracts should be limited. NCI should track the new approach carefully and should seek to determine whether using contracts generates more or less positive outcomes.
2. Investigator initiated research: SBIR/STTR funding at NIH is now more closely targeted at IC priorities, in contrast to the traditional model of investigator-initiated research. NIH should assess whether targeting generates improved or less favorable outcomes for the SBIR/STTR companies and programs overall, and also to what extent awards are still being made to investigator-initiated projects. As part of this assessment, NIH should gather data on the extent to which the traditional model of investigator-initiated research is under pressure in the NIH SBIR/STTR programs.

[134]See Finding V-D.

Appendixes

Appendix A

Overview of Methodological Approaches, Data Sources, and Survey Tools

This series of reports on the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) programs at the Department of Defense (DoD), National Institutes of Health (NIH), National Aeronautics and Space Administration (NASA), Department of Energy (DoE), and National Science Foundation (NSF) represents a second-round assessment of the program undertaken by the National Academies of Sciences, Engineering, and Medicine.[1] The first-round assessment, conducted under a separate ad hoc committee, resulted in a series of reports released from 2004 to 2009, including a framework methodology for that study and on which the current methodology builds.[2]

The current study is focused on the twin objectives of assessing outcomes from the programs and of providing recommendations for improvement.[3] Sec-

[1]Effective July 1, 2015, the institution is called the National Academies of Sciences, Engineering, and Medicine. References in this report to the National Research Council or NRC are used in an historic context identifying programs prior to July 1.

[2]National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology,* Washington, DC: The National Academies Press, 2004.

[3]The methodology developed as part of the first-round assessment of the SBIR program also identifies two areas that are excluded from the purview of the study: "The objective of the study is *not* to consider if SBIR should exist or not—Congress has already decided affirmatively on this question. Rather, we are charged with providing assessment-based findings of the benefits and costs of SBIR . . . to improve public understanding of the program, as well as recommendations to improve the program's effectiveness. It is also important to note that, in accordance with the Memorandum of Understanding and the Congressional mandate, the study will *not* seek to compare the value of one area with other areas; this task is the prerogative of the Congress and the Administration acting through the agencies. Instead, the study is concerned with the effective review of each area." National Research Council, *Assessment of the SBIR Program: Project Methodology*, op. cit. In implementing this approach in the context of the current round of SBIR assessments, we have opted to focus more deeply on operational questions.

tion 1c of the Small Business Administration (SBA) SBIR Directive states program objectives as follows:

> *"The statutory purpose of the SBIR Program is to strengthen the role of innovative small business concerns (SBCs) in federally-funded research or research and development (R/R&D). Specific program purposes are to:*
>
> *(1) Stimulate technological innovation;*
> *(2) use small business to meet federal R/R&D needs;*
> *(3) foster and encourage participation by socially and economically disadvantaged small businesses (SDBs), and by women-owned small businesses (WOSBs), in technological innovation; and*
> *(4) increase private sector commercialization of innovations derived from Federal R/R&D, thereby increasing competition, productivity and economic growth."*[4]

The parallel language from the SBA's STTR Policy Directive is as follows:

> *"(c) The statutory purpose of the STTR Program is to stimulate a partnership of ideas and technologies between innovative small business concerns (SBCs) and Research Institutions through Federally-funded research or research and development (R/R&D). By providing awards to SBCs for cooperative R/R&D efforts with Research Institutions, the STTR Program assists the small business and research communities by commercializing innovative technologies."*[5]

The SBIR/STTR programs, on the basis of highly competitive solicitations, provide modest initial funding for selected Phase I projects (up to $150,000) and for feasibility testing and further Phase II funding (up to $1 million) for qualifying Phase I projects.[6]

From a methodology perspective, assessing this program presents formidable challenges. Among the more difficult are the following:

- **Lack of data.** NIH has only limited ability to track outcomes data, both in scope (share of awards tracked) and depth (time tracked after the end of the award). There are no published or publicly available outcomes data.
- **Intervening variables.** Small innovative businesses can be deflected from a development by a wide range of positive and negative variables. A single breakthrough contract—or technical delay—can make or break a company.
- **Lags.** Not only do outcomes lag awards by a number of years, but also the lag itself is highly variable. Some companies commercialize within

[4]Ibid., 3.

[5]Small Business Administration, Office of Investment and Innovation, "Small Business Technology Transfer (STTR) Program— Policy Guidance," updated February 24, 2014.

[6]These figures reflect standard sizes. NIH and other agencies have the flexibility to adjust the award sizes to accommodate the needs of particular projects and technologies.

6 months of award conclusion; others take decades. And often, revenues from commercialization peak many years after products have reached markets.

ESTABLISHING A METHODOLOGY

The methodology utilized in this second-round study of the SBIR/STTR programs builds on the methodology established by the committee that completed the first-round study.

Publication of the 2004 Methodology

The committee that undertook the first-round study and the agencies under study acknowledged the difficulties involved in assessing SBIR/STTR programs. Accordingly, that study began with development of the formal volume on methodology, which was published in 2004 after undergoing the standard Academies peer-review process.[7]

The established methodology stressed the importance of adopting a varied range of tools based on prior work in this area, which meshes with the methodology originally defined by the first study committee. The first committee concluded that appropriate methodological approaches—

> "build from the precedents established in several key studies already undertaken to evaluate various aspects of the SBIR/STTR. These studies have been successful because they identified the need for utilizing not just a single methodological approach, but rather a broad spectrum of approaches, in order to evaluate the SBIR/STTR from a number of different perspectives and criteria.
>
> This diversity and flexibility in methodological approach are particularly appropriate given the heterogeneity of goals and procedures across the five agencies involved in the evaluation. Consequently, this document suggests a broad framework for methodological approaches that can serve to guide the research team when evaluating each particular agency in terms of the four criteria stated above. Table A-1 illustrates some key assessment parameters and related measures to be considered in this study."[8]

The tools identified in Table A-1 include many of those used by the committee conducting the first-round study of the SBIR/STTR programs. Other tools have emerged since the initial methodology review.

[7]National Research Council, *Assessment of the SBIR Program: Project Methodology*, 2.
[8]National Research Council, *Assessment of the SBIR Program: Project Methodology*, 2.

TABLE A-1 Overview of Approach to SBIR/STTR Programs Assessment

SBIR/STTR Assessment Parameters →	Quality of Research	Commercialization of SBIR/STTR Funded- Research/ Economic and Non-economic Benefits	Small Business Innovation/Growth	Use of Small Businesses to Advance Agency Missions
Questions	How does the quality of SBIR/STTR-funded research compare with that of other government funded R&D?	How effectively does SBIR/ STTR support the commercialization of innovative technologies? What non-economic benefits can be identified?	How to broaden participation and expand the base of small innovative firms?	How to increase agency support for commercializable technologies while continuing to support high-risk research
Measures	Peer-review scores, publication counts, citation analysis	Sales, follow-up funding, other commercial activities	Patent counts and other IP/employment growth, number of new technology firms	Innovative products resulting from SBIR/STTR work
Tools	Case studies, agency program studies, study of repeat winners, bibliometric analysis	Phase II surveys, program manager discussions, case studies, study of repeat winners	Phase I and Phase II surveys, case studies, study of repeat winners	Program manager surveys, case studies, agency program studies, study of repeat winners
Key Research Challenges	Difficulty of measuring quality and of identifying proper reference group	Skew of returns; significant interagency and inter-industry differences	Measures of actual success and failure at the project and firm levels; relationship of federal and state programs in this context	Major interagency differences in use of SBIR/STTR to meet agency missions

NOTE: Supplementary tools may be developed and used as needed. In addition, since publication of the methodology report, this committee has determined that data on outcomes from Phase I awards are of limited relevance.

SOURCE: National Research Council, *An Assessment of the Small Business Innovation Research Program: Project Methodology*, Washington, DC: The National Academies Press, 2004, Table 1, p. 3. The contents of the table have been adjusted to focus on the specific program at the NIH.

Tools Utilized in the Current SBIR/STTR Study

Quantitative and qualitative tools being utilized in the current study of the SBIR/STTR programs include the following:

- **Surveys.** An extensive survey of NIH SBIR/STTR award recipients was commissioned as part of the analysis. These are described in depth below.[9]
- **Case studies.** In-depth case studies of 20 SBIR/STTR recipients of NIH awards were commissioned. These companies were geographically and demographically diverse and were at different stages of the company lifecycle.
- **Workshops.** Several workshops were commissioned to allow stakeholders, agency staff, and academic experts to provide insights into the programs' operations, as well as to identify questions that should be addressed.
- **Analysis of agency data.** NIH provided the committee with a range of datasets covering various aspects of agency SBIR/STTR activities, which were analyzed and included as appropriate.
- **Open-ended responses from SBIR/STTR recipients.** For the first time, the survey—the 2014 Survey—solicited textual survey responses. More than 500 recipients provided narrative comments.
- **Agency meetings.** Discussions about program operations were held with NIH staff members. Most were helpful in providing information both about the program and the challenges that they faced.
- **Literature review.** Since the start of the committee's research in this area, a number of papers have been published addressing various aspects of the SBIR/STTR programs. In addition, other organizations—such as the Government Accountability Office (GAO)—have reviewed particular parts of the SBIR/STTR programs. These works were relevant and are referenced in the course of this analysis.

Taken together with committee deliberations and the expertise brought to bear by the individual committee members, these tools provide the primary inputs into the analysis.

For the first-round study and for the current study, multiple research methodologies feed into every finding and recommendation. No findings or recommendations rested solely on data and analysis from the survey; conversely, survey data were used to support analysis throughout the report.

[9]The survey conducted as part of the current, second-round assessment of the SBIR/STTR programs is referred to as the "2014 Survey."

COMMERCIALIZATION METRICS AND DATA COLLECTION

Recent congressional interest in the SBIR/STTR programs has to a considerable extent focused on bringing innovative technologies to market. This enhanced attention to the economic return from public investments made in small business innovation is understandable. However, in contrast to the Department of Defense (DoD), which may procure selected SBIR/STTR technologies, commercialization at NIH takes place almost entirely in private-sector markets.

In its 2009 report on the NIH SBIR/STTR programs,[10] the committee charged with the first-round assessment held that a binary metric of commercialization was insufficient. It noted that the scale of commercialization is also important and that there are other important milestones both before and after the first dollar in sales that should be included in an appropriate approach to measuring commercialization.

Challenges in Tracking Commercialization

Despite substantial efforts at NIH, described below, significant challenges remain in tracking commercialization outcomes for the NIH SBIR/STTR programs. These include the following:

- **Data limitations.** NIH, like most other agencies, has not maintained a comprehensive electronic reporting system for post-award data. It also does not penalize companies for failing to report outcomes. Companies face few incentives to report their successes and failures in commercialization.
- **Linear linkages.** Tracking efforts usually seek to link a specific project to a specific outcome. Separating the contributions of one project is difficult for many companies, given that multiple projects typically contribute to both anticipated and unanticipated outcomes.
- **Lags in commercialization.** Data from the extensive DoD commercialization database suggest that most projects take at least 2 years to reach the market *after the end of the Phase II award*. They do not generate peak revenue for several years after this. Therefore, efforts to measure program productivity must account for these significant lags.
- **Attribution problems.** Commercialization is often the result of several awards, not just one, as well as other factors, so attributing company-level success to specific awards is challenging at best.

Why New Data Sources Are Needed

Congress often seeks evidence about the effectiveness of programs or indeed about whether they work at all. This interest has in the past helped to drive the

[10]National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, Washington, DC: The National Academies Press, 2009.

development of tools such as the Company Commercialization Report (CCR) at DoD, which captures the quantitative commercialization results of companies' prior Phase II projects. However, in the long-term the importance of tracking may rest more in its use to support program management. By carefully analyzing outcomes and CCR's associated program variables, program managers will be able to manage their SBIR/STTR portfolios more successfully.

In this regard, the NIH SBIR/STTR programs can benefit from access to the survey data. The survey work provides quantitative data necessary to provide an evidence-driven assessment and, at the same time, allows management to focus on specific questions of interest. For example, at NIH the survey was tuned to include additional information on company efforts to meet U.S. Food and Drug Administration (FDA) requirements for clinical trials prior to commercialization.

SURVEY ANALYSIS

Traditional modes of assessing the NIH SBIR/STTR programs include case studies, interviews with program staff, review of documents, and other qualitative methods of assessment. These remain important components of the overall methodology, and a chapter in the current report is devoted to lessons drawn from case studies. However, qualitative assessment alone is insufficient.

2014 Survey

The 2014 Survey offers some significant advantages over other data sources. Specifically, it—

- provides a rich source of textual information in response to open-ended questions;
- probes more deeply into company demographics and agency processes;
- for the first time addresses principal investigators (PIs), not just company business officials;
- allows comparisons with previous data-collection exercises;
- generates the first SBIR/STTR-related data on clinical trials; and
- addresses other Congressional objectives for the program beyond commercialization.

For these and other reasons, a survey was determined to be the most appropriate mechanism for developing quantitative approaches to the analysis of the SBIR/STTR programs. At the same time, however, there are limitations of survey research in this case. Box A-1 describes a number of areas where caution is required when reviewing results.

To take account of these limits, while retaining the utility and indeed explanatory power of survey-based methodology, the current report contextualizes

BOX A-1
Multiple Sources of Bias in Survey Response[a]

Large innovation surveys involve multiple sources of potential bias that can skew the results in different directions. Some potential survey biases are noted below.

- Successful and more recently funded companies are more likely to respond. Research by Link and Scott demonstrates that the probability of obtaining research project information by survey decreases for less recently funded projects and increases the greater the award amount.[b] About 60 percent of respondents to the 2014 Survey received NIH awards during fiscal years (FY) 2006-2010. Winners from more distant years are difficult to reach: small businesses regularly cease operations, are acquired, merge, or lose staff with knowledge of SBIR/STTR awards. While there is evidence of bias for project-performance count variables such as the number of publications or patents associated with a publicly-subsidized project, there is also evidence that there may not be a response bias for commercialization measures.[c]
- Non-respondent bias. Very limited information is available about SBIR/STTR award recipients: company name, location, and contact information for the PI and the company point of contact, agency name, and date of award (data on woman and minority ownership are not considered reliable). No detailed data are available on applicants who did not win awards. It is therefore not feasible to undertake detailed analysis of non-respondents, but the possibility exists that they would present a different profile than would respondents.
- Success is self-reported. Self-reporting can be a source of bias, although the dimensions and direction of that bias are not necessarily clear. In any case, policy analysis has a long history of relying on self-reported performance measures to represent market-based performance measures. Participants in such retrospective analyses are believed to be able to consider a broader set of allocation options, thus making the evaluation more realistic than data based on third-party observation.[d] In short, company founders and/or PIs are in many cases simply the best source of information available.
- Survey sampled projects from PIs with multiple awards. Projects from PIs with large numbers of awards were underrepresented in the sample, because PIs could not be expected to complete a questionnaire for each of numerous awards over a 10-year time frame.
- Failed companies are difficult to contact. Survey experts point to an "asymmetry" in the survey's ability to include failed companies for follow-up surveys in cases where the companies no longer exist.[e] It is worth noting that one cannot necessarily infer that the SBIR/STTR project failed; what is known is only that the company no longer exists.
- Not all successful projects are captured. For similar reasons, the survey could not include ongoing results from successful projects in companies that merged or were acquired before and/or after commercialization of the project's technology. This is the outcome for many successful companies in this sector.
- Some companies may not accurately acknowledge SBIR/STTR contribution to project success. Some companies may be unwilling to acknowledge that

continued

BOX A-1 Continued

they received important benefits from participating in public programs for a variety of reasons. For example, some may understandably attribute success exclusively to their own efforts. Other companies may overstate the importance of SBIR/STTR.

- Commercialization lags. Although the 2005 Survey broke new ground in data collection, the amount of sales made—and indeed the number of projects that generated sales—are inevitably undercounted in a snapshot survey taken at a single point in time. On the basis of successive data sets collected from NIH SBIR/STTR award recipients, it is clear that total sales from all responding projects will be considerably greater than can be captured in a single survey.[f] This underscores the importance of follow-on research based on the now-established survey methodology. Figure Box A-1 illustrates this impact in practice at DoD: projects from FY2006 onward have not yet completed commercialization as of August 2013.

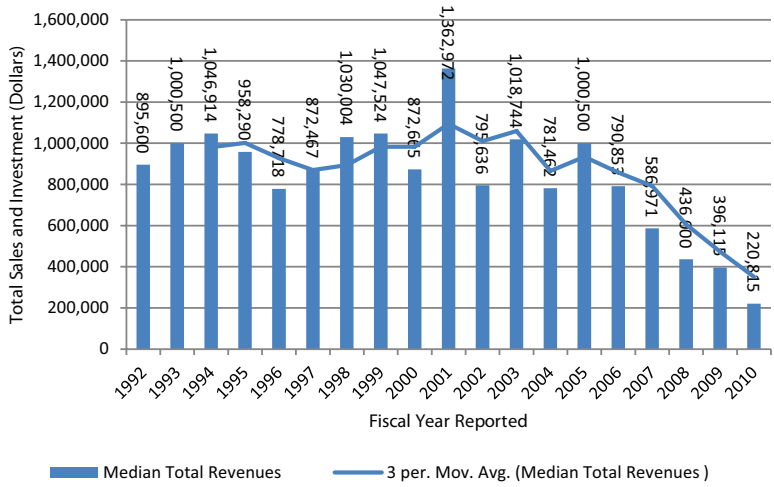

FIGURE BOX A-1 The impact of commercialization lag.
SOURCE: DoD Company Commercialization Database.

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[a] The limitations described here are drawn from the methodology outlined for the previous survey in National Research Council, *An Assessment of the SBIR Program at the Department of Defense*, Washington, DC: The National Academies Press, 2009.

[b] Albert N. Link and John T. Scott, *Evaluating Public Research Institutions: The U.S. Advanced Technology Program's Intramural Research Initiative,* London: Routledge, 2005.

[c] See, for example, Dora Gicheva and Albert N.Link, "Leveraging Entrepreneurship through

continued

BOX A-1 Continued

Private Investments: Does Gender Matter?," *Small Business Economics*, 40:199-210, 2013 (finding that the probability of securing outside finance do not find any response bias); Alfred N. Link and John T. Scott, "Private Investor Participation and Commercialization Rates for Government-sponsored Research and Development: Would a Prediction Market Improve the Performance of the SBIR Programme?" *Economica*, 76:264-281, 2009 (finding that there is no response bias in the estimates for the probability of commercialization).

[d] Although economic theory is formulated on what is called "revealed preferences," meaning that individuals and companies reveal how they value scarce resources by how they allocate those resources within a market framework, quite often expressed preferences are a better source of information, especially from an evaluation perspective. Strict adherence to a revealed preference paradigm could lead to misguided policy conclusions because the paradigm assumes that all policy choices are known and understood at the time that an individual or company reveals its preferences and that all relevant markets for such preferences are operational. See Gregory G. Dess and Donald W. Beard, "Dimensions of Organizational Task Environments," *Administrative Science Quarterly,* 29:52-73, 1984; Albert N. Link and John T. Scott, *Public Accountability: Evaluating Technology-Based Institutions* Norwell, MA: Kluwer Academic Publishers, 1998.

[e] Link and Scott, *Evaluating Public Research Institutions.*

[f] Data from the National Research Council assessment of the SBIR program at NIH indicate that a subsequent survey taken 2 years later would reveal substantial increases in both the percentage of companies reaching the market and the amount of sales per project. See National Research Council, *An Assessment of the SBIR Program at the National Institutes of Health*, Washington, DC: The National Academies Press, 2009.

the data by comparing results to those from the survey conducted as part of the first-round assessment of the SBIR/STTR programs (referred to below as the "2005 Survey"). This report also adds transparency by publishing the number of responses for each question and indeed each subgroup. As noted later in the discussion, the use of a control group was found infeasible for comparing Phase II and Phase I recipients, but feasible for comparing Phase IIB and Phase II recipients.

Grunwald Associates LLC was contracted to administer a survey to award recipients. The Academies' 2014 Survey is built closely on the 2005 Survey, but it is also adapted to draw on lessons learned and includes some important changes discussed in detail below. A subgroup of this committee with particular expertise in survey methodology also reviewed the survey and incorporated current best practices. The 2014 survey covered NIH and the Department of Energy (DoE) simultaneously.[11]

[11] Delays at NIH and DoE in contracting with the Academies, combined with the need to complete work contracted with DoD, National Science Foundation (NSF), and the National Aeronautics and Space Administration (NASA) led us to proceed with the survey at the remaining three agencies first, in 2011, followed by the NIH-DoE survey in 2014.

The primary objectives of the 2014 Survey (in combination with the 2010 Phase IIB Survey) were as follows:

- Provide an update of the program "snapshot" taken in 2005, maximizing the opportunity to identify trends within the program;
- Probe more deeply into program processes, with the help of expanded feedback from participants and better understanding of program demographics; and
- Reduce costs and shrink the time required by combining three 2005 questionnaires—for the company, Phase I, and Phase II awards, respectively—into a single 2014 Survey questionnaire.

The survey was therefore designed to collect the maximum amount of data, consistent with the commitment to minimizing the burden on individual respondents.

In light of these competing considerations, the decision was made to administer the survey to PIs—the lead researcher on each project—rather than to the registered company point of contact (POC), who in many cases would be an administrator rather than a researcher. This decision was reinforced by difficulties in accessing current POC information. Key areas of overlap between the 2005 and 2014 surveys are captured in Table A-2.

Starting Date and Coverage

The 2014 Survey included awards made from FY2001 to FY2010 inclusive. This end date allowed for completion of Phase II-awarded projects (which nominally fund 2 years of research) and provided a further 2 years for commercialization. This time frame was consistent with the previous survey, administered in 2005, which surveyed awards from FY1992 to FY2001. It was also consistent with a previous GAO study, which in 1991 surveyed awards made through 1987.

The aim in setting the overall time frame at 10 years was to reduce the impact of difficulties in generating information about older awards, because some companies and PIs may no longer be in place and memories fade over time.

Determining the Survey Population

Following the precedent set by both the original GAO study and the first round of Academies analysis, we differentiate between the total population of SBIR/STTR recipients, the preliminary survey target population, and the effective population for this study, which is the population of respondents that were reachable.

The effective survey population is the denominator for the survey, used to determine response rates.

TABLE A-2 Similarities and Differences: 2005 and 2014 Surveys

Item	2005 Survey	2014 Survey
Respondent selection		
Focus on Phase II winners	✓	✓
All qualifying awards		✓
PIs		✓
POCs	✓	
Max number of questionnaires per respondent	<20	2
Distribution		
Mail	✓	No
Email	✓	✓
Telephone follow-up	✓	✓
Questionnaire		
Company demographics[a]	Identical	Identical
Commercialization outcomes	Identical	Identical
IP outcomes	Identical	Identical
Women and minority participation	✓	✓
Additional detail on minorities		✓
Additional detail on PIs		✓
New section on agency staff activities		✓
Information about technological categories		✓
New section on company recommendations for SBIR/STTR		✓
New section capturing open-ended responses		✓

[a] While company demographics in the two surveys appear to be identical, we note that the information collected about companies in the 2014 survey is not directly comparable to the surveys used in 2005. In addition, information about the company's age was not included in the 2014 survey, but, as pointed out in reviewer comments, should be included in future evaluations of SBIR.

Initial Filters for Potential Recipients

Determining the effective study population required the following steps:

- acquisition of data from the sponsoring agencies—NIH and DoE—covering record-level lists of award recipients;
- elimination of records that did not fit the protocol agreed upon by the committee—namely, a maximum of two questionnaires per PI (in cases

where PIs received more than two awards), awards were selected first by program (STTR, then SBIR), then by agency (DoE and NIH, in that order), then by year (oldest first), and finally by random number; and
- elimination of records for which there were significant missing data—in particular, where emails and/or contact telephone numbers were absent.

This process of excluding awards either because they did not fit the selection profile approved by the committee or because the agencies did not provide sufficient or current contact information reduced the total award list provided by NIH from 3,851 awards to a preliminary survey population of 3,375 awards.

Secondary Filters to Identify Recipients with Active Contact Information

This nominal population still included many potential respondents whose contact information was complete but who were no longer associated with the contact information provided and hence effectively unreachable. This is unsurprising given that small businesses experience considerable turnover in personnel and that the survey reaches back to awards made in FY2001. Recipients may have switched companies, the company may have ceased to exist or been acquired, or telephone and email contacts may have changed, for example. Consequently, we utilized two further filters to help identify the effective survey population.

- First, contacts for which the email address bounced twice were eliminated. Because the survey was delivered via email, the absence of a working email address disqualified the recipient. This eliminated approximately 30 percent of the preliminary population.
- Second, email addresses that did not officially "bounce" (i.e., return to sender) may still in fact not be active. Some email systems are configured to delete unrecognized email without sending a reply; in other cases, email addresses are inactive but not deleted. So a non-bouncing email address did not equal a contactable PI.

Deployment

The 2014 Survey opened on December 3, 2014, and was deployed by email, with voice follow-up support. Up to four emails were sent to the effective population (emails discontinued once responses were received). In addition, two voice mails were delivered to non-respondents between the second and third and between the third and fourth rounds of email. In total, up to six efforts were made to reach each questionnaire recipient. After the members of the data subgroup of our committee concluded that sufficient data for the purposes had been collected, the survey closed on April 7, 2015. It was open for a total of 18 weeks.

Response Rates

Standard procedures were followed to conduct the survey. These data collection procedures were designed to increase response to the extent possible within the constraints of a voluntary survey and the survey budget. The population surveyed is a difficult one to contact and obtain responses from as evidence from the literature shows. Under these circumstances, the inability to contact and obtain responses always raises questions about potential bias of the estimates that cannot be quantified without substantial extra efforts that would require resources beyond those available for this work.

The lack of detailed applications data from the agency makes it impossible to estimate the possible impact of non-response bias. We, therefore, have no evidence either that non-response bias exists or that it does not.

Table A-3 shows the response rates at NIH by phase, based on both the preliminary study population prior to adjustment and the effective study population after all adjustments.

All subsequent references to the 2014 Survey in this report address only responses for awards made by NIH.

Effort at Comparison Group Analysis

Several readers of the reports in the first-round analysis of the SBIR/STTR programs suggested the inclusion of comparison groups in the analysis. We concurred that this should be attempted. There is no simple and easy way to acquire a comparison group for Phase II SBIR/STTR awardees. These are technology-based companies at an early stage of company development, which have the demonstrated capacity to undertake challenging technical research *and* to provide evidence that they are potentially successful commercializers. Given that the operations of the SBIR/STTR programs are defined in legislation and limited by

TABLE A-3 2014 Survey Response Rates at NIH

Preliminary population	3,375
Not contactable	1,723
Effective population	1,652
Responses	726
Surveys as Percentage of Awards Contacted	43.9
Surveys as Percentage of Sample	21.5

SOURCE: 2014 Survey.

TABLE A-4 SBIR/STTR Responses by Year of Award (Percent Distribution)

	NIH	SBIR	STTR	PHASE IIB
Fiscal Year of Award	TOTAL	—	—	—
2001	7.5	8.2	3.6	
2002	9.1	9.3	8.1	
2003	7.8	9.1	0.9	
2004	6.1	6.6	3.6	
2005	9.3	8.4	13.5	10.3
2006	10.8	11.5	7.2	24.1
2007	10.5	10.2	11.7	20.7
2008	11.7	10.9	15.3	20.7
2009	11.4	10.8	14.4	13.8
2010	16	14.9	21.6	10.3
BASE: ALL RESPONDENTS	669	558	111	29

SOURCE: 2014 Survey.

the Small Business Administration (SBA) Policy Guidance, randomly assigned control groups were not a possible alternative. Efforts to identify a pool of SBIR/STTR-like companies were made by contacting the most likely sources—Dunn and Bradstreet and Hoovers—but these efforts were not successful, because sufficiently detailed and structured information about companies was not available.

In response, we sought to develop a comparison group from among Phase I awardees that had not received a Phase II award from the three surveyed agencies (DoD, NSF, and NASA) during the award period covered by the survey (FY2001-2010). After considerable review, however, the committee concluded that the Phase I-only group was not appropriate for use as a statistical comparison group.

NIH Responses and Respondents

Table A-4 shows NIH SBIR/STTR responses by year of award. The survey primarily reached companies that were still in business: overall, 94 percent of respondents indicated that the companies were still in business.[12]

[12]2011 Survey, Question 4A.

Appendix B

Major Changes to the SBIR Program Resulting from the 2011 SBIR Reauthorization Act, P.L. 112-81, December 2011

1. **The SBIR program received an increased share of federal agencies' extramural budget:**[1]

   a. Congress increased the SBIR/STTR share from 2.5 percent to 2.6 percent in FY2012 and by 0.1 percent per year thereafter through FY2017, when the share would be 3.2 percent.

2. **STTR's share of the overall combined program was increased:**[2]

   a. It is to grow from 0.25 percent to 0.3 percent in FY2011, 0.35 percent in FY2012 and 2013, 0.40 percent in FY 2014 and 2015, and 0.45 percent in FY2016 and thereafter.

3. **Award levels were increased:**[3]

   a. The existing limit of $100,000 for Phase I SBIR and STTR awards was increased to $150,000.
   b. The existing limit of $750,000 for Phase II SBIR and STTR awards was increased to $1,000,000.
   c. These limits were also for the first time indexed to inflation.

[1]U.S. Congress, P.L. 112-81, Sec. 5102 (a)(1)(a).
[2]Sec. 5102(b).
[3]Sec. 5103.

4. Agency flexibility to issue larger awards was curtailed:[4]

a. Awards may no longer exceed 150 percent of guidelines (i.e., $1.5 million for Phase II) without a specific waiver from the SBA Administrator.
b. The waiver can apply only to a specific topic, not to the agency as a whole. The agency must meet specific criteria and must show in its application that these criteria have been met before a waiver can be issued.
c. For every award under a waiver, agencies must maintain additional information about the recipient, including the extent to which they are owned or funded by venture capital or hedge fund investors.

5. Agencies are permitted to utilize awards from other agencies:[5]

a. Agencies gained the ability to adopt Phase I awards from other agencies for Phase II funding; however, senior agency staff must certify that this is appropriate.
b. Similarly, the legislation now permits between-phase crossovers between SBIR and STTR.

6. Phase II invitations were eliminated for SBIR:[6]

a. The requirement that a company be invited by the agency before it could propose work for Phase II is now eliminated.

7. Pilot programs to skip Phase I were established:[7]

a. The legislation allows NIH, DoD, and the Department of Education to undertake pilot programs in this area. Discussions with agency staff indicate that for now DoD does not expect to utilize this new flexibility.

8. For SBIR, limited participation by previously excluded firms with majority venture capital or hedge fund ownership is now permitted (although subsidiaries of large operational companies are still excluded):[8]

a. NIH, NSF, and DoE are permitted to award up to 25 percent of their program funding to such companies.
b. Other agencies are limited to 15 percent.

[4]Sec. 5103.
[5]Sec. 5104.
[6]Sec. 5105.
[7]Sec. 5106.
[8]Sec. 5107.

c. For each award to such an entity, the Agency or component head must certify that this award is in the public interest based on criteria laid out in Sec. 5107(A)(dd)(2).
d. Access to venture capital or hedge fund support may not be used as an award selection criterion by agencies.
e. Special "affiliation" rules are provided for venture capital- and hedge fund-owned companies:

    i. Portfolio companies partially owned by venture firms or hedge funds are not deemed to be "affiliated" for purposes of determining whether an applicant meets size limitations, unless they are wholly owned or the owning company has a majority of board seats on the portfolio company.

9. Explicit procurement preference were given for SBIR and STTR projects:[9]

a. The legislation states that agencies *and prime contractors* (emphasis added) must give preference to SBIR and STTR projects where practicable. However, there are no explicit targets included in the legislation.

10. Sequential Phase II awards were permitted:[10]

a. The legislation now explicitly permits agencies to award one additional Phase II award after the first Phase II has been completed.
b. The language implies that the provision of more than one sequential Phase II is prohibited.

11. Commercialization support was expanded:[11]

a. Agencies are permitted to spend up to $5,000 per year per award on support for commercialization activities.
b. Individual firms can now request up to $5,000 per year *in addition to their SBIR or STTR award* (emphasis added) to pay for commercialization activities from agency-approved vendors.

12. The commercialization readiness pilot at DoD was converted to a permanent program—the Commercialization Readiness Program (CRP). Details include in particular the following:[12]

[9]Sec. 5108.
[10]Sec. 5111.
[11]Sec. 5121.
[12]Sec. 5122.

a. An SBIR Phase III insertion plan is now required for all DoD acquisition programs with a value of $100 million or more.
b. SBIR/STTR Phase III reporting is now required from the prime contractor for all such contracts.
c. The Secretary of Defense (SecDef) is now required to set goals for the inclusion of SBIR/STTR Phase II projects in programs of record and fielded systems and must report on related plans and outcomes to the SBA Administrator.
d. The legislation explicitly requires the SecDef to develop incentives toward this purpose and to report on the incentives and their implementation.

13. CRP may be expanded to other agencies:[13]

a. Other agencies may spend up to 10 percent of their SBIR/STTR program funds on commercialization programs.
b. CRP awards may be up to three times the maximum size of Phase II awards.
c. CRP authority expires after FY2017.

14. Phase 0 pilot partnership program at NIH was enabled:[14]

a. NIH is permitted to use $5 million to establish a Phase 0 pilot program.
b. The funding must go to universities or other research institutions that participate in the NIH STTR program.
c. These institutions must then use the funding for Phase 0 projects for individual researchers.

15. Data collection and reporting were enhanced:[15]

a. Overall, the legislation calls for substantially increased data collection for individual recipients and for much more detailed reporting from agencies to SBA and to Congress.
b. Specific areas for improved reporting include:

    i. Participation of (and outreach toward) woman- and minority-owned firms and the participation of woman and minority principal investigators;
    ii. Phase III take-up (from both agencies and prime contractors);
    iii. Participation of venture capital- and hedge fund-owned firms;

[13]Sec. 5123.
[14]Sec. 5127.
[15]Especially Sec. 5132, Sec. 5133, Sec. 5138, and Sec. 5161, but specific requirements are found throughout the legislation.

iv. Appeals and noncompliance actions taken by SBA;
v. Sharing of data between agencies electronically;
vi. Extra-large awards;
vii. SBIR and STTR project outcomes (from participants);
viii. University connections (especially for STTR projects);
ix. Relations with the FAST state-level programs;
x. Use of administrative funding for SBIR;
xi. Development of program effectiveness metrics at each agency; and
xii. SBIR activities related to Executive Order 1339 in support of manufacturing.

c. SBA is charged with developing a unified database to cover all SBIR and STTR awards at all agencies, as well as company information and certifications.[16]

16. Funding was provided for a pilot program to cover administrative, oversight, and contract processing costs:[17]

a. Agencies are limited to spending 3 percent of their SBIR/STTR funding on this pilot.
b. The pilot is initially designated to last for 3 fiscal years following enactment.
c. Part of the funding must be spent on outreach in low-award states.

17. Minimum commercialization rates for participating companies are required:[18]

a. Agencies must establish appropriate commercialization metrics and benchmarks for participating companies, for both Phase I and Phase II (subject to SBA Administrator approval).
b. Failure to meet those benchmarks must result in 1-year exclusion for that company from the agency's SBIR and STTR programs.

[16]Sec. 5135.
[17]Sec. 5141.
[18]Sec. 5165.

Appendix C

National Academies of Sciences, Engineering, and Medicine 2014 SBIR/STTR Survey

Introduction

Welcome to the National Academies SBIR/STTR Survey. Thank you for participating. This survey seeks responses related to the Phase II project entitled [insert project title], funded by [insert agency name], at [insert company name]. Funding was awarded in [insert FY].

Note: If you need to revisit the survey before finally completing it, you can return at the point you left off by clicking on the survey link in your email.

Finally, please use the navigational buttons within the survey. The back and forward buttons on your browser will not work.

Privacy and Confidentiality Policy

Responses to this survey will be held in confidence by the survey team. No identifiable information will be provided to other Academy staff or to the Public Access File which provides researchers with access to project data.

In order to implement this commitment, the following steps have been taken, covering three areas:

a. Data in the published report
b. Management of raw data files
c. Additional review of textual (open-ended) responses

a. Data in the published report.

All data except for text responses will be presented only in aggregated form in the report; no individually identifiable cells will be published.

b. Managing raw data.

In order to provide researchers with access while meeting the confidentiality commitment, the following steps will be taken by the Contractor prior to providing an expurgated data set to the Academy for inclusion in the Public Access File:

1. Replace company name with a new company ID
2. Replace PI name with a new PI ID
3. Delete the following fields:

    a. Agency record ID
    b. Company address except for State field
    c. Project title
    d. Project abstract
    e. Flag for woman owned business
    f. Flag for minority owned business

The raw (unexpurgated) data set will be retained by the Contractor for two years after publication of the report. All copies of the raw data will then be destroyed. The expurgated data set will be retained indefinitely in the Public Access File related to the project.

c. Review of textual responses.

Two independent reviewers will analyze open ended responses with a view to redacting material that could provide clues as to the identity of the respondent prior to their inclusion in the Public Access File. In particular, this review will redact all company names, product names, and PI or other company official names, as well as other potential identity clues.

Do you approve the privacy and confidentiality policy as shown above?
[Yes/No. If no, jump to page 55.]

This information is required only to determine your current status, and to ensure that we have accurate contact information. Your information will be strictly private and will not be shared with any private entity or government agency; aggregated data will be shared in a published report.

1. For the project referenced above, were you (during the time period covered by this award) . . .*

   Select all that apply.
   a. A Principal Investigator (PI) on this project
   b. The CEO
   c. A company founder
   d. Senior researcher (other than PI)
   e. Not CEO but a senior executive with the company identified above
   f. None of the above (exit questionnaire)

Part 1. Information About You

2. Please verify or correct the following information about yourself. Please indicate any corrections in the boxes provided. If all this information is accurate, click "Next" to continue.

   First name: [Text box]
   Last name: [Text box]
   Current email address: [Text box]
   Current work telephone number (for follow up questions if necessary): [Text box]

Part 2. Company Information Section

3. Have you already completed a questionnaire about another SBIR or STTR project for this National Academy survey related to [insert company name]?*
   [Yes/No. If yes, skip to Part 3: PI/Senior Executive Information]

4. Is [insert company name] still in business?
   [Yes/No]

5. Thinking about the number of founders of the company, what was . . .?

   Min = 0 Max = 20 Must be numeric
   a. The total number of founders [number box]
   b. The number of other companies started by one or more of the founders (before starting this one) [number box]
   c. The number of founders who have a business background [number box]
   d. The number of founders who have an academic background [number box]
   e. The number of founders with previous experience as company founders [number box]

6. What was the most recent employment of the company founders prior to founding the company?

   Select all that apply.
   a. Other private company
   b. Government
   c. Research institution
   d. FFRDCs or National Labs
   e. Other

7. Was the company founded because of the SBIR/STTR program?

   Yes
   In part
   No

8. What was the company's total revenue for the most recent fiscal year?

   $0
   Under $100,000
   $100,000-499,999
   $500,000-999,999
   $1,000,000-4,999,999
   $5,000,000-19,999,999
   $20,000,000-99,999,999
   $100,000,000 or more

9. What percentage of the company's revenues during its most recent completed fiscal year was Federal SBIR/STTR funding (Phase I and/or Phase II)?

   0%
   1-10%
   11-25%
   26-50%
   51-75%
   76-99%
   100%

10. What percentage of the company's total R&D effort (man-hours of scientists and engineers) was for SBIR/STTR activities during the most recent fiscal year?

    0%
    1-10%
    11-25%
    26-50%
    51-75%
    76-100%

11. Which if any of the following has the firm experienced since your first SBIR/STTR award?

    Select all that apply.
    Made an initial public offering
    Established one or more spin off companies
    Been acquired by/merged with another firm
    Planning to make an initial public offering in the next two years
    Entered into strategic partnership with major industry player
    None of the above

12. How many patents have resulted, at least in part, from the company's SBIR/STTR awards?

    Min = 0 Max = 999 Must be numeric
    Whole numbers only Positive numbers only
    [number box]

13. Does the company have one or more full time staff for marketing or business development?
    [Yes/No]

14. Number of company employees (including all affiliates):

    Min = 0 Max = 99999 Must be numeric
    Whole numbers only Positive numbers only
    a. At the time of the award in [pipe in award year] [Number box]
    b. Currently [Number box]

15. What was the ownership status of the company at the time of the award?

Select all that apply.

a. Woman-owned
b. Minority-owned
c. Neither of the above

If the answer is "Minority-owned," please indicate the ethnic minority group[s] that company owners [at the time of the award] belonged to.

Select all that apply.

Asian-Indian
Asian-Pacific
Black
Hispanic
Native American
Other [Text box]

Part 3. PI/Senior Executive Information

16. The Principal Investigator for this [SBIR/STTR] Award was a . . .

Select all that apply.

a. Woman
b. Minority
c. Neither of the above

If the answer is "Minority," please indicate the ethnic minority group[s] the Principal Investigator for this award belongs to.

Select all that apply.

Asian-Indian
Asian-Pacific
Black
Hispanic
Native American
Other [Text box]

17. At the time of the award, the age of the leading PI was . . .

[Under 25, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+]

18. What was the immigration status of the PI at the time of the award?

    American-born US citizen
    Naturalized US citizen
    US Green card
    H1 visa
    Other [Text box]

19. What is the current status of the project funded by the referenced award?

    Select the one best answer.

    a. Project has not yet completed SBIR/STTR funded research.
    b. Efforts at this company have been discontinued. No sales or additional funding resulted from this project.
    c. Efforts at this company have been discontinued. The project did result in sales, licensing of technology, or additional funding.
    d. Project is continuing post-award technology development.
    e. Commercialization is underway.
    f. Products/Processes/Services are in use by target population/customer/consumers.
    g. Products/Processes/Services are in use by population/customer/consumers not anticipated at the time of the award (for example, in a different industry).

20. If the answer is either b) or c), did the reasons for discontinuing this project include any of the following?

    Select one of the reasons as the Primary Reason.
    Select all that apply as Other contributing reasons.

    Another firm got to the market before us
    Level of technical risk too high
    Principal Investigator left
    Technical failure or difficulties
    Inadequate sales capability
    Project goal was achieved (e.g. prototype delivered for federal agency use)
    Licensed to another company
    Market demand too small
    Company shifted priorities
    Other (Please specify in comments box below)

    Comments
    [Text box]

Part 4. Project Status Information

21. Please select the technology sector or sectors that most closely fit(s) the work of the SBIR/STTR project.

Select all that apply.

Aerospace and Defense
- Aerospace
- Defense-specific products and services

Energy and the environment
- Renewable energy production (solar, wind, geothermal, bio-energy, wave)
- Energy storage and distribution
- Energy efficiency
- Other energy or environmental products and services

Engineering
- Engineering services
- Scientific instruments and measuring equipment
- Robotics
- Sensors
- Other engineering

Information technology
- Computers and peripheral equipment
- Telecommunications equipment and services
- Business and productivity software
- Data processing and database software and services
- Media products (including web-, print- and wireless-delivered content)
- Other IT

Materials
- Materials (including nanotechnology for materials)

Medical technologies
- Pharmaceuticals
- Medical devices
- Biotechnology (including therapeutic, diagnostic, combination)
- Health IT (including mobile, big data, training modules)
- Research tools
- Other medical products and services

Other (please specify) [Text box]

22. Did you experience a gap between the end of Phase I and the start of Phase II for this award?

[Yes/No. If no, skip to question 25]

23. During the funding gap between Phase I and Phase II for this award, which of the following occurred?

    Select all answers that apply.
    a. Stopped work on this project during funding gap.
    b. Continued work at reduced pace during funding gap.
    c. Continued work at pace equal to or greater than Phase I pace during funding gap.
    d. Received gap funding between Phase I and Phase II.
    e. Company ceased all operations during funding gap
    f. Other (specify) [Text box]

24. In your opinion, in the absence of this SBIR/STTR award, would the company have undertaken this project?

    a. Definitely yes [Answer questions 25-27.]
    b. Probably yes [Answer questions 25-27.]
    c. Uncertain
    d. Probably not
    e. Definitely not

25. If you had undertaken this project in the absence of SBIR/STTR, this project would have been . . .
    a. Broader in scope
    b. Similar in scope
    c. Narrower in scope

26. In the absence of SBIR/STTR funding . . . (Please provide your best estimate of the impact)

    a. . . . how long would the start of this project have been delayed? [text box] months
    b. . . . the expected duration/time to completion would have been . . .
        1) longer
        2) the same
        3) shorter
    c. . . . in achieving similar goals and milestones, the project would be . . .
        1) ahead
        2) the same place
        3) behind

27. Did this award require matching funds or other types of cost sharing in the Phase II Proposal?
    [Yes/No. If No, skip questions 28-39.]

28. Matching or co-investment funding proposed for Phase II was received from . . .

    Select all that apply.
    Non-SBIR/STTR federal funds
    a. **Private investment: U.S. Sources**
        i) venture capital (VC)
        ii) U.S. angel funding or other private equity investment (not VC)
        iii) Friends and family
        iv) Strategic investors/partners
        v) Other sources
    b. **Foreign investment**
        i) Financial investors
        ii) Strategic investors/partners
    c. **Other sources**
        (1) State or local governments
        (2) Research institutions (such as colleges, universities or medical centers)
    d. **Internal sources**
        (1) Your own company (Including money you have borrowed)
        (2) Personal funds

29. How difficult was it for the company to acquire the funding needed to meet the matching funds requirements?

    a. No additional effort needed except paperwork
    b. Less than 2 weeks Full Time Equivalent (FTE) for senior company staff
    c. 2-8 weeks effort FTE for senior company staff
    d. 2-6 months of effort FTE for senior company staff
    e. More than 6 months of effort FTE for senior company staff

Part 5. Project Outcomes

30. To date, what has been the total additional developmental funding for the technology developed during this project?

None $0
Under $100,000
$100,000-499,999
$500,000-999,999
$1,000,000-4,999,999
$5,000,000-9,999,999
$10,000,000-19,999,999
$20,000,000-49,999,999
$50,000,000 or more

31. What have been the sources of additional development funding?

Select all that apply.
Non-SBIR/STTR federal funds

a. **Private investment: U.S. Sources**
   i) venture capital (VC)
   ii) U.S. angel funding or other private equity investment (not VC)
   iii) Friends and family
   iv) Strategic investors/partners
   v) Other sources

b. Foreign investment
   i) Financial investors
   ii) Strategic investors/partners

c. **Other sources**
   (1) State or local governments
   (2) Research institutions (such as colleges, universities or medical centers)

d. **Internal sources**
   (1) Your own company (Including money you have borrowed)
   (2) Personal funds

32. Has the company and/or licensee had any actual sales of products, processes, services or other sales incorporating the technology developed during this project?

    Select all that apply.

    a. No sales to date nor are sales expected. [Skip questions 33-39.]
    b. No sales to date, but sales are expected. [Skip to question 33-39.]
    c. Sales of product(s)
    d. Sales of process(es)
    e. Sales of services(s)
    f. Other sales (e.g. rights to technology, licensing, etc.)

33. For the company and/or the licensee(s), when did the first sale occur resulting from the technology developed during [name of project]?

    If multiple SBIR/STTR awards contributed to the ultimate commercial outcome, report only the share of total sales appropriate to this SBIR/STTR project.

    For the company[Pulldown with choices from 1990-2014]
    For any licensees[Pulldown with choices from 1990-2014]

34. For the company, what is the approximate amount of total sales dollars of product(s), process(es) or services to date resulting from the technology developed during the [name of project]?

    [Pulldown with choices:
    None $0
    Under $100,000
    $100,000-$499,999
    $500,000-$999,999
    $1,000,000-$4,999,999
    $5,000,000-$9,999,999
    $10,000,000-$19,999,999
    $20,000,000-$49,999,999
    $50,000,000 or more]

35. What is the approximate amount of other total sales dollars (e.g. rights to technology, sale of spin-off company, etc.) to date resulting from the technology developed during the [name of project]?

    [Pulldown with choices:
    None $0
    Under $100,000
    $100,000-$499,999
    $500,000-$999,999
    $1,000,000-$4,999,999
    $5,000,000-$9,999,999
    $10,000,000-$19,999,999
    $20,000,000-$49,999,999
    $50,000,000 or more]

36. To date, approximately what percent of total sales from the technology developed during this project have gone to the following customers?

    Round percentages. Answers required to add to 100%.

    a. Domestic private sector [Number box]
    b. Export Markets [Number box]
    c. Department of Defense (DoD) [Number box]
    d. NASA [Number box]
    e. Prime contractors for DoD [Number box]
    f. Prime contractor for NASA [Number box]
    g. Agency that awarded the Phase II (if not NASA or DoD) [Number box]
    h. Other federal agencies [Number box]
    i. State or local governments [Number box]
    j. Other [Number box] (Specify below, if applicable)

    If applicable please specify what "other" types of customers you have sold to as a result of this project.
    [Text box]

37. Please list any significant commercial partnerships (including licensing agreements) based on the SBIR/STTR-funded technology.
    [Text box]

38. Please give the number of patents, copyrights, trademarks received and articles published in scientific publications for the technology developed as **a result of** [name of project].

Enter numbers. If none, enter 0 (zero).
Patents [Number box]
Copyrights [Number box]
Trademarks [Number box]
Published articles [Number box]

39. How many SBIR and/or STTR awards has the company received that are related to the project/technology supported by this award?

a. Number of related Phase I awards [Text box]
b. Number of related Phase II awards [Text box]

NIH Only

40. Does your product require FDA approval before it can be marketed?
[Yes/No. If no, skip to question 47]

41. What is the current status of the project with regard to the FDA process?

Process abandoned
Preparation under way for clinical trails
IND granted
In Phase 1 clinical trials
In Phase 2 clinical trials
In Phase 3 clinical trials
Completed clinical trials

42. What sources of funding have been employed in relation to the FDA process?

Select all that apply.
SBIR Phase II
SBIR Phase IIB
Other NIH Funding
BARDA funding
Internal company and personal funding
Angel Funding
Venture funding
Funding from other companies
Other (specify) [Text box]

43. For projects still in process, when approximately—assuming all goes well with clinical trials—do you anticipate completing the FDA certification process?
    [Text box]

44. What non-financial support in relation to FDA approval have you received from NIH before and during the clinical trials process?
    [Text box]

45. If applicable, how useful was this support?

    Extremely useful (5)
    4
    3
    2
    Not useful at all (1)

    Comments
    [Text box]

46. How much difference did Phase IIB funding make to the eventual outcome of the project (or its current status if research is not completed)?

    A tremendous difference (5)
    4
    3
    2
    It made no difference at all (1)

    Comments
    [Text box]

47. Was the additional funding sufficient to allow you to complete any of the following?

    Select all that apply.
    Preclinical trial preparation
    Phase 1 trials
    Phase 2 trials
    Phase 3 trials
    No/None of the above

48. What additional measures should NIH take to support companies like yours during the process?
    [Text box]

49. Many agencies offer commercialization assistance in connection with SBIR or STTR awards. Did you (or another company staff member) participate in a technical assistance related to this award that was offered by your funding agency?
    [Yes/No]

Part 6. SBIR Process and Recommendations

49. Many agencies offer commercialization assistance in connection with SBIR or STTR awards. Did you (or another company staff member) participate in a technical assistance related to this award that was offered by your funding agency?
    [Yes/No. If no, skip questions 50-73.]

    Phase I
    Phase II
    Both

50. What company provided assistance to you?

    Dawnbreaker
    LARTA
    Foresight
    Other (specify) [Text box]

51. How valuable was the commercialization assistance?

    Extremely valuable
    Very valuable
    Somewhat valuable
    Not very valuable
    Not at all valuable

52. New rules permit companies to use up to $10,000 of SBIR/STTR funding for their own marketing purposes, outside the agency program.

    Would you . . .

    Continue to use the agency's program
    Use the funding for your own marketing consultant
    Neither

53. In comparison to other Federal awards or Federal funding, how would you rate the process of applying for Phase II funding? Applying for SBIR/STTR Phase II funding was . . .

    a. Much easier than applying for other Federal awards
    b. Easier
    c. About the same
    d. More difficult
    e. Much more difficult
    f. Not sure, not applicable, or not familiar with other Federal awards or funding

54. How adequate was the amount of money you received through SBIR/STTR Phase II funding for the purposes you applied for? Was it . . .

    a. More than enough
    b. About the right amount
    c. Not enough

55. Congress recently increased the standard limit on awards to $1 million for SBIR/STTR. Should the size of Phase II awards be increased even if that means a proportionately lower number of Phase II awards are made?

    a. Yes
    b. No
    c. Not sure

56. Overall, would you recommend that the SBIR/STTR program be . . . ?

    a. Expanded (with equivalent funding taken from other federal research programs that you benefit from and value)
    b. Kept at about the current level
    c. Reduced (with equivalent funding applied to other federal research programs you benefit from and value)
    d. Eliminated (with equivalent funding applied to other federal research programs you benefit from and value)

57. To what extent did the SBIR/STTR funding significantly affect long term outcomes for the company?

    a. Had a highly positive or transformative effect
    b. Had a positive effect
    c. Had no effect
    d. Had a negative effect
    e. Had a highly negative or disastrous effect

58. Can you explain these impacts in your own words?
    [Text box]

Part 7. Working with Project Managers

This section seeks information about your interactions with your agency point of contact, who for the purposes of this survey is referred to as a "Project Manager."

59. How often did you engage with your Project Manager in the course of your award?

    a. weekly
    b. monthly
    c. quarterly
    d. annually

60. How valuable was your Project Manager on a scale of 1-5, with 1 being no help and 5 being invaluable?

    Invaluable (5)
    4
    3
    2
    No help (1)

61. How knowledgeable was your Project Manager about the SBIR/STTR program. Were they able to guide you effectively through the SBIR/STTR process?

    a. Not at all knowledgeable
    b. Quite knowledgeable
    c. Somewhat knowledgeable
    d. Extremely knowledgeable

62. On a scale of 1-5, with one being least and 5 being most, how much did your project manager help during the Phase II award in the following areas: [1-5 scale for each row]

    a. Providing direct technical help
    b. Finding markets for our technology or products/services
    c. The Phase II application process
    d. Introducing us to university personnel or government labs that could contribute to the project
    e. Introducing us to other firms that could provide technical expertise

63. How closely did you work with your Project Manager as you pursued additional funding beyond Phase II?

    a. The officer provided a lot of guidance during the application process
    b. We discussed the application in detail
    c. Not much
    d. Not at all
    e. We did not apply for additional agency funding

64. How effective was the Project Manager in connecting the company to sources of Phase III funding (such as acquisition programs or venture/angel funding)?

    Very helpful
    Somewhat helpful
    Not very helpful
    Not at all helpful

65. How easy was it to reach your Project Manager when you had questions or concerns?

    Very easy
    Easy
    Hard
    Very hard

66. Was your Project Manager replaced during the course of your award?
    [Yes/No]

67. How do you see the time allocated for your Project Manager to work on your project?

    More than sufficient
    Sufficient
    Insufficient

68. Additional comments on working with your Project Manager
    [Text box]

69. Is a Federal System or Acquisition Program using the technology from this award?

    Yes (Answer question 70)
    No (Skip to question 71)

70. Please provide the name of the Federal System or Acquisition Program that is using the technology.
    [Text box]

71. This questions address any relationships between your firm's efforts on this project and any partnering Research Institution (RI) (including universities, medical centers, Federal research labs).

    Select all that apply.

    a. The PI for this project was at the time of the project an RI faculty member
    b. The PI for this project was at the time of the project an RI adjunct faculty member
    c. Faculty member(s) or adjunct faculty member(s) worked on this project in a role other than PI
    d. Graduate students worked on this project
    e. The technology for this project was licensed from an RI
    f. The technology for this project was originally developed at an RI by one of the participants in this project
    g. An RI was a subcontractor on this project
    h. None of the above [Skip questions 72-73.]

72. Which research institution (or institutions) worked with your firm on this project?
    [Text box]

73. If you worked with an FFRDC or a National Lab as part of this project, please briefly describe this aspect of the project, and add any further comments based on this aspect of the project.
    [Text box]

Part 8. STTR

74. To what extent did your STTR award change your relationship with the research institution?

    a. Substantially enhanced it
    b. Somewhat enhanced it
    c. Made no real difference
    d. Made it somewhat worse
    e. Made it substantially worse

    If you have additional comments and/or recommendations about working with a research institution in the context of SBIR/STTR, please enter them here.

75. Did you collaborate with this research institution before receiving this STTR award?
    [Yes/No]

76. Have you ever received a Small Business Innovation Research (SBIR) award?
    [Yes/No. If no, skip to question 80]

77. Have you had prior SBIR awards in which you collaborated with a research institution?
    [Yes/No]

78. From your perspective, are there significant differences between SBIR and STTR awards?
    [Yes/No. If no, skip to question 80.]

79. Please explain these differences in your own words.
    [Text box]

80. If you have received both SBIR and STTR awards, did you find that

    a. STTR is easier to manage than SBIR
    b. They are about the same
    c. STTR is harder to manage than SBIR

81. Do you think that the funding proportion that can be allocated to the research institution should be increased?

    a. Strongly agree
    b. Somewhat agree
    c. Neither agree nor disagree
    d. Somewhat disagree
    e. Strongly disagree

82. Have you tried to switch an STTR Phase I award to an SBIR Phase II award, or the other way around?
    [Yes/No]

83. Are these specific ways in which outcomes from your SBIR/STTR awards as a company have helped meet the mission of the funding agency?
    [Text box]

84. Other comments or recommendations based on your experience with the STTR program?
    [Text box]

Appendix D

Research Institutions (RIs) Working on NIH SBIR/STTR Awards

A total of 727 responses were received for the National Institute of Health (NIH). These responses revealed that a Research Institution (RI) worked on 255 projects and that a total of 488 RIs were involved.

Row Labels	Count of Research Institution Name
Albert Einstein College of Medicine	1
Alfred I duPont Hospital for Children	1
Allegheny Singer Research Institute	1
Arizona State University	3
Arkansas State University	1
Baylor College of Dentistry	2
Baylor College of Medicine	3
Beth Israel Deaconess Medical Center	1
Boston Biomedical Research Institute	1
Boston University	4
Boys Town National Research Hospital	1
Brigham and Women's Hospital	2
Brooklyn Hospital	1
Burnham Institute	1
California Institute of Technology	1
California State Polytechnic University	1
Carle Clinic Urbana IL	1
Carnegie Mellon University	2

Row Labels	Count of Research Institution Name
Case Western Reserve University	6
CDC	3
Cedars-Sinai Medical Center	1
Children's Hospital Boston	5
Children's Hospital of Wisconsin	1
Children's National Medical Center	1
Cincinnati Children's Hospital Medical Center	1
City University	1
City University of New York	1
Cleveland Clinic	4
Cleveland Clinic Foundation	2
Colorado State University	3
Columbia	1
Columbia University Medical Center	1
Cornell University	5
Dallas VA	1
Dana Farber Cancer Institute	2
Dartmouth College	4
Duke University	10
East Tennessee State University	1
Einstein	1
Emory University	2
Florida International University	1
Fox Chase Cancer Center	1
Fred Hutchinson Cancer Research Center	2
George Mason University	2
George Washington University	1
Georgetown University	2
Georgia Institute of Technology	4
Golisano Children's Hospital	1
Greater Los Angeles VA Medical center	1
Harvard University	5
Hauptman Woodward Research Institute	1
HDF Group	1
Hines VA (Chicago)	1
House Ear Institute	1
Huntsman Cancer Institute	1
IDRI	1
IMM	1
Indiana University	6

Row Labels	Count of Research Institution Name
Institute for Human Virology	2
Intermountain Healthcare	1
Iowa State University	2
Iowa State University	1
Johns Hopkins University	8
Lawrence Berkeley National Labs	1
Lehigh University	2
Lerner College of Medicine	1
Los Alamos National Laboratory	1
Los Angeles Biomedical Research Institute	1
LSU Health Sciences Center	2
Massachusetts Institute of Technology	7
Mayo Clinic	5
MD Anderson Cancer Center	5
Medical College of Wisconsin	4
Medical University of South Carolina	5
Memorial Hospital of Rhode Island	1
Memorial Sloan Kettering Cancer Center	1
Memorial Sloan Kettering Cancer Institute	2
Michigan State University	1
Michigan Technological University	1
Minneapolis Medical Research Foundation	1
Montana State University	2
Mount Sinai School of Medicine	1
Nathan Klein Institute	1
New York Medical College	2
North Carolina State University	1
North Shore Long Island Jewish	1
Northwestern University	1
NYU	1
Oak Crest Institute of Science	2
Ohio State University	2
Oklahoma Medical Research Foundation	1
Oregon Health & Science University	5
Oregon Research Institute	2
Oregon State University	2
Pennsylvania State University	6
Phoenix VA	1
Pomona College	1
Portland State University	2

Row Labels	Count of Research Institution Name
PRF	1
Public Health Research Institute	1
Purdue University Medical Center	1
Queen's Hospital	1
Rennselaer Polytechnic Institute	3
Rhode Island Hospital	1
Robert Wood Johnson - Cooper Medical Center	1
Rutgers University	1
Saint Louis University	1
San Diego State University	2
Sanford Burnham Medical Research Institute	1
South Dakota State University	1
South Florida Veterans Administration Foundation for Research and Education	1
Southern Arizona Limb Salvage Association	1
Southern Illinois University	1
Southern Methodist University	1
Springfield College	1
Stanford Research International	1
Stanford University	2
SUNY Binghamton	2
SUNY Buffalo	2
SUNY Downstate	2
SUNY Stony Brook	4
SUNY Syracuse	1
Temple University	2
Texas A&M University	5
Texas Tech University	1
Tufts University	3
UC Berkeley	4
UC Irvine	2
UC San Diego	2
UC San Francisco	5
UC Santa Barbara	1
UC Los Angeles	4
University Hospitals of Cleveland	1
University of Alabama Birmingham	1
University of Alabama	1
University of Arizona	6
University of British Columbia	1

Row Labels	Count of Research Institution Name
University of Chicago	5
University of Cincinnati	1
University of Colorado	5
University of Connecticut	5
University of Denver	1
University of Florida	9
University of Illinois	1
University of Illinois Chicago	7
University of Illinois Urbana Champaign	2
University of Iowa	2
University of Kansas	2
University of Kentucky	7
University of Louisville	4
University of Maryland	2
University of Massachusetts	1
University of Massachusetts Lowell	2
University of Massachusetts Medical School	6
University of Medicine & Dentistry of New Jersey	1
University of Miami	4
University of Michigan	14
University of Minnesota	5
University of Missouri	2
University of Nebraska	2
University of Nebraska Medical Center	1
University of New Hampshire	1
University of New Mexico	4
University of North Carolina Chapel Hill	7
University of North Carolina Charlotte	1
University of North Florida	1
University of North Texas	1
University of Northern Colorado	1
University of Oklahoma	1
University of Pennsylvania	4
University of Pittsburgh	7
University of Rhode Island	2
University of Rochester	4
University of South Alabama	1
University of South Florida	1
University of Southern California	4
University of Southern Mississippi	1

Row Labels	Count of Research Institution Name
University of St Louis	1
University of Tennessee Health Science Center	1
University of Texas	2
University of Texas Austin	3
University of Texas Health Science Center Houston	1
University of Texas Health Science Center San Antonio	1
University of Texas Houston	2
University of Texas Medical Branch	2
University of Texas Southwestern Medical Branch	1
University of Utah	9
University of Vermont	4
University of Vermont (now)	1
University of Virginia	7
University of Washington	2
University of Washington	2
University of Wisconsin Madison	6
University of Wisconsin Milwaukee	1
University of Wyoming	1
University of Connecticut	1
USAMRIID	1
Utah State University	1
Utah State University	1
VA Hospital in Indianapolis	1
Vanderbilt	1
Vanderbilt Northwestern	1
Vanderbilt University	6
Walter Reed Army Research Institute	1
Washington University of St Louis	4
Wayne State University	3
Western Michigan University	1
Western Pennsylvania Hospital	1
Woodhull Hospital	1
Yale University	1
Yale University School of Medicine	1
Yale University University of Connecticut	1
Yale-Griffin Prevention Research Center	1
Zero Breast Cancer	1
Grand Total	488

Appendix E

Case Studies[1]

To complement our review of program data, we commissioned case studies of 15 companies that received Phase II awards from the National Institutes of Health (NIH). Case studies were an important part of data collection for this study, in conjunction with other sources such as agency data, the survey, meetings with agency staff and other experts, and workshops on selected topics. The impact of SBIR/STTR funding is complex and often multifaceted, and although these other data sources provide important insights, case studies allow for an understanding of the narrative and history of recipient firms—in essence, providing context for the data collected elsewhere.

Overall, this portfolio sought to capture many of the types of companies that participate in the program. Given the multiple variables at play, the case studies are not presented as any kind of quantitative record. Rather, they provide qualitative evidence about the individual companies selected, which are, within the limited resources available, as representative as possible of the different components of the awardee population. The featured companies have verified the case studies presented in this appendix (see Box E-1) and have permitted their use and identification in this report.

[1]Each of the companies profiled in this case study appendix was contacted in the second half of 2015 with a request to verify and update its information. Two draft case studies included provisionally in the prepublication version of this report have been deleted from the final version, at the request of the companies, Biomedica Management Corporation and Vical, Inc.

BOX E-1
NIH Company Case Studies

The following company case studies are included in this appendix:

23andMe
Advantagene, Inc.
ArmaGen Technologies
Auritec Pharmaceuticals
Avanti Polar Lipids, Inc.
Avaxia Biologics, Inc.
Conversion Energy Enterprises
Danya International, Inc.
GMS Biotech
Lpath Therapeutics, Inc.
NOVA Research Company
Sanaria, Inc.
Stratatech Corporation
Targeson, Inc.
TissueTech, Inc.

23andMe[2]

Meeting with
Anne Wojcicki, CEO and co-founder
Joyce Tung, PhD, Vice President of Research
Interviewed June 18, 2014
Mountain View, California

23andMe, Inc. is a privately held business headquartered in Mountain View, California. Founded in April 2006 by Linda Avey, Paul Cusenza, and Anne Wojcicki, the company's mission is to help people access, understand, and benefit from the human genome. The company offers a direct-to-consumer personal genome service and conducts research that aims to make meaningful discoveries that can lead to successful treatment of disease. 23andMe enables the company's more than 1 million customers to consent to research if they so choose. 23andMe researchers and its collaborators are able to then cross reference genetic data against information gathered through surveys administered to those individuals who have consented to participate in research. Understanding the relationship between human genetics and the incidence of disease could improve preventative, acute, and long-term care of patients while saving consumers, insurers, and medical institutions billions of dollars per year. 23andMe provides customers with personalized genetic reports using recent advances in DNA analysis technologies. (More accurate description would be genotyping.)

23andMe also offers their customers the opportunity to opt-in to participate in research using an institutional review board (IRB)-approved consent. They may also volunteer to answer survey questions on a variety of health and lifestyle topics.

PRODUCTS

At present, 23andMe's commercial sales are concentrated on the provision of personal genetic information to consumers.

23andMe® Personal Genome Service

The 23andMe Personal Genome Service (PGS) provides information and tools for individuals to learn about their DNA. Customers order the PGS kit on the 23andMe website. Using the kit, the customer sends a saliva sample to 23andMe's laboratories where lab technicians extract DNA from the cells in the saliva and replicate the DNA until there is enough to be genotyped. The DNA is analyzed using a fully custom chip based on the Illumina HumanOmniExpress-24 chip.

[2]Primary sources for this case study are the meeting with 23andMe executives and a review of the 23andMe website (http://www.23andme.com) and related company documents.

Human genomes are nearly identical from person to person. There are, however, specific positions on the genome that differ. These differences can mark ethnicity as well as predisposition to certain diseases. Customized by 23andMe, the Illumina chip used by 23andMe is sensitive to DNA at those locations that 23andMe scientists have determined are important in mapping ancestry, traits, and health.[3]

23andMe provides its US-based customers with both the un-interpreted raw genetic data and a genetic ancestry report. Due to an FDA warning letter received by the 23andMe in November of 2013, 23andMe currently does not provide genetic health reports. 23andMe is working with the FDA in order to be able to provide health reports to its customers. In February 2015, 23andMe's Bloom Syndrome Carrier Status Test report was given marketing authorization by the FDA through the *de novo* pathway—making the test the first direct-to-consumer genetic test granted marketing authorization by the agency. In addition to the authorization to market the Bloom Syndrome Carrier Status test report, the U.S. Food and Drug Administration (FDA) stated that it intended to classify autosomal recessive carrier screening tests as class II and exempt such carrier status tests from premarket review under special controls. 23andMe expects to launch a new user experience that includes carrier status reports in the US, as well as enhanced tools and functionality for all customers globally before the end of the 2015.

BUSINESS MODEL

23andMe provides a personal genotyping service directly to consumers. Individual customers purchase the 23andMe PGS because they want to know their own genetic makeup, to understand either their ancestry or the genetic risk for certain diseases. With 80 percent of its more than 1 million customers consenting to participate in 23andMe's research, 23andMe is also using this data set to better understand the underlying genetics behind certain diseases, and eventually to develop therapies to help treat disease.

Thus 23andMe is building a unique pair of businesses:

1. The consumer business which delivers information directly to customers and allows customers to participate in research.
2. Research services for researchers in both public and private sectors. Currently, 23andMe has more than 14 active collaborations with companies in the pharmaceutical industry, and more than 30 ongoing collaborations with academic and nonprofit institutions.

23andMe's direct-to-consumer PGS revenue outweighs revenue generated by 23andMe research collaborations with pharmaceutical companies, and, according to Ms. Wojcicki, 23andMe's consumer business will remain its primary focus.

[3]The techniques used are discussed at https://www.23andme.com/ancestry/techniques/.

The majority of 23andMe customers who contribute data to research are based in the United States. Long-term success is dependent on maintaining an engaged customer base to acquire new research data and test hypothesis. After setting a goal of reaching 1 million customers by the end of 2013, 23andMe sales slowed following receipt of the FDA warning letter in November of 2013. Customer growth in 2014 was slightly lower than 2013, due to the FDA warning letter.

The consumer business provides two sets of information: the data derived from genomic analysis of submitted samples and—equally critical—health outcomes and lifestyle data from surveys of the customer base of those consented to participate in research. According to Ms. Wojcicki, customers understand the need to provide this information—known as phenotypic information—as a basis for improved treatments, and participation in 23andMe surveys has been very high. More than 80 percent of 23andMe customers consent to participate in research.

23andMe currently has two revenue streams—revenue from providing individual consumers with reports profiling and interpreting their genes and revenue generated from research collaborations. In 2015, the company also established an internal therapeutics group led by 23andMe Chief Science Officer Dr. Richard Scheller, former head of R&D and early stage therapeutics development at Genentech. Industry observers widely believe the consumer business is not yet profitable and is being sustained by the approximately $126 million in Series A-D venture funding rounds that 23andMe has received.[4] 23andMe has not disclosed revenue generated by its collaborations with industry researchers.

So far as its research business is concerned, 23andMe will continue to collaborate with the pharmaceutical industry, and invest in its own therapeutics group to develop drugs. For example, the database could help drug companies understand better how medicines affect specific populations, and what role genetics may play in triggering certain side effects.[5] So far, although 23andMe has produced some useful genetic insights, there is not yet clear evidence that they will find the health care breakthroughs that the company needs for the success of the research business.[6]

Competitors include Pathway Genomics in the United States; deCODE (acquired by Amgen), bio-logis, and i-gene in Europe; and AncestryDNA™ and MapMyGenome in Asia.[7] However, compared to its competition in the direct-to-

[4]Katie Brenner, "23andMe Wants to Change the Face of Health Care," *Fortune*, December 12, 2012

[5]Matthew Herper, "For 23andMe, The Real Value Could Be In Its Data," http://www.forbes.com/sites/matthewherper/2013/06/13/expect-to-see-23andme-ads-as-the-company-tries-to-take-genetic-tests-mainstream/.

[6]Jonathan Latham, "23andMe Disproves its Own Business Model," http://www.independentsciencenews.org/news/23andme-disproves-its-own-business-model/.

[7]Alex Khomenko, "Who are 23andMe's Competitors?" (2012) http://www.quora.com/23andMe/Who-are-23andMes-competitors. Alex was the Director of Engineering for 23andMe; for an older list, see http://www.dnapolicy.org/resources/DTCTableAug2011Alphabydisease.pdf.

consumer genomic market, 23andMe is much better capitalized and has a larger database of individual genomic data.

For long-term success, 23andMe must reduce the cost of processing an individual genome to make the data acquisition business self-sustaining and further develop its research services and therapeutics group to monetize the database that the company is creating. In December 2013, 23andMe adopted a new version of the custom chip from Illumina, which increases processing speed substantially.

FDA AND PRODUCT REGULATION

In July 2010, FDA contacted 23andMe. It asserted that direct-to-consumer genomics companies were offering services that constituted a medical device for their customers. Consequently, these services should be regulated. As part of this process, 23andMe would need to demonstrate that the PGS accurately predicts disease risk. This regulatory process affected only one component of the PGS—the provision of personalized health risk assessments based on assigning risk factors to specific genetic markers.

Initially, 23andMe responded by starting the 510k process for FDA approval of the PGS. According to FDA, 23andMe abruptly ceased communicating with it in July 2012 and hence dropped out of the process. In November 2013, FDA sent a Warning Letter indicating that it had still not received sufficient proof that 23andMe's service accurately predicts disease risk. Consequently, it asked 23andMe to cease marketing its PGS as a health diagnostic. 23andMe has complied and now provides only raw, un-interpreted genetic data and ancestry analysis in its service for U.S. customers.[8] In February of 2015 the FDA authorized for marketing the 23andMe Bloom Syndrome Carrier Status Test report—the first direct-to-consumer genetic test to be authorized for marketing by the FDA.

Not being able to offer health-related reports as part of its U.S. product has slowed the acquisition of new customers. According to Ms. Wojcicki, 23andMe is continuing to seek FDA authorization and expects to offer a product with health-related reports to U.S. customers by the end of 2015.

PATENTS AND OTHER INTELLECTUAL PROPERTY

The efficient and low-cost processing for the PGS underlies the business model and rests on a partnership with another company, Illumina, to customize the genomic analysis chip at the core of 23andMe's offering, Illumina's HumanOmniExpress-24 (recently superseded by a fourth generation chip).[9]

[8]Robert C. Green, Nita A. Farahany, "Regulation: The FDA is Overcautious on Consumer Genomics," *Nature*, http://www.nature.com/news/regulation-the-fda-is-overcautious-on-consumer-genomics-1.14527.

[9]"23andMe and Illumina Forge Consumer Genomics Goliath," BioIT World, http://www.bio-itworld.com/newsitems/2007/august/08-16-07-consumer-genotyping.

TABLE E-1 23andMe Patents

Patent Number	Patent	Year
8,645,343	Processing data from genotyping chips	2014
8,589,437	De-identification and sharing of genetic data	2013
8,543,339	Gamete donor selection based on genetic calculations	2013
8,510,057	Summarizing an aggregate contribution to a characteristic for an individual	2013
8,463,554	Finding relatives in a database	2013
8,428,886	Genotype calling	2013
8,187,811	Polymorphisms associated with Parkinson's disease	2012

SOURCE: U.S. Government Patent Office.

23andMe has made a concerted effort to engage with the scientific community. Its website lists more than 30 peer-reviewed papers based on its data or coauthored by 23andMe staff. It has published a number of white papers covering its analytic methods, as well as statements covering its efforts to eliminate bias in its funded research.[10] (See Table E-1 for 23 andMe's Patents.)

Interestingly—perhaps drawn from the company's close relationships with the information technology (IT) community in Silicon Valley—23andMe appears to be adopting something of an open source approach to the identification of health traits related to genetic markers. In its open letter to the scientific community, 23andMe states, "We invite you to review both the standards we use to determine whether a particular genetic association is robust enough to include in our service and the statistical methods we use to illustrate for customers how their particular genotypes relate to the incidence of a disease, condition, or trait. You can also see a list of the associations we currently report in Health and Traits, along with excerpts from the scientific content that will be provided to our customers. . . . To that end, we hope you will contact us with your thoughts and suggestions about our genotyping technology, statistical methods and association study review process."[11]

23andMe comes from a culture that values speed of action and transparency. It is not yet clear how this will mesh with the much slower and more careful cultures that dominate both FDA and the medical community more generally.

FUNDING

23andMe has relied mostly on venture capital to fund its development.

[10]23andMe website, https://www.23andme.com/for/scientists/.

[11]https://23andme.https.internapcdn.net/res/pdf/9us590NqjJHqGnp_KSpl4w_23andMe_scientific_community.pdf.

Equity Investment

In May 2007, 23andMe successfully closed on $8.95 million in Series A funding. In three succeeding rounds, 23andMe closed on increasingly larger and larger financings, totaling $27.8 million in the Series B round, $31.2 million in the Series C round, and $58.4 million in its Series D round. (See Table E-2.)

Following its Series D round of financing, 23andMe announced that it would seek to accelerate the acquisition of customers in its database by reducing the cost of its PGS from $299 to $99. It planned to use this expanded data set to help researchers develop new treatments for disease and, at the individual level, help people improve personal health and disease prevention.

Non-Dilutive Grants: SBIR

Since 2010, 23andMe has received NIH SBIR funding to help improve the effectiveness of its data collection and analytics. 23andMe has received five NIH SBIR grants (mostly for the development of tools for evaluating the genetic information database that it is collecting). The total commitment from the NIH SBIR program has been $2.1 million through 2014, according to the company.

USES AND ROLE OF SBIR AT 23ANDME

It is perhaps surprising that 23andMe has sought SBIR funding at all. Companies with access to sufficient capital do not typically seek SBIR funding because grant success is highly uncertain and because the lags in the process mean that reliance on SBIR can imply delays in the project, especially in very fast-moving sectors.

TABLE E-2 Equity Investors for 23andMe

Round	Date	Known Investors	Amount (Millions of Dollars)
Series D	Dec-12	New Enterprise Associates, Google Ventures, MPM Capital, Sergey Brin, Anne Wojcicki, Yuri Milner	58.4
Series C	Nov-10	MPM Capital, Johnson & Johnson Development Corporation, New Enterprise Associates, Google Ventures, Roche Venture Fund	31.2
Series B	Apr-09	New Enterprise Associates, Google Ventures	27.8
Series A	May-07	Genentech Corporation, New Enterprise Associates, Google Ventures	9.0
Total			126.4

SOURCE: Venture Deal. Accessed February 24, 2014.

23andMe is also deeply immersed in the Silicon Valley culture, where the speed of change means that relatively few companies seek SBIR funding; the standard funding routes even for very early stage startups focus on accelerators, angels, and venture capital (VC) funding, not SBIR awards.

23andMe has used SBIR funding to develop tools to improve its research platform and to investigate new [products]. Four of the five projects are intended to improve data quality, reduce errors, and demonstrate the accuracy of the 23andMe approach. 23and Me has also had grants for allergy research, Exome research, and pharmacogenomics.

According to Ms. Wojcicki, there were other reasons for seeking SBIR funding as well. SBIR also has had a powerful validating effect for the company, underscoring its efforts to present itself as a research organization as well as a direct-to-consumer genomics company. Ms. Wojcicki observed that while this had not affected funding, it had supported efforts to start the non-consumer components of the business. SBIR funding has had the effect of de-risking the technical approach adopted by 23andMe, making further investment more attractive.

In addition, Ms. Wojcicki observed that NIH SBIR funding has helped balance perspectives on the two components of the business within the investment community; much of the VC investment in 23andMe has come from investors focused on the IT/Internet/digital sector, which tends to prioritize the direct-to-consumer component, rather than biomedical investors with a longer-term perspective. NIH funding has underscored the potential importance of the biomedical information business.

RECOMMENDATIONS

23andMe has relatively limited experience with the NIH SBIR program and had few comments about program operations. However, 23andMe executives said that the current process took so long that in the very fast-paced innovation environment in which they operated, SBIR was not a primary option.

They recommended that NIH explore two core concepts:

1. an increased focus on smaller grants of approximately $50,000 for true feasibility testing for very early-stage highly innovative ideas
2. development of an entirely different award and monitoring model that could provide extremely rapid funding for smaller awards, with limited application requirements and limited initial reporting

Although the executives acknowledged that government funding required some safeguards, they argued that supporting the rapid testing of many more ideas could be a valuable approach that could support projects that otherwise could not attract funding.

Advantagene, Inc.[12]

Meeting with
Dr. Estuardo Aguilar-Cordova, CEO and founder
December 3, 2014

Advantagene, Inc. is a private company founded in 1999 by Dr. Estuardo Aguilar-Cordova. The company is developing cancer immunotherapy drugs that stimulate the body's immune system to destroy various types of solid tumors. Advantagene is headquartered in Auburndale, Massachusetts.

At the time of company formation, Dr. Aguilar-Cordova was on the faculty first at Baylor and then at Harvard, where he was involved in some important clinical trials. At the time, Harvard had a rigid policy requiring complete divestment from all for-profit enterprises or exclusion from all work on studies affiliated with the products of such enterprises. Dr. Aguilar-Cordova chose to leave Harvard and work full time at Advantagene.

In his view, options for commercializing the science were limited. He had been an advisor to other small companies and thought their product development processes could be substantially improved. Initially, the technology was licensed to a large pharmaceutical company, but after a series of mergers and changes in corporate strategy, the company relinquished control of the technology back to Baylor College of Medicine. In turn, Advantagene was able to license the technology from Baylor, first on a non-exclusive basis and then in 2007 exclusively.[13]

The core innovation that supports Advantagene's product portfolio is a technique called Gene Mediated Cytotoxic Immunotherapy (GMCI™). GMCI™ is a platform for developing tumor-specific vaccines that use widely available antiviral drugs to attack cancer and stimulate a systemic anti-tumor response in the body.

Advantagene has applied GMCI™ to develop clinical trials in various solid tumors, including currently active programs in prostate cancer, adult and pediatric brain cancer, pancreatic cancer, pleural effusion, and mesothelioma. It has also done studies in other indications, including ovarian cancer and esophageal cancer.

Advantagene's lead product is ProstAtak®. Having entered Phase 3 clinical trials in 2012, ProstAtak™ is a product designed to stimulate the immune system to attack the tumor and help reduce the recurrence of prostate cancer in patients with localized cancers following early detection. Advantagene is also developing other GMCI™-based applications. The most advanced product candidate targets malignant glioma, an aggressive and usually fatal cancer of the brain. It has completed Phase II clinical trials with very encouraging overall survival results. The company is planning to follow those studies with definitive Phase 3 trials.

[12]Primary sources for this case study are the meeting with Dr. Estuardo Aguilar-Cordova, and a review of the Advantagene website (http://www.advantagene.com) and related company documents.

[13]https://www.bcm.edu/research/office-of-research/baylor-licensing-group/search/advantagene.htm.

Advantagene has approximately 10 employees. It has relationships with a number of universities and research institutions such as Johns Hopkins University, the University of Pennsylvania, Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Lurie Children's Hospital (Chicago).[14]

TECHNOLOGY PLATFORM (GMCI™)

GMCI™ is a platform for developing tumor-specific vaccines. With over 650 courses of treatment already administered through multiple clinical trials, GMCI™-based vaccines are demonstrably safe and lack the grueling side effects associated with many current cancer therapies. GMCI™ therapies are adjuvant, combining with current surgical, radiation, and chemotherapeutic treatments to improve patient outcomes.

GMCI™ uses gene transfer technology combined with traditional cancer therapies and widely available antiviral drugs to stimulate the immune system to destroy solid tumors. Injection into a tumor of a replication defective adenovirus, which typically causes cold symptoms, containing inactive genetic material from the herpes virus (called AdV-tk™) followed by an anti-herpetic prodrug (such as valacyclovir) causes rapid cell death in cancer cells already weakened by radiation or chemotherapy. Through a complex set of immunological reactions, the body's immune system becomes sensitized to the cancer and attacks the residual tumor cells and micrometastases that become the origins of a recurrence.

Local anticancer therapies, such as surgery and radiation, often fail to eradicate every tumor cell and cannot be used in the treatment of metastasis. If the natural immune response does not eradicate the leftover cells, the therapy fails. GMCI™ does not replace the current standard of care, but instead works with current therapies to stimulate the immune system so it better targets potentially lethal tumor cells not eliminated in the initial treatment.

PRODUCTS

Advantagene is developing therapies that create a systemic resistance to prostate cancer and malignant glioma and block recurrence or metastases of cancers treated with surgery, radiation, or chemotherapy. Applications for other types of cancer are at earlier stages in the product pipeline.

Localized Prostate Cancer—PROSTATAK™

Each year, approximately 240,000 men are diagnosed with prostate cancer and 30,000 will die. Approximately 50 percent are at significant risk for recur-

[14]Hoovers, "Advantagene, Inc.—Sales Preparation," http://www.hoovers.com/company-information/cs/sales-preparation.Advantagene_Inc.0d367be3909fccae.html.

rence, and in approximately 30 percent of cases, prostate cancer will recur. Standard therapies for newly diagnosed prostate cancer are primarily surgery or radiation. After recurrence it is androgen deprivation (medical castration), chemotherapy or radio-chemotherapy. These treatments are not curative and have very significant economic, societal, and quality-of-life costs.

Advantagene developed ProstAtak® as an immunotherapy to prevent recurrence of prostate cancer. In conjunction with standard therapies, the ProstAtak® approach kills tumor cells and stimulates a cancer vaccine effect. Clinicians administer ProstAtak® through a series of three injections into the prostate followed by 14 days of valacyclovir pills.

Malignant Glioma

Brain cancers respond poorly to treatment. According to the American Cancer Society, in the U.S. brain cancer is diagnosed approximately 22,000 times each year and approximately 13,000 people die from this disease. Malignant glioma accounts for the majority of these deaths. Despite aggressive new therapies, the average survival time following diagnosis is still less than 15 months.

Malignant glioma is particular likely to recur due to infiltration by cancer cells from the main tumor mass into the surrounding brain tissue. A GMCI™-enabled response that stimulates an immune reaction against residual cells and small metastases is particularly well-suited to this type of malignancy.

Advantagene has completed a Phase 2 study for malignant glioma with very encouraging overall survival results presented at the most recent ASCO meeting. It is currently further analyzing the results in preparation for a Phase 3 study.

Product Pipeline

Advantagene is also developing therapies to stimulate immune responses for pancreatic cancer, pleural effusion/mesothelioma, and pediatric gliomas. These are all conditions with poor prognoses and limited therapeutic alternatives. (See Table E-3.)

TABLE E-3 Advantagene Therapies in Development

Indication	Incidence (*per annum*) (U.S.)	Average Lifespan after Diagnosis	Clinical Trial
Pancreatic Cancer	43,000	6 months	Phase 2
Pleural Effusion / Mesothelioma	150,000	4 months	Phase 1
Pediatric Glioma	4,000	-	Phase 1

BUSINESS MODEL

Advantagene's business proposition for its primary prostate product is based on the avoidance of future medical costs through the prevention of cancer recurrence. Pharmaco-economic analysis has been completed using a Markoff model. This established that about 30 percent of patients undergoing radiation therapy for prostate cancer later suffer a recurrence. Excluding the effects on quality of life and productivity, each recurrence averages a cost of more than $100,000 annually for treatment. There are currently about 230,000 new prostate cancer diagnoses annually, and of these about 70,000 recur. Thus over the entire health care system, the steady-state cost of recurrence is more than $7 billion annually.

If successful, Advantagene's technology could substantially reduce these costs. Based on clinical evidence, the cost could be reduced by about one-half. However, while the financial benefits are clear, payment mechanisms are much less so. Early-stage prostate cancer is a slow-growing disease, with patients surviving for long periods. As a result, for most patients, the costs avoided from recurrence are saved by Medicare and Medicaid. The payer and savings are aligned for patients undergoing first-treatment after turning 65years of age—however for younger patients, the costs for ProstAtak® is mostly paid by private insurance companies, and they would not likely benefit from the cost savings.

There is therefore a disconnect between the ultimate beneficiaries—government programs—and potential sources of funding—insurance companies. The Centers for Medicare & Medicaid Services (CMS), which manages Medicare and Medicaid, is unwilling or unable to spend money now on drug development in an effort to save money later; insurance companies are equally unwilling to spend now to benefit CMS later.

PROGRESS WITH FDA

Advantagene has already made groundbreaking progress in the course of its regulatory filings. After 7 years of discussions, additional data submissions, resubmissions, and support from the academic community, the company was granted an SPA for a completely novel end-point for newly diagnosed prostate cancer. In great part, it was able to accomplish this because of SBIR funding. Grant funding afforded the company the ability to invest the necessary time to let the data mature, most VC or institutional investors could not afford the patience for such a long development time according to Dr. Aguilar-Cordova. The new protocol allows for evaluation of study results within 2 years for newly diagnosed prostate cancer cases—something never previously approved despite the effort of large pharmaceutical companies such as Eli Lilly and Abbott Laboratories.

Advantagene is now focused on raising money for the Phase 3 clinical trial for ProstAtak™. which will require 711 patients and will cost tens of millions of dollars, according to Dr. Aguilar-Cordova. This will require additional resources from institutional investors.

Advantagene has also received an NIH award to help fund a clinical trial for addressing malignant gliomas. Initial data are highly encouraging. The 2-year survival rate is up from 27 percent to 52 percent, and researchers are very excited. The principal investigator is the chair of neurosurgery at Brigham and Women's Hospital in Boston.

FUNDING

Advantagene has received support from SBIR, other grant providers, and private investors.

Non-Dilutive Grants

Between 2003 and 2014, SBIR funded six projects with Advantagene. Advantagene received 15 SBIR awards amounting to $11.41 million from the Department of Health and Human Services (HHS). Sixty-four percent of SBIR funding has supported clinical and immunological evaluation for ProstAtak™. Most of the remainder has funded research on the application of a GMCI™-based vaccine to malignant glioma.

In 2011, the Massachusetts Life Sciences Center provided a $500,000 matching grant through its Small Business Matching Grant Program to support further corporate development.

Equity Funding

In addition to grants from NIH, Advantagene has received private investment. The presence on the Board of Directors of a partner from Leviathan Biopharma Group, an investment vehicle for successful entrepreneurs and senior business executives in the pharmaceutical and biotechnology industry, suggests one of the sources. Leviathan does not, however, advertise its investments, and Advantagene does not report its investors.

SBIR

Product development is of course very expensive, and although Advantagene began with funding from angel investors, by 2004-2005 money was running out. Reluctantly, Advantagene entered discussions with a venture capital group which demanded the company drop all research and development except one indication, which was not prostate cancer. Dr. Aguilar-Cordova said this completely missed the potential of Advantagene's technology as a platform for addressing multiple diseases and the opportunity for multiple products, any one of which might be successful. At that point, SBIR Phase II funding was received, and the company decided to develop its platform technology instead of accepting VC funding at that stage.

According to Dr. Aguilar-Cordova, SBIR does not suffer from the same limitations as VC funding; the latter requires both a tight focus on a specific product and a very specific timeline to a funding event that will allow for an exit. SBIR permits companies to take more risks, for example in developing an approach to prostate cancer, which is both high risk and long cycle. SBIR supports high-risk and longer-term projects and also in particular supports problems that may not be interesting to venture firms, such as newly diagnosed prostate cancer, which is not attractive for several reasons from a venture perspective. Similarly, SBIR supports research in smaller or less remunerative markets, for example cervical cancer, which is primarily a problem in developing countries. SBIR thus provides an alternative to venture funding and is quite different from private sector investment, with different goals and different timelines.

Advantagene has been partially supported by a Fast-track Phase I-Phase II award from NIH and later received additional time to complete its work because of the regulatory requirements that it faced (the existing grant eventually spread out over 7 years).

The SBIR awards process at NIH is however very slow, especially in comparison with industry timelines. An application made in May might eventually be funded in May of the following year. Assuming resubmission is not required, 12 months is a very long lead time in industry.

Dr. Aguilar-Cordova noted that he had been a reviewer multiple times and that the review process had changed significantly in recent years. Reviews used to be conducted primarily in person, with one primary reviewer per project, one secondary reviewer, and one reader. The whole review panel would primarily listen to the discussion between the reviewers. More recently, the process has shifted and is now primarily an asynchronous review via the web. Reviewers now only see the comments of the primary and secondary reviewers, followed by a vote in which the group almost always follows the primary and secondary reviewer. Dr. Aguilar-Cordova believes that the overall quality of reviews has significantly declined as a result.

Dr. Aguilar-Cordova also observed that while SBIR is funding for small business, the majority of reviewers are academics. This sometimes results in a misunderstanding of R&D as conducted in the private sector. For example, one recent review criticized a proposal because “two key people were from the same company,” an absurd comment for private sector research programs.

At a wider level, SBIR reviewers often misunderstand the relationship between innovation and novelty and product development. The long process of product development is sometimes criticized by academic reviewers who see it as insufficiently innovative. The fact is that the innovation has occurred earlier, and the development stage is about bringing the product to market. He observed that the entire project may be an innovative solution—as are Advantagene’s—but that the grind of proving out the concepts may in itself not look much like innovative research.

RECOMMENDATIONS

Dr. Aguilar-Cordova offered several suggestions for improving the program:

- Reviewers need better guidance. In particular, they should be given better instructions defining product development as part of innovation. This would help reduce the pro-academic bias of the current review process.
- Selection should be an iterative process. Reviews are already uploaded into the system a week or two in advance of the review panel meeting; it would be minimal additional effort to permit companies to see preliminary reviews and to offer additional information—perhaps only a page—to be added to the record. This would be a "fantastic way to improve things," according to Dr. Aguilar-Cordova and would make the review process more like the peer review process for scholarly publications.
- Resubmission currently causes a 2-year delay because comments are returned too late to meet the next submission cycle. Speeding up the delivery of comments by just a few weeks would save companies a year of time and cost.
- There is a need to support investigator-initiated proposals. This is one of the hallmarks of the NIH program, but in his view it is being steadily eroded by a push toward program initiatives (contracts) defined in advance by the Centers.
- Economic analysis of very large projects is necessary. Dr. Aguilar-Cordova believed that the $5 million in funding provided by NIH allowed Advantagene to complete work that would have cost more than $100 million in a large pharmaceutical company, but he also noted that large funding decisions should be based in part on a better understanding of the project's likely economic and social impact if it were to be successful.
- It would be most productive to fund programs to proven need, not to artificial caps.

ArmaGen Technologies[15]

Meeting with
Dr. William Pardridge, founder
June 24, 2014
Calabasas, California

ArmaGen Technologies is a privately held business headquartered in Calabasas, California. Founded in 2004 by Dr. William Pardridge, the company owns technology to transport various therapeutic molecules (such as recombinant proteins, therapeutic monoclonal antibodies, and siRNA) across the blood-brain barrier (BBB).

Dr. Pardridge has been working on overcoming the BBB to deliver therapeutic molecules into the brain since the 1970s. He argues that this issue represents a huge and rapidly growing societal challenge: he estimates the cost of caring for Alzheimer's disease and stroke victims at more than $500 billion by 2025, because the 65 and older population will grow by 50 percent during that period.

THE NEED FOR TOOLS TO CROSS THE BLOOD-BRAIN BARRIER

Currently, there is no effective therapy for Alzheimer's disease, Parkinson's, and stroke aside from L-Dopa which came into use almost 60 years ago for Parkinson's. Dr. Pardridge said that the primary problem is that 98 percent of small molecule and 100 percent of biologic drugs do not cross the BBB. Drug delivery across the BBB is the mechanism of choice for therapeutic drugs today.

The BBB problem has remained unaddressed despite huge and growing R&D expenditures aimed at these diseases. Until recently, large pharmaceutical companies saw the BBB as essentially an insoluble problem, and according to Dr. Pardridge there is still not a single academic neuroscience program focused on the blood-brain barrier. Instead, companies and drugs have been focused on the diseases that do respond to standard drug treatments: affective disorders, epilepsy, insomnia, and chronic pain. He observed that drugs for depression alone accounted for 30 percent of the world's drug market for the brain. These standard treatments for the brain are the classical lipid soluble small molecule drugs that were the focus of the chemistry-based R&D drug effort in the 20th century. A small fraction of these small molecule drugs do cross the BBB. However, today, the focus is increasingly a biology-based R&D effort at the discovery of large molecule drugs such as recombinant proteins, therapeutic antibodies, and nucleic acid drugs. None of these large molecule drugs produced by biotechnology cross the BBB.

[15] Primary sources for this case study are the meeting with Dr. William Pardridge and a review of the ArmaGen Technologies website and related company documents. http://www.armagen.com.

Efforts to deliver treatment and brain delivery technologies over the past 20 years have been ineffective. Primarily employing subcutaneous injections and then direct delivery into the brain, these treatments have failed. Although treatment sometimes works in mouse or rat models, Dr. Pardridge explained that the failure of expensive Phase 3 clinical trials was to be expected, because diffusion in a mouse brain is much easier than in the massively larger human brain. So efforts to deliver neurotrophins by direct injection into the brain and into the spinal cord have not been successful. In the most recent trials, a consortium of the largest pharmaceutical companies had an expensive failure of an Alzheimer's disease treatment based on monoclonal antibodies, again because they could not cross the BBB.

Dr. Pardridge founded ArmaGen while working as a professor at the University of California, Los Angeles (UCLA), in part because experience in dealing with pharmaceutical companies had convinced him that they were not interested in the BBB problem and that it would have to be solved elsewhere. He had successfully maintained an unbroken stream of academic research grants for 35 years before retiring from academia, and indeed the commercial work on ArmaGen grew directly out of the academic research funded during the 1980s and 1990s.

THE SEARCH FOR FUNDING

The company depended primarily on SBIR funding for about a decade, while Dr. Pardridge sought venture funding. Initial efforts in this area in 2002 were discouraging. Dr. Pardridge noted that, working with a well-connected Silicone Valley lawyer, he initially approached 25 venture firms for funding and received one interview and no further responses.

SBIR funding permitted the company to open its first 3,000-square-foot research facility in Santa Monica in 2003, and to hire a team of five researchers. The period after the initial awards, from 2003 to 2007, was in Dr. Pardridge's words, "the flat part of the learning curve." The company had to learn to do for itself many of the functions routinely performed at existing drug companies, but many of the research techniques that were known in the private sector had not been necessary in academia.

Starting in 2007, progress at ArmaGen accelerated, and from 2007 to 2012, ArmaGen published more than 40 peer-reviewed papers describing some of its research, covering ways in which its approach to the BBB could be used to deliver to the brain very well-known drugs such as Aldurazyme®, Enbrel®, or Humira®.

In 2010, ArmaGen again sought VC funding, armed this time with the numerous papers explaining and validating its approach, as well as a growing track record of research funded by the NIH SBIR program. However, none of the VCs approached showed any interest. ArmaGen then adopted a different strategy, focused on identifying more strategic partners from the pharmaceutical industry. Dr. Pardridge approached the newly formed Boehringer Ingelheim Venture Fund (BIVF), and this partnership led in 2012 to a series A round for $17 million.

BIVF was jointed by three other potential strategic partners: Shire plc, Takeda Ventures, Inc., and Mitsui & Co. Global Investment, Inc. Dr. Pardridge noted that none of the investors acquired any additional rights to license or utilize ArmaGen technology as a result of this equity investment.

After its first round of venture funding in November 2012, ArmaGen brought in professional management and, in December 2012, hired as CEO James Callaway, a biotech executive with nearly 30 years of experience in biotechnology R&D with both ties to big pharma and experience running venture-backed biotech start-ups.

ArmaGen is currently working to validate its core technology in clinical trials. Under an orphan drug designation—which allows both accelerated approval and various R&D tax credits—ArmaGen is moving toward clinical trials for enzyme replacement therapies targeting Hunter and Hurler syndromes.

Although these conditions represent very small markets, FDA approval would demonstrate the value of the core technology, supporting either an exit or follow-on funding for other indications with much larger market value (such as Alzheimer's disease, Parkinson's disease, neuroinflammation, stroke, or brain cancer). These are all indications for which ArmaGen has undertaken extensive research using SBIR funding.[16]

TECHNOLOGY

Because of the BBB, effective therapeutics have not been developed for most brain disorders. The BBB protects the central nervous system and prevents most molecules from passing from blood into the brain. Lipid soluble small molecules can diffuse through the barrier, but all other molecules that enter the brain must pass through transport systems that exist in the brain's endothelial wall.

The ArmaGen technology uses basic molecular biology techniques to fuse protein-based therapeutics of interest (i.e., recombinant proteins, therapeutic monoclonal antibodies, and even, indirectly, siRNA) to an antibody designed to bind to a receptor on the BBB. The antibody transports the therapeutic drug of interest across the barrier. ArmaGen describes this antibody metaphorically as a "molecular Trojan Horse."

After crossing the BBB, the antibody does not appear to interfere with the efficacy of the therapeutic molecules. ArmaGen has demonstrated that the therapeutic molecules can act in four different ways:

- binding to other proteins (e.g., inflammatory cytokines such as TNF)
- binding to protein receptors on the surface of a neuron to transmit a message (such as neuroprotective neurotrophin receptors)

[16]"ArmaGen Technologies, Inc." *Los Angeles Business Journal*, <http://www.labusinessjournal.com/news/2013/aug/12/special-report-innovation-tech-transfer-ucla-armag/>.

- binding to surface receptors on brain cells and delivering the therapeutic payload to the neuron (such as in enzyme replacement therapy)
- binding to surface receptors on brain cells and delivering the therapeutic payload to the neuron for absorption by the nucleus (such as in siRNA-based therapies)

PRODUCTS

Using SBIR funding, ArmaGen has improved its technology platform and investigated application of the technology for different medical indications.

Hurler and Hunter Syndromes

As an initial demonstration of this technology, ArmaGen is developing enzyme replacement therapies that can cross the BBB for a pair of lysosomal storage diseases called Hurler syndrome and Hunter syndrome.

Fewer than 10,000 people have these diseases in the United States. They are metabolic disorders caused by different malfunctions in the process by which the body's lysosomes break down glycosaminoglycans. Over time, these molecules accumulate in the cells, causing progressive cellular damage that affects appearance, abilities, organ function, and mental development of patients.

Although enzyme replacement therapy appears both safe and effective in treating the peripheral symptoms of the disease, the BBB has blocked delivery of these enzymes into the central nervous system, causing mental development to continue mostly unimpeded.[17]

Since 2003 ArmaGen has received $5.12 million from NIH to fund research on these two lysosomal storage diseases. Also, ArmaGen has received an additional $1.15 million to study a third lysosomal storage disease called Metachromatic Leukodystrophy (MLD), and an additional $1.15 million to study a fourth lysosomal storage disease called Sanfillipo Type A.

Under an orphan drug designation to accelerate the approval process and get additional tax credits, ArmaGen is using its Trojan Horse technology to enable enzyme replacement therapeutics to enter the central nervous system. These have been code-named AGT-181 and AGT-182. Both drugs received an Investigational New Drug (IND) designation from FDA.

Dr. Pardridge said that two clinical trials were now, or would soon be, under way for Hurler Syndrome and Hunter Syndrome, with the first Phase 1 trial to be completed in 2014 and the second in early 2015. Dr. Pardridge anticipates that the small-scale Phase 2 clinical trial, which will be a test of safety and initial efficacy on a population of approximately 24 children, should follow shortly and will require only a limited period of time.

[17] "Lysosomal Storage Disease," http://emedicine.medscape.com/article/1182830-overview.

Other Indications

On the basis of SBIR research, therapies targeting other conditions are in the company's product pipeline. These include various treatments for Alzheimer's disease, Parkinson's disease, neuroinflammation, stroke, brain cancer, and even nerve gas exposure.

Despite its recent round of venture funding, ArmaGen still lacks resources to pursue all development opportunities and is looking for collaborations with pharmaceutical companies either to accelerate development and commercialization of the products in their pipeline or co-develop additional products by using ArmaGen's technology to enable delivery of its partner's drugs across the BBB.

Since 2003 ArmaGen has received $10.21 million to fund research examining applications of its technology for indications other than lysosomal storage diseases.

PATENTS AND OTHER INTELLECTUAL PROPERTY

ArmaGen owns eight issued patents on compositions and methods to enable therapeutic drugs to cross the BBB and treat conditions of the central nervous system. (See Table E-4.) Additional patent applications are pending.

FUNDING

During its first 10 years of operation, ArmaGen relied on SBIR and other grants to support its research. With new management and venture funding, it is

TABLE E-4 ArmaGen Patents

Patent Number	Patent	Year
8,741,260	Fusion proteins for delivery of GDNF to the CNS	2014
8,715,661	Methods and compositions for increasing arylsulfatase A activity in the CNS	2014
8,497,246	Methods for diagnosing and treating CNS disorders by trans-blood-brain barrier delivery of protein compositions	2013
8,486,399	Methods and compositions for increasing arylsulfatase A activity in the CNS	2013
8,142,781	Fusion proteins for blood-brain barrier delivery	2012
8,124,095	Fusion proteins for delivery of erythropoietin to the CNS	2012
8,053,569	Nucleic acids encoding and methods of producing fusion proteins	2011
7,741,446	Fusion antibodies that cross the blood-brain barrier in both directions	2010

SOURCE: U.S. Patent and Trademark Office.

now positioned to begin clinical trials on the two most promising drug candidates in its pipeline.

Non-Dilutive Grants

Between 2003 and 2009, ArmaGen received 11 Phase I and 5 Phase II SBIR grants from HHS to develop its core technology and its application in treating various conditions of the central nervous system. In total, SBIR funding has amounted to 16 grants for $13.38 million, $3.79 million in Phase I and $9.59 million in Phase II. From 2010 to 2013, SBIR initiated four additional projects with ArmaGen (most of which are related to lysosomal storage diseases) for $3.60 million while continuing to fund ongoing projects. Total SBIR funding from 2003 to 2013 totaled $16.81 million.

Equity Investment

In April 2013, ArmaGen successfully closed on $17 million in Series A funding; participants included Boehringer Ingelheim Venture Fund; Shire plc; Takeda Ventures, Inc.; and Mitsui & Co. Global Investment, Inc. Shire and Takeda Ventures are the corporate venture funds of large pharmaceutical companies and reflect a current trend by corporate VCs to take equity positions in early rounds.[18]

ARMAGEN AND SBIR

SBIR was the lifeblood of ArmaGen from it foundation in 2004 until the series A round closed in late 2012. Dr. Pardridge observed that "ArmaGen has traversed the valley of death and our horse was SBIR." He has also served on SBIR study sections and has a number of comments and suggestions related to SBIR.

1. Support for clinical trials. Dr. Pardridge said that the $1 million annually for 3 years potentially available for clinical trial support was simply insufficient to accomplish its goals. ArmaGen had received such an award but had quickly realized that the funding would be insufficient and had been forced to hold off on filing the IND. Overall costs for a small trial were on the order of $5 million minimum, when the company has to first execute GMP manufacturing of a novel biologic and perform extensive GLP safety pharmacology of the biologic agent in primates before filing the IND.
2. Study section composition. Dr. Pardridge said that he did not see a significant difference between RO1 and SBIR study sections. He had served

[18]Mark Lennon, "Corporate Venture Investors Starting To Look A Lot More Like Private VCs," http://techcrunch.com/2013/11/05/corporate-venture-investors-starting-to-look-a-lot-more-like-private-vcs/.

on both for many years, and both were dominated primarily by academic scientists. He wondered whether an entirely separate organization to help select small business awards might be a better approach.

3. Long timelines. If a $3 million continuation award supported early stage trials, including toxicology studies and perhaps manufacturability, the absence of additional funding thereafter risked delays that could break the project, as drugs developed for Phase 1 had at best a 2-year shelf life.
4. Rebuttal. Dr. Pardridge said that he thought the idea of an ability to respond to initial reviewer comments was highly promising, but he was concerned that it might not be practical.
5. Eliminate Phase I altogether. Although this represented a radical change in the program, Dr. Pardridge was convinced that its existence means that any project effectively requires 2 years before it can find significant funding from SBIR. This is too long in the current (and accelerating) environment. In his experience, reviewers were very reluctant to support FastTrack applications, and he was skeptical that direct to Phase II would be widely adopted. He noted that the need for Phase I feasibility stage grants was not a feature of academic RO1 and similar awards.
6. Patent costs. Dr. Pardridge said that patent costs represented part of the outcome from the grants and that protecting intellectual property (IP) was likely to generate better commercial outcomes. It was therefore in the interests of the taxpayer to permit some use of SBIR funding for prosecution costs of specific patent applications.

High-quality program officers. Dr. Pardridge noted that almost uniformly and across several institutes the program officers with whom he had worked were highly engaged and committed to successful translational research. Indeed, they were much more committed than most academics working in the field for whom success had other metrics.

Auritec Pharmaceuticals: SBIR Case Study[19]

Meeting with
Dr. Thomas Swift
June 24, 2014
Pasadena, California

Auritec Pharmaceuticals is a privately held business headquartered in Pasadena, California. Founded in 2002 by Dr. Thomas Smith, it owns two platform technologies for extended-release drug delivery and has tested them to improve treatment for a broad range of medical indications.

Dr. Smith has spent the past 25 years working on extended-release drug delivery. In 1990, he co-founded Control Delivery Systems, Inc. (CDS). Over the following decades, CDS developed 38 patents and a close research partnership with Chiron and Bausch & Lomb which led to the development of Vitrasert™ (Food and Drug Administration [FDA] approval in 1996) and Retisert™ (FDA approval in 2005). In 2006, CDS merged with pSivida Corporation, an Australian firm, to form pSivida Inc., a publicly traded U.S. company (NASDQ:PSDV). pSivida has licensed extended-release implant technology for several indications to Auritec.

Auritec's strategy is to choose diseases with unmet medical need where its technologies can lead to medically and commercially important products. Internal R&D is meant to lead to "proof of concept," at which point the product is licensed to a larger corporation that will take it through FDA approval and marketing. For example, Auritec has a partnered with an arthritis company. Similar efforts are at various stages of development for other areas such as endometriosis, breast cancer, and HIV/AIDS. In each case, the core concept was the focus on drug delivery technology: the remedial drug was known to work, but there were problems with effective delivery that Auritec could help solve.

In pursuit of this strategy, in the first years of Auritec's existence Dr. Smith invested a substantial amount of his own money to allow the company to function. Since about 2007 however, the company has primarily relied on SBIR funding to continue its research and development program. According to Dr. Smith, he received his first SBIR award 25 years ago and has been deeply involved in the program since then. In order to highlight the success of his companies, he observed that there is a huge mismatch between the number of small biotech firms and the number of drugs originating from that that are actually approved by the FDA: he pointed out that 5,200 small biotech companies received funding from the recent discovery tax credit, while only 1-2 related drugs are approved each

[19]Primary sources for this case study are the interview with Dr. Smith and a review of the Auritec Pharmaceuticals website (http://www.auritecpharma.com) and related company documents.

year by companies of that size. Companies founded by Dr. Smith have achieved approval of 3 NDAs.

With SBIR funding, Auritec has investigated application of the implant technology licensed from pSivida to other medical indications (Versa). Over the past couple of years, it has received multiple SBIR grants to support research and clinical trials for FDA approval of its Versaring™ products: implant-based product intravaginal rings designed to provide women protection from infection with HIV and genital herpes. Auritec expects to license Versaring™—as CDS did with Vitrasert™ and Retisert™—to a pharmaceutical company with the production, marketing, and distribution capabilities for successful commercialization.

Auritec shares space and equipment with the Oak Crest Institute of Science in a 7,000 square foot open-plan laboratory.

TECHNOLOGY

Auritec Pharmaceuticals owns two platform technologies for the sustained release of drugs.

Versa™

The Versa™ platform is an implant-based delivery system in which a solid implant is placed in the patient. Versa™ implants consist of a solid drug core coated with a semi-permeable polymer envelope. Water from surrounding tissues diffuses through the coating and dissolves the drug, creating a saturated solution within the polymer envelope. The drug in the solution diffuses out of the envelope. Because the solution inside the envelope remains saturated until nearly all of the drug is dissolved, the diffusion of the therapeutic effects out of the implant remains roughly constant over the entire release period.

The technology licensed from pSivida for the Retisert™ and Vitrasert™ products is the basis for the Versa™ platform. By varying drug load and coating characteristics, Auritec can create sustained-release implants with timescales ranging up to several months or even years.

Plexis™

The Plexis™ platform is a depot injection-based delivery system that miniaturizes the Versa™ implants as polymer-coated drug particles. Particle size and coatings are selected to enable high drug load, predictable and continuous release, and intramuscular or subcutaneous depot injection.

Auritec has investigated application of the Plexis™ platform in various indications including schizophrenia, Parkinson's disease, graft rejection, arthritis, macular edema, and HIV/AIDS.

Between 2002 and 2008, 95 percent of Auritec's SBIR funding went to study potential applications of the Plexis™ platform. Since 2008, Auritec's research focus has been more balanced, with 55 percent of SBIR funding going to applications of the Versa™ platform, mostly for commercialization of the Versaring™ intravaginal ring.

PRODUCTS

With SBIR funding, Auritec has investigated different ways to broaden the application of its implant-based Versa™ technology (paralleling Retisert™ and Vitrasert™) and identify initial applications for its depot injection-based Plexis™ platform.

Versaring™ Intravaginal Ring

Globally, each year 1.2 million women are infected with HIV and a further 10.2 million are infected with Herpes Simplex Virus (HSV).[20] Improved prophylaxis against HIV and HSV using a topical microbicide, a tenofovir gel, has been demonstrated in a population of sexually active women.[21] Because protection increases with increased adherence and because intravaginal rings (IVRs) may increase adherence, Auritec is developing an intravaginal ring for the long-term delivery of tenofovir, acyclovir and other microbicides for HIV/HSV prophylaxis.

The Versaring™ intravaginal ring is a silicone ring embedded with drug "pods." Based on the technology licensed from pSivida, the drug pellets are coated with first a permeable polymer and then a semi-permeable layer. Each ring can hold up to 10 pods, and each pod can be identical or composed of different drugs. Furthermore, the release rate for each pod can be tuned independently.

Since 2009 NIH has invested $4.03 million through SBIR in Versaring™. These grants have supported basic research, development of manufacturing capability, and the performance of preclinical trials.

Other Indications

Since its founding in 2002, Auritec has used a series of SBIR Phase I and Phase II grants to evaluate various medical conditions for potential application

[20]"Women and HIV/AIDS," AVERT, http://www.avert.org/women-and-hiv-aids.htm; "Worldwide HIV & AIDS Statistics," AVERT, accessed at http://www.avert.org/worldwide-hiv-aids-statistics.htm. Looker, et. al. "An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection," Bulletin of the World Health Organization, accessed at http://www.who.int/bulletin/volumes/86/10/07-046128/en/.

[21]Use of tenofovir gel reduced incidence of new HIV infections by 40 percent in sexually active Sub-Saharan women; for women who adhered strongly to the regimen, the reduction in the incidence of new infections was 50 percent. Paul Sax, "CAPRISA Study: First Vaginal Gel Microbicide to Prevent HIV and HSV," Medscape, accessed athttp://www.medscape.com/viewarticle/726159.

of its extended-release technologies. Specifically, these conditions have been arthritis, Parkinson's disease, schizophrenia, macular degeneration, transplant rejection, mother-to-child HIV transmission, and chronic ear disease. Since 2002 Auritec has received $5.32 million through NIH's SBIR program to support investigation of other indications.

Most of these projects appear to have been dead ends from the perspective of product development. The exception was a 2007 study investigating ways to use extended release with corticosteroids to treat inflammatory diseases of the inner ear. This work was undertaken in partnership with the company O-Ray Pharma, which Auritec spun off in 2005. Auritec retains an equity interest in O-Ray, which has received three SBIR grants and is investigating the use of four different drugs in extended-release formulations for inner ear disease.[22]

RESEARCH PARTNERSHIPS

Auritec partners with numerous research organizations. These partners have included the University of Southern California; Albert Einstein College of Medicine; Oak Crest Institute of Science; International Partnership for Microbicides; CONRAD; Centers for Disease Control and Prevention; The University of North Carolina; University of California, Irvine; Emory University; North Carolina State University; and The University of Massachusetts.

In 2011, Auritec worked with a major pharmaceutical company to study the performance of Auritec's technology in a proprietary molecule produced by the company. Auritec developed a sustained release formulation of the molecule and tested it in animal models.

PATENTS AND OTHER INTELLECTUAL PROPERTY

PSivida has assigned exclusive rights for the implant-based technology for the Retisert™ and Vitrasert™ products to Faber Research for indications related to the inner ear, malaria, HIV/AIDS, influenza, tuberculosis, and osteomyelitis. In addition Auritec has a broad patent issued in Australia and Canada and pending in the United States, Europe, and Japan for Plexis technology. In addition the company has a broad patent application pending for its Versa technology ring and implant program.

SBIR AND OTHER FUNDING

According to the SBA TECH-Net database, between 2004 and 2010 Auritec received eight Phase I and four Phase II SBIR grants from the Department of Health and Human Services to investigate the development of extended drug

[22]"About Us," O-Ray Pharma, accessed at http://oraypharma.squarespace.com/about-us/.

release technologies. In total, SBIR funding has amounted to 12 grants for $4.9 million total—$0.91 million in Phase I and $3.88 million in Phase II.[23]

The NIH RePORT database indicates that Auritec has received funding for seven additional grants (mostly related to development of intravaginal ring technology) and shows a total commitment through SBIR by HHS of $9.45 million between 2004 and 2013.[24]

AURITEC AND SBIR

Dr. Smith offers multiple perspectives on the SBIR program. Aside from the awards he has received from NIH over the past 25 years, he has been a study section reviewer and a chairman.

SBIR funding provides the critical bridge funding that allows small companies to reach the end of Phase 2 clinical trials, which Dr. Smith sees as the key point at which strategic partnerships with larger companies or direct investments from financial sources become feasible.

Currently, Auritec depends on SBIR for ongoing funding. However, with two projects in clinical trials and another open investigational new drug (IND), Dr. Smith believes that the necessary Phase 2 clinical trials data will soon provide support that will allow outside funding sources to become available.

SBIR COMMENTS AND RECOMMENDATIONS

Dr. Smith's experience with study sections provides a valuable perspective on their operations. He made a number of comments.

Institutionally, Dr. Smith believes that NIH is heavily focused on novelty at the expense of innovation. He observed that "if research is the transformation of money into knowledge, innovation is the translation of knowledge into money."[25]

At NIH, the focus is almost exclusively on research. This is in part a result of the academic preponderance on study sections and on the importance of novelty in academic research. As a result, there is insufficient emphasis on the practical aspects of innovation—the likelihood that knowledge will indeed be transformed into practical treatment that improves lives.

Dr. Smith observed that novelty comes very early in the discovery process. Once a possibly therapeutic approach is identified, subsequent work to prove the concept and then to adapt it to a range of different circumstances constitutes the critical innovation that turns an idea into reality, but this process does not always require novelty. In his view, not only is NIH institutionally over-focused

[23]TECH-Net, http://web.sba.gov/tech-net/public/dsp_search.cfm, accessed June 12, 2014.

[24]NIH RePORT database, http://report.nih.gov/index.aspx, accessed June 12, 2014.

[25]Attributed to Geoffrey Nicholson, 3M. See Patrick Barkham, "Happy 30th birthday, post-it notes," *The Guardian*, April 25, 2010.

on novelty, SBIR study sections strongly reflect this bias. Most are dominated by academic scientists.

Further, he observed that Scientific Research Officers (SROs) who manage study sections in general subscribe to and support the focus on novelty. He identified a number of cases in which potentially important innovations were rejected by study sections on the grounds that they were insufficiently novel.

Dr. Smith recommended that NIH work to refocus the role of SROs so that they become defenders of innovation. This could be accomplished in his view relatively easily if NIH decided that this shift was appropriate. SROs could provide detailed instruction on the definition of innovation at the start of the study section and could also provide ongoing direction to ensure instructions were followed.

Dr. Smith noted that the members of study sections were, by design, not experts in the subject matter of proposals under review. As a result, in some cases it was clear that there were significant misunderstandings, and in others, reviews were rejected for relatively minor or easily resolved questions. In many cases, these minor difficulties or misunderstandings resulted in a long delay (8 months) before a proposal could be resubmitted.

Dr. Smith said that a very brief rebuttal process could accelerate this process sharply, reducing costs for companies and improving the efficiency of the review process for NIH. He said that a response of less than one page could easily be generated before a study section met—or indeed in the course of the meeting itself. Dr. Smith also noted that this kind of interactive approach was standard at the FDA, where IND applications were generally subject to a number of rounds of correction and improvement.

Rebuttals could also help mitigate the impact of a single study section member who had strong views. Providing companies with an opportunity to address criticisms and concerns should limit these impacts and improve the quality of the overall process.

Dr. Smith observed that in his experience a majority of applications were very poor quality and that a white paper process in which applicants were required to submit a brief summary for review by program officers could lead to a sharp reduction in the number of eventual applications, which would reduce the workload for both companies and reviewers. He cautioned, however, that this process should not be used as a hard filter and that projects that got negative responses to the white paper should still be permitted to apply.

Dr. Smith noted that debriefings which provide the basis for a resubmission are delivered too late for the next submission deadline, imposing an 8-month delay. He observed that this was not the case for HIV/AIDS proposals and suggested that NIH should work to make this more rapid process available to all applicants; for small companies, this kind of delay could be very serious.

He approved the recent changes to award size and stressed in particular that the shift of Phase I awards at NIH to $225,000-250,000 had been very positive; rather than a loss leader undertaken in the hope of Phase II funding, Phase I was

now funded appropriately. However, he saw the move toward large awards at Phase II as reflecting institutional pressures within NIH to reduce the average pay line as increasing the funding for lower scoring projects results directly in a lower average pay line.

Dr. Smith also approved of the recent NIH decision to pilot direct-to-Phase II awards: he noted that many companies already had feasibility data for projects and could therefore move forward without the need for Phase I. This pilot would also have the effect of substantially accelerating the overall project by providing more funding more quickly. Dr. Smith noted, however, that this might also tend to squeeze out startups that relied on Phase I funding for early data.

Dr. Smith strongly supported the development of mechanisms that helped to provide funding for clinical trials. He observed that while a full-scale clinical trial could cost many millions of dollars, it was possible to find ways to reduce the cost, and NIH funding could make the difference for many projects.

Avanti Polar Lipids, Inc.[26]

Meeting with
Dr. Walter Shaw, President
September 5, 2014
Alabaster, Alabama

Avanti Polar Lipids ("Avanti") is a private company founded in 1969 by Dr. Walter Shaw. It is a contract manufacturing organization that produces ingredients and end products for biotech and pharmaceutical companies developing products based on lipids and hydrophobic small molecules. Its production facilities are certified by FDA to conform to current Good Manufacturing Practice (cGMP). Avanti can produce small-scale batches for research, preclinical, and clinical trials; at the same time, it can scale up production to support commercial launch of FDA-approved drugs.

At present, Avanti operates a 25-acre campus in Alabaster, Alabama, and employs approximately 103 people. Manufacturing and quality assurance are performed in a series of five FDA-inspected and -approved laboratories covering 50,000 square feet and spread across five buildings at Avanti's headquarter complex in Alabaster, Alabama.

COMPANY HISTORY

Avanti was founded in 1969 by Walter Shaw when he was a lab director at the Medical College of Virginia, which at the time had a large group studying lipid-lipid and lipid-protein interactions. While working on a study on the absence of adipose tissue enzyme and its impacts, he found that important work was being done by a team at UC San Diego, which he joined on a temporary basis. This team determined that some patients were in fact missing this enzyme.

The move from Virginia to Alabama was fortuitous. The director of the research team in Virginia sought to deliver services to a more rural population, and moved to Alabama to do so. Dr. Shaw moved with the team, and thus took his own company to Alabama where he pursued a doctorate at the University of Alabama at Birmingham. Initially, the company rented a 700-square-foot garage as a lab.

At the time, Dr. Shaw saw an opportunity in making enzyme substrates for the lipid research market, and the company originally focused on meeting the need of analytical lipid standards. However, as his first year revenues were only $12,000 he also relied on teaching and research posts at the University for funding.

[26]Primary sources for this case study are the meeting with Walt Shaw, President and founder of Avanti Polar Lipids, and a review of the Avanti website (http://www.avantilipids.com) and related company documents.

Soon afterward, major breakthroughs in this area followed the discovery of liposomes by Alex Bangham in the late 1960s, and the subsequent work of other researchers following this new research pathway. This expanding new research field required products and services that could be generated by Avanti, and the company moved rapidly to address these new opportunities.

Avanti was perfectly positioned to meet the new market. There were, according to Dr. Shaw, no competitors who could meet the very high quality demands of the research labs: commercial providers of lipids such as egg lecithin did not see this as a major market.

As a result, the higher quality products provided by Avanti allowed it to dominate its market niche of providing lipids to the research community, where it quickly became the preferred provider. As biomedical research on the liposome and lipids has grown over the past 40 years, Avanti has expanded and now provides a broad range of products and services to organizations requiring research-grade lipids.[27] Dr. Shaw's view is that this niche market is large enough to support one company the size of Avanti but not much more, and its well-established position makes market entry difficult for potential competitors.

Developing a Manufacturing Capability

In 1985 Avanti developed important new capabilities when it became a major partner in developing and manufacturing Exosurf, a lung surfactant product developed by Burroughs, a major pharmaceutical company. This product changed health care and outcomes for neonates almost overnight. Prior to Exosurf, neonates were served via a hypobaric chamber, which often resulted in brain and kidney damage. Exosurf (which is no longer on market) is partly composed of phospholipid. It was delivered by eyedrop into the lungs of a baby. After spreading through the lungs, the effect was remarkable: within 20 minutes a blue baby turned pink and was breathing.

This partnership put Avanti into the pharmaceutical manufacturing business (Exosurf was approved in 1990 after FDA stopped the Phase 3 trial to allow immediate delivery to the market). In becoming a manufacturer, Avanti moved into a former abattoir completely renovated into a high-quality manufacturing and research center that is state of the art for lipid production.

Avanti now sells more than 2,000 products, the majority of which are sold to researchers. It has more than 100 employees and 11 buildings.

[27]Rajendrani Mukhopadhyay, "How Walter and Rowena Shaw grew Avanti Polar Lipids into the Company It Is Today," *ASBMB today*, http://www.asbmb.org/asbmbtoday/asbmbtoday_article.aspx?id=17821&page_id=1.

BUSINESS MODEL

Avanti Polar Lipids provides various products and services to researchers and entrepreneurs working with lipids in the biotech industry. As an investigator's needs change across the R&D process, Avanti can provide various different types of manufacturing support.

Standard Lipids: Avanti's catalog presents a range of more than 2,000 lipids used generally by laboratories and biotech companies studying activity in the liposome. In its laboratories, Avanti can produce basic inputs (such as synthetic cholesterol or various widely used monoclonal antibodies) for use in biomedical research or as ingredients in other manufacturers' processes. Avanti provides these products through a network of domestic and international distributors in North America, Europe, and Asia.

Custom Lipids: As a contract manufacturer, Avanti also develops new production and assurance processes to support its clients' development and commercialization of the new lipid-based molecules. In developing a custom product, Avanti assigns a development team of organic chemists and analysts to oversee process development and scale up as product volume increases from supporting FDA preclinical trials to enabling commercial launch. A typical development path might include:

Definition of process for product synthesis:

- Scale-up of process for product synthesis (both non-cGMP and cGMP)
- Analytic validation of product
- Scaled manufacturing of product with quality assurance process/analytics
- Regulatory support with FDA (IND, NDA) across commercialization process
- Supply chain management

Avanti also offers these different activities independently as services (i.e., lipid analytics, supply chain management, regulatory process management) to clients that do not require the full service package.

PRODUCTS AND SERVICES

In its product catalog, Avanti offers the following types of standard lipids:

- Sphingolipids
- Phospholipids
- Sterols
- Bioactive Lipids
- Coenzyme A & Derivatives
- Neutral Lipids
- Fatty Acid Modified Lipids

- Headgroup Modified Lipids
- Cationic Lipids (Transfection)
- Detergents
- Fluorescent Lipids
- Polymers & Polymerizable Lipids

As part of its analytic services package, Avanti offers these capabilities:

- Extraction and Characterization of Lipids
- Thin Layer Chromatography
- Fourier Transform Infra-Red Spectroscopy
- Wet Chemistry Methods
- High Performance Liquid Chromatography
- NMR and Electrospray Mass Spectrometry
- Capillary Gas Chromatography
- Fatty Acid Methyl Ester (FAME) Analysis
- Elemental Analysis
- Stability Testing of Lipid-related Products

Avanti also offers probes and other lipid-related equipment.

PATENTS AND OTHER INTELLECTUAL PROPERTY

To support its manufacturing and quality control processes, Avanti has substantial technical competence in the production and characterization of lipids. At present Avanti does not own a U.S. patent, but it does have several patents pending.

AVANTI AND SBIR

Unlike many SBIR recipients, Avanti is a mature company with a 45-year history of profitability. It has not received angel or venture funding and has grown to its current size based on the profitability and quality of its core manufacturing processes.

Non-Dilutive Grants

Between 1997 and 2009, SBIR funded six projects with Avanti. Avanti received eight SBIR awards amounting to more than $6.89 million from HHS. These grants were not intended to develop manufacturing capability. Rather they investigated the application of lipids to various different medical indications (such as cystic fibrosis, pancreatic insufficiency, cancer, and acute respiratory distress syndrome) to therapies directed at symptoms (such as coagulation) and to improvement of the efficiency of therapeutic techniques (such as gene transfection).

Avanti's entrance into SBIR was unplanned and not part of the mainstream of the business. Dr. David Yesair, a client and professional contact of Dr. Shaw, had developed a unique approach to solve the problems of cystic fibrosis (CF) patients: development of a fat that was essentially pre-digested and hence could be tolerated by CF patients, through which they could absorb essential fatty acids.

After developing the concept, Dr. Yesair sought to test the approach prior to developing a commercial scale product. He partnered with Dr. Shaw who became interested in the product, and with staff at Children's Hospital in Philadelphia to develop a plan for a clinical trial.

Such a trial was too expensive for any of the participants, so the team turned to SBIR. Dr. Shaw had some previous experience with SBIR, having received some earlier Phase I awards for research related to lipids. The team developed a proposal for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and received a $100,000 Phase I award to examine the physical properties of the new complex the team had developed.

The Phase I results were encouraging but Phase II would need to cover the clinical trials. The original budget submitted was for $2 million, which included a before and after study of patients. NIH rejected this methodology in favor of a classic, double-blind, placebo-controlled study but this required a budget of $6 million. After considerable discussion, NIH agreed to provide the entire $6 million in Phase II SBIR funding for the clinical trial at Children's Hospital. In the end, the study came in under budget, and some funding was left unspent.

Avanti not only provided some of the inputs into the new complex, but also undertook the blood analysis of the patients needed to establish results.

The trial has concluded, and results are now being compiled into papers that will be available shortly. The study showed success in making the product, feeding the patients, and deploying the analytical framework. Preliminary indications are that there were no adverse effects on patients, and that for some patients at least there were weight gains. Further detailed results will be available shortly.

Although the SBIR project provided critical funding, Dr. Shaw indicated that the level of paperwork required, and the need to provide detailed tracking of time and material (which is not usually required in a product-oriented company like Avanti) meant that he was not eager to undertake additional SBIR projects. He preferred to work as a subcontractor to other research groups—for example, Avanti is working with a Louisville research group on a wound-healing product that the Department of Defense (DoD) is seeking to fund.

Avaxia Biologics, Inc.[28]

Meeting with
Dr. Barbara Fox, CEO
October 29, 2013
Waltham, Massachusetts

Avaxia Biologics, Inc. is a privately held business headquartered in Lexington, Massachusetts. It was founded in 2005 by Dr. Barbara Fox, an experienced entrepreneur and scientist, and David Poorvin, a senior executive with Schering-Plough and Pfizer Pharmaceutical. The company has developed an oral delivery platform for antibodies to address disease processes either occurring or influenced by receptors located in the gastrointestinal tract.

The company products focus on developing gut-targeted therapeutics that work against serious diseases that can be treated locally via the gastrointestinal tract. In order to keep the company organization as lean as possible, it uses contract research organizations (CROs) to address its research goals. The overall strategy is to commercialize by developing its products through early clinical trials (up to Phase 2) and exiting either by selling or licensing its IP or by selling the company outright. In a discussion, Dr. Fox indicated that the latter was the primary likely outcome for Avaxia.

Avaxia accepted its first and second rounds of venture funding in February 2012 and June 2013, and has since then expanded its management team, adding vice presidents for research, technical operations, corporate development, and finance and administration. As a result of this influx of venture funding, Avaxia no longer qualifies as a woman-owned company.

TECHNOLOGY

Avaxia's key technology is a proprietary oral antibody platform, on which it plans to develop specific gut-targeted therapeutics that address serious diseases such as inflammatory bowel disease, Type 2 diabetes, celiac disease, gastrointestinal acute radiation syndrome, and oral mucositis. These are large-scale diseases with very substantial potential markets.

Gut-targeted therapeutics are drugs that are administered orally and act locally in the GI tract. Possible targets include many diseases of the mouth, throat, and intestines. This approach has several advantages:

[28]Primary sources for this case study are the meeting with Dr. Fox and a review of the Avaxia website and related company documents.

- Direct connection to new receptors
- Delivery of existing drugs through new modalities and potentially at higher doses
- Reduced side effects, and localization of side effects to the gut

The intestines are lined with receptor proteins. Recent research has shown that these receptors can influence disease processes even for those that manifest outside the gut such as Type 2 diabetes and hypertension. Because these receptors are only accessible from the interior of the intestines, drugs designed to access such targets offer opportunities for new therapeutic interventions and for delivery of preexisting therapeutics at high dosages. Both approaches could improve efficacy and outcomes. Furthermore, because gut-targeted therapeutics remain in the GI tract rather than being transported throughout the body, they should minimize potential side effects in other parts of the body. This is especially important for drugs that suppress the immune system.

Avaxia has to date focused much of its research on inflammatory disease processes. Three of its projects use oral anti-tumor necrosis factor (TNF) antibodies. TNF is a component in the body's inflammatory response, and dysfunction can produce a wide range of inflammatory diseases such as rheumatoid arthritis, Crohn's disease, psoriasis, and asthma.

Such antibody-based drugs are a proven therapy. The current market for such products exceeds $50 billion annually. Adalimumab and Infliximab are recent successes in the anti-inflammatory market. Antibody drugs, however, cannot be administered orally. All currently marketed antibody drugs are susceptible to the digestive processes of the mouth, stomach, and intestines and cannot survive delivery through the GI tract. Thus, such drugs are administered by injection or infusion and usually travel throughout the body with the accompanying risk of unwanted side effects.

Because Avaxia's proprietary oral delivery platform resists digestion of antibodies, it is well suited for use in gut-targeted therapeutics. Avaxia's oral antibodies can target any receptor sites accessible via the digestive tract, including the mouth, throat, and intestines. Potential targets include the following:

- Targets present within the intestine such as gluten and other food antigens
- Targets present on the interior surfaces of the intestines such as sugar transporters and receptors
- Targets present below the mucosal barrier that defines the interior surface of the intestine such as inflammatory factors like TNF. Disease processes cause the mucosal barrier to leak and expose such targets.

Bovine colostral antibodies resist digestion naturally, making them potentially ideal for use as gut-targeted therapeutics. Using a proprietary process, Avaxia immunizes pregnant cows with an engineered form of human TNF and

isolates antibodies from the milk (colostrum) produced by the cows just after they give birth. According to Dr. Fox, this approach is readily scalable and does not present any significant barrier to business expansion.

Avaxia is pursuing related products in five areas: inflammatory bowel disease, celiac disease, gastrointestinal acute radiation syndrome (GI-ARS), diabetes, and oral mucositis. In addition, Avaxia has identified many additional targets potentially accessible to oral antibody treatments.

PATENTS AND OTHER INTELLECTUAL PROPERTY

Avaxia has three issued patents and numerous other applications under review in the United States and other major market countries. Avaxia owns all its patent rights. (See Table E-5.)

Interestingly, Avaxia does not own patents for the use of anti-TNF antibodies to treat inflammatory bowel disease. Avaxia's lead product (AVX-470) targets inflammatory bowel disease.

PRODUCTS

Inflammatory Bowel Disease

Avaxia's most advanced product is an oral antibody treatment for inflammatory bowel disease (IBD). The treatment is currently in a Phase 1B clinical trial for patients with ulcerative colitis.

IBD includes two types of chronic inflammation of the intestines: ulcerative colitis and Crohn's disease. Ulcerative colitis affects only the colon in the large intestine; Crohn's disease primarily affects the small intestine. The primary symptoms are abdominal pain and diarrhea. Other symptoms can include vomiting, bleeding, and weight loss. These symptoms can significantly reduce the quality of life and increase the risk of life-threatening complications and diseases including cancer. Approximately 2.5 million people suffer from IBD globally.[29]

"TNF is an inflammatory cytokine that has been linked to IBD. To date, some of the most effective treatments for IBD are injectable anti-TNF antibodies. These antibodies bind to and neutralize TNF, which reduces inflammation."[30] Such injections may have "serious side effects from untargeted immuno-suppression—for example, lymphoma or reactivation of tuberculosis. Because of these side effects,

[29]According to the Centers for Disease Control and Prevention, "Each year in the United States, IBD accounts for more than 700,000 physician visits, 100,000 hospitalizations, and disability in 119,000 patients. Over the long term, up to 75 percent of patients with Crohn's disease and 25 percent of those with ulcerative colitis will require surgery." http://www.cdc.gov/ibd/, accessed December 18, 2013.

[30]Avaxia Biologics, Inc. website, <http://www.avarx.com>. Accessed September 14, 2015.

TABLE E-5 Avaxia Patents

Number	Patent	Year
8,268,971	Antibody therapy for modulating function of intestinal receptors and methods of treating diabetes and obesity	2010
8,182,818	Methods of using anti-TNF antibodies for treating radiation damage to the digestive tract	2010
8,071,101	Antibody therapy for treatment of diseases associated with gluten intolerance	2006

SOURCE: U.S. Patent and Trademark Office.

anti-TNF antibodies are most often used only as a second- or third-line therapy for IBD despite evidence that earlier use could improve patient outcomes."[31]

Avaxia Biologics has developed AVX-470, an orally administered anti-TNF antibody that accesses and neutralizes TNF from within the intestine. Preclinical studies showed that the "TNF-specific antibodies in AVX-470 were comparable to the existing anti-TNF drug Remicade® (infliximab) in terms of binding, functional activity, and some other characteristics. The initial preclinical work has been completed and has shown IBD efficacy. A 28-day GLP toxicology study showed no drug-related adverse effects up to the highest levels tested."[32]

Avaxia initiated a Phase 1B clinical trial of AVX-470 in ulcerative colitis patients in February 2013 after FDA cleared an IND for this trial in late November 2012. The results of this trial should be available by December 2013.

AVX-470 could transform IBD therapy by allowing an antibody-based therapeutic as a first-line therapy for IBD. Wider and earlier use would expand the anti-TNF market well beyond its current size of $2.5 billion annually.

In 2010, Avaxia received a Phase I SBIR grant for $213,589 from HHS to study oral anti-TNF antibody for inflammatory bowel disease. This was extended in 2012 with a Phase II grant for approximately $1.5 million.

Celiac Disease

Celiac disease is an autoimmune disease caused by an inappropriate immune response to gluten in ingested grains. The disease has a variety of clinical manifestations, including diarrhea, abdominal pain, osteoporosis, anemia, and an increased risk of diabetes and malignancies. The overall prevalence of celiac disease in the United States is approximately 1 in 133 for healthy people; incidence

[31]Ibid.
[32]Ibid.

is higher for less healthy individuals.[33] At present, no products on the market target celiac disease, and the only available treatment is a strict gluten-free diet.

Avaxia is developing orally administered anti-gluten antibodies for celiac disease. The antibodies will neutralize low levels of gluten in the small intestine and are designed for use with a gluten-free diet. The Avaxia product will primarily be taken with meals when low levels of gluten cannot be avoided (e.g., during travel, social, and business functions).

In 2011, Avaxia received a Phase I SBIR grant from HHS to further develop its 2006 patent for an oral antibody-based therapeutic for celiac disease.

Gastro-intestinal Acute Radiation Syndrome (Gi-ARS)

Damage to the gastrointestinal tract is one of the primary causes of morbidity and mortality following radiation exposure. Whether resulting from industrial mishap or a national security breach, a safe and effective treatment for damage to the GI tract is a crucial element of treatment for individuals exposed to high levels of ionizing radiation.

Avaxia's GI-ARS product will be a polyclonal anti-TNF antibody formulated as a dried powder sachet that is stable at room temperature and is reconstituted immediately before use. It could be stockpiled for use following a nuclear accident, attack, or explosion.

In 2012, Avaxia contracted with HHS's Biomedical Advanced Research and Development Authority (BARDA) to develop an orally delivered, anti-TNF antibody as a nuclear threat medical countermeasure for GI-ARS. This is a 2-year, $2.9 million contract that expands Avaxia's research on oral mucositis, a common side effect of radiation and chemotherapy treatments for cancer (see below). It also potentially opens the door to a radical expansion of Avaxia's business, as much larger contracts appear possible, according to Dr. Fox.

Oral Mucositis

Oral mucositis is a common and often debilitating side effect of cancer chemotherapy and radiation therapy. Patients experience painful inflammation and ulceration of the mucous membranes lining the mouth, and this problem is associated with increased mortality and morbidity. Current treatment involves systemic narcotics and the insertion of a feeding tube for nutrition. It also requires reduction in the dose and frequency of cancer treatment, which in turn leads to a significant decrease in both short-term efficacy and long-term disease-free survival.

Avaxia is developing a polyclonal anti-TNF antibody therapeutic to block the inflammatory cascade that is central to the development and worsening of oral

[33]Celiac Disease Facts and Figures, University of Chicago Celiac Disease Center, n.d., http:// www.uchospitals.edu/pdf/uch_007937.pdf, accessed December 18, 2013.

mucositis. In 2009, Avaxia received a Phase I SBIR grant for $125,242 from HHS to develop an anti-TNF antibody for oral mucositis, and in 2010 Avaxia received a related patent for the use of anti-TNF antibodies for treating radiation damage to the digestive tract.

FUNDING

Early in its history, Avaxia relied upon SBIR grants to advance development of its research antibody delivery platform. Recently, however, it has successfully engaged angel and early-stage venture investors.

Non-Dilutive Grants

Avaxia has received about $6.0 million in non-dilutive grants to support its research activities. It reports $2.9 million from a single 2-year grant from BARDA and $2.0 million from a series of four SBIR grants from HHS. The balance, around $1.0 million, included a loan from the Massachusetts Life Sciences Center.

Dr. Fox said that the BARDA award is expected to be the precursor of much larger awards as the technology proves out: the BARDA contract supports the R&D of an oral antibody therapy to mitigate the GI damage that follows potential radiation exposure after a nuclear incident. Should Avaxia's approach prove successful, BARDA is in a position to make awards at least an order of magnitude greater than the initial grant.

The connection to BARDA has reduced Avaxia's current interest in pursuing SBIR awards. Dr. Fox noted that the opportunities embedded in the BARDA program were very attractive and demanded a high degree of focus to execute. There was accordingly neither time nor resources available to pursue further SBIR awards outside the scope of the BARDA-funded project.

Equity Investment

In February 2012, Avaxia successfully closed on $4.1 million in Series A investment. These funds were used to manufacture oral anti-TNF antibody therapy for the Phase 1B clinical trial and to conduct final preclinical studies in advance of the trial. Building on this success, Avaxia successfully closed on $11.4 million in Series B funding in June 2013, adding venture and institutional investors to its capital table. (See Table E-6 for details.) The B round will enable Avaxia to complete its early-stage trial for AVX-470, manufacture sufficient drugs for its Phase 2 clinical trial, and provide some resources to design that study.

The B round of funding is particularly marked by the presence of corporate venture fund, AbbVie Biotech Ventures (ABVI). ABVI is a subsidiary of AbbVie pharmaceutical company and invests strategically to support AbbVie's business

TABLE E-6 Equity Investors for Avaxia Biologics, Inc.

Round	Investors	Amount (Millions of Dollars)
Series B	Cherrystone Angels, Golden Seeds, AbbVie Biotech Ventures (CVC—Abbot) NEW, Ariel Southeast Angel Partners NEW, Tech Coast Angels NEW, Beacon Angels, Boston Harbor Angels, Launchpad Venture Group, Mass Medical Angels, North Country Angels, Beta Fund, Granite State Angels, Keiretsu Forum, Maine Angels, and individual investors.	11.4
Series A	Cherrystone Angels, Golden Seeds, Beacon Angels, Boston Harbor Angels, Launchpad Venture Group, Mass Medical Angels, North Country Angels, Beta Fund, Granite State Angels, Keiretsu Forum, Maine Angels, and individual investors.	4.1
Total		15.5

SOURCE: Avaxia Biologics, Inc.

goals. AbbVie was spun out of Abbott Laboratories early in 2013 and includes Abbott's proprietary pharmaceutical business. It owns Adalimumab, which is the most successful IBD drug currently on the market.

Although this early institutional presence speaks to the strength of Avaxia's technology, ABVI did not receive any product rights from the investment, leaving Avaxia free to find other development partners. Nor does AbbVie have any first claim rights toward a potential acquisition of Avaxia. Avaxia management sees the investment primarily at least initially as an access point into AbbVie's expertise in gastroenterology. Dr. Fox observed, "We're pleased to have AbbVie join our board and engage their expertise in gastroenterology as we advance the development of innovative, gut-targeted therapeutics like AVX-470."[34]

Following the Series B, senior management is looking for a partner to license or co-develop the drug and to, in particular, help design a strong Phase 2 clinical trial and stabilize production of AVX-470. Such a partnership could provide a future pipeline into trials and then the market for other drugs in the portfolio.

AVAXIA AND SBIR

Dr. Fox has a strongly positive view of the SBIR program at NIH. She noted that it offered critical non-dilutive funding at an early stage, and also that it provided an important stamp of approval with potential investors.

[34]Business Wire, "Avaxia Biologics Closes Series B Financing with Total Proceeds of $11.4 Million," June 7, 2013.

One important and often ignored element of the SBIR program was in her view the need for persistence. Dr. Fox had applied for a number of NIH SBIR awards before receiving her first Phase I in 2009. She noted that many potential applicants become discouraged when they do not receive awards early on, and she thought that perhaps the agency could find ways to convey the need to persist to potential applicants.

As noted above, although SBIR played an important role in the first years of the company, Avaxia is now focused on its work with BARDA and consequently is not focused on pursuing further SBIR awards at this point.

It would perhaps be fair to conclude that unlike many SBIR awardee companies, Avaxia fits into a linear model of development: on the basis of a single Phase II award and two Phase I awards, it has attracted sufficient external funding to advance its technology and is now working on much bigger projects than can be supported through SBIR. It is of course too early to tell whether Avaxia will be a commercial success, but it has moved a substantial distance down that path.

UPDATE

Avaxia successfully completed the Phase 1B clinical trial of AVX-470 in ulcerative colitis and is currently pursuing private funding to advance the product into Phase 2. The company has been granted multiple patents in both the United States and foreign markets that cover the product for IBD. Since this summary was written, BARDA has discontinued its early-stage research activities, returning to its focus on late-stage development, and Avaxia was unable to secure additional funding from this source. Should Avaxia decide to continue to work on GI-ARS, it will likely apply to the National Institute for Allergy and Infectious Diseases for support through the SBIR program.

Conversion Energy Enterprises[35]

Meeting with
Barbara Soltz, CEO
January 31, 2014

Conversion Energy Enterprises (CEE) is a privately held business headquartered in Spring Valley, New York. In 1993, Barbara and Robert Soltz cofounded Conversion Energy as a consulting firm to develop design concepts for diode-based therapies. The company is currently developing products that use its proprietary light-activated collagen technology both to cause tissue adhesion and kill microorganisms.

According to Dr. Barbara Soltz, CEE began as a consulting firm focused on the design of lasers especially for the medical sector, after the closure of a McDonnell Douglass division ended her previous employment. In the early 2000s, CEE made a strategic decision to move into research and development, starting with the design of lasers. The company then decided to focus on a laser-related biological application, and determined that the best available market would be for a laser activated tissue adhesive. This eventually transitioned into a collagen-based light activated biologic that provides rapid wound closure, wound dressing, and repair, and attachment of surgical meshes or prostheses.

Most recently, CEE has improved and enhanced its technology to create a second product that added antimicrobial characteristics to its base product.

Conversion Energy currently operates two sites, its headquarters in Spring Valley, New York, and its laboratory facilities on the campus of the New York Medical College, Valhalla, New York.

PRODUCTS

Conversion Energy is developing two products. The first is a biological adhesive system to close and seal wounds, and the second a new product that builds on the adhesive system to provide a light-activated antimicrobial dressing with a significant bioburden reduction and low susceptibility of developing microbial resistance.

Tissue Adhesion System (TAS)

There are approximately 50 million surgeries annually in the United States, each requiring some form of wound closure.[36] Conversion Energy has developed

[35]Primary sources for this case study are the meeting with Barbara Soltz and a review of the Conversion Energy website and related company documents. http://www.conversionenergy.com.

[36]CDC FastStats, http://www.cdc.gov/nchs/fastats/insurg.htm.

a biological adhesive system based on light curing of a biological composite fabricated from collagen. Such biological adhesives reduce infection by eliminating foreign matter at the wound site. They also accelerate wound repair and reduce scarring of the healed tissue.

Conversion Energy's tissue adhesion system has been proven to reliably join large vasculature, skeletal, and gastrointestinal tissue. The collagen-based adhesive shows high strength (at least 10 times that of other sealants on the market or in clinical trials), is resorbable, and is non-toxic. Laser activation enables more precise placement of tissue welds.

The tissue adhesion system comprises four components: (1) a miniature laser, (2) an optical probe, (3) a surgical tool, and (4) the biological adhesive.

According to Dr. Soltz, the company has completed a series of preclinical trials to determine efficacy and safety including an expensive trial in pigs. These studies provided clear evidence of repair strength when compared to sutures and staples.

Antimicrobials

Approximately 2 million U.S. patients annually develop an infection at the incision site of a surgery, resulting in approximately 100,000 deaths annually.[37] The development of microbial resistance to antibiotics is limiting medicines capacity to treat such infections. CEE is presently developing light-activated collagen dressings that exhibit bactericidal effects with low toxicity and low susceptibility to microbial resistance.

In-vitro and in-vivo experiments have successfully demonstrated significant inhibition of bacterial growth for infections from microbes such as *Staphylococcus aureus*, MRSA, *Pseudomonas aeruginosa*, and *Escherichia coli*. Current research is intended to optimize CEE's technology to encourage wound closure and further reduce infection rates as a precursor to clinical trials and FDA approval.

The antimicrobial product has some significant differences to the original tissue adhesive system: it uses visible wavelength lasers that, according to Dr. Soltz, do not require expensive sensors needed to protect patients against laser burns at other wavelengths. The final commercial cost will be approximately the same for the two products.

Dr. Soltz noted that there are potentially different markets for the two products: for example, one large medical equipment company is interested in using the TAS for attaching electrical leads for pain management or monitoring; in this case antimicrobial effects would be unimportant.

[37]CDC, "Estimating HC Associated Infections," <http://www.cdc.gov/hai/pdfs/hai/infections_deaths.pdf>. These incidence and mortality figures are reported on the Conversion Energy website but are from a widely cited 2002 CDC report. It is likely that these numbers have increased. They are reported here to provide a rough order of magnitude.

BUSINESS STRATEGY AND ACTIVITIES

CEE has now largely completed its strategic transition into an R&D company, and is now working further to bring its two potential products to market. It has developed and patented systems that demonstrate the effectiveness of its light activated collagen-based technology for tissue adhesion and antimicrobial uses. The goal now is to obtain FDA approval for these applications and complete commercialization of these applications of its core technology.

The company faces some significant challenges in moving through the next phases. In order to prepare materials for Phase 1 clinical trials, CEE must find a materials provider experienced in collagen-based materials willing to provide batch level quantities from within an ISO 9000 certified environment, which the company's current location in a New York incubator cannot meet.

However, some funding has been provided by a potential partner, a large medical device manufacturer, and CEE is in discussions with two manufacturers to develop partnerships that will see the projects through the next stage of development. Ms. Soltz anticipated that these steps were likely to bear fruit in 2016.

CEE conducts R&D both in house and also with universities. Animals or in vitro tests tend to require collaboration with universities or research groups that have doctors on staff who can do the necessary surgeries. All processing of material, quality testing, and assembly of light devices is done in-house.

The company current faces two key challenges: (1) Finding a trusted source to manufacture low volumes of material under ISO 9000 conditions and (2) Funding expensive Phase 1 clinical trials.

The company anticipates that preliminary testing by a commercial partner will be completed by the end of March 2016 and that subsequent further partnerships will provide funding for the necessary clinical trials.

PATENTS AND OTHER INTELLECTUAL PROPERTY

At present, Conversion Energy is the assignee for the more recent patented technologies. The early patents (four) are assigned to TATI which is a holding company for CEE. A summary of CEE patent status is shown in Table E-7, Barbara Soltz et. al. have authored various patents for different elements of Conversion Energy's tissue adhesion system. Two patents related to its research on antimicrobials are listed in Table E-7 and were issued in April 2015.

SBIR AND OTHER FUNDING

The NIH RePORT database reports seven Phase 1 and three Phase 2 awards for a total commitment through SBIR by HHS of $3.16 million between 1997 and 2013.

Dr. Soltz stated that the SBIR program (along with STTR) had been a life saver for the company. Without SBIR funding, the business could not have been

TABLE E-7 Conversion Energy Patents

Status	Patent or Application Number	Title	Date of Issue of Application
Issued	US 6,939,364[a]	Composite Tissue Adhesive	Issued September 6, 2005
Issued	US 6,875,427	Light Energized Tissue Adhesive	Issued April 5, 2005
Issued	US 6,780,840[a]	Method for Making a Light Energized Tissue Adhesive	Issued August 24, 2004
Issued	US 6,773,699[a]	Light Energized Tissue Adhesive Conformal Patch	Issued August 10, 2004
Issued	US 7,704,247[b]	Dual FiberOptic Surgical Apparatus	Issued April 27, 2010
Issued	US 9,006,182[b]	Light Activated Composite Tissue	Issued April 14, 2015
Issued	US 9,012,406[b]	Light Activated Composite Tissue Adhesive	Issued April 21, 2015
Pending	Application #12/378,568[b]	Surgical Material Applicator	Initially filed February 17, 2009; Docketed new case June 17, 2012
Pending	Application #13/567,985[b]	Optical Bandage to Sterilize Wounds	Filed August 6, 2012
Pending	Application #14/647,113[b]	Surgical Mesh Joining and Fixation Using Photoactivated Collagen	Filed November 18, 2014

[a]Assigned to TATI, a holding company for Conversion Energy Enterprises.
[b]Assigned to Conversion Energy Enterprises.

launched. Instead, her group would have relied on consulting income, with products as a hobby at best. She remains very grateful for the opportunities it opened.

At the same time, Dr. Soltz said that there was one significant and growing problem with the program: the increasing tendency to make awards to university researchers rather than small operating companies. She participated in some NIH review panels, and was very concerned about this tendency. She believes that the heavy preponderance of academic reviewers tended to tilt the playing field toward university-based applicants (her most recent panel had two small business participants out of a total of eight). Not only did these researchers have significant advantages through access to the huge base of university resources (including low cost labor in the form of graduate students, facilities, and sometime university IP), but also they were in general much less prepared to turn good ideas into commercially successful projects.

Dr. Soltz also sees this new development as driving cost inflation in NIH SBIR projects. University overhead is, according to Dr. Soltz, an allowable cost and at rates of 50-60 percent or more can add very substantially to the overall cost of projects.

Dr. Soltz identified further potential sources of inflation generated from university-based projects. For example, some tended to load projects with additional (and expensive) consultants. One recent (approved) project included 10 consultants. And although animal studies are always expensive, they can become much more so when applicants insist on using premier providers. Dr. Soltz noted that there seemed to be little appetite inside selection reviewers to examine these types of costs and to push for more cost effective approaches. On the basis of participation in several review panels, she has concluded that most reviewers glanced at commercialization plans to primarily consider the potential of the project, but did not analyze commercial plans in depth. Reviewers have not been educated on this topic.

Danya International, Inc.[38]

Meeting with
Dr. Jeffrey Hoffman, CEO
October 30, 2014
Silver Spring, Maryland

Danya International is a private company founded in 1996 by Jeffrey Hoffman. Dr. Hoffman said that SBIR was key to funding the company, because Danya won four SBIR awards during its first year, which provided immediate revenue. The company designs, implements, and evaluates programs that address social issues. To manage such programs, the company has developed strengths in program management, communications, monitoring and evaluation, training and technical assistance, and information technology solutions and services.

The company focuses on public health communications, although as it has grown it has extended the types of services it offers. At present, it manages programs in health, education, and food security.

Danya has both government agencies and commercial businesses as clients. Among its public sector clients, Danya has served the U.S. Agency for International Development (USAID), U.S. Department of Defense (DoD), U.S. Department of Education (ED), U.S. Department of Health and Human Services (HHS), U.S. Department of Housing and Urban Development (HUD), U.S. Department of State (DOS), U.S. Department of Transport (DOT), and various state-level government agencies.

Danya is headquartered in Silver Spring, Maryland, and has other offices in Atlanta, Georgia, and Nairobi, Kenya. It currently has approximately 150 full-time employees and has access to a network of 400 consultants. Danya is affiliated with the Danya Institute (a nonprofit seeking to promote the health and well-being of individuals and communities) and the Danya Learning Center (an online continuing education resource for health care professionals).

Dr. Hoffman noted that although company size peaked at about 260 employees immediately before the financial crisis of 2008-2009, his company faces a changing economic and contracting environment. Over the past 2-4 years, government contracting has become much more competitive, and Danya is generally not eligible for set asides for small firms, which means that Danya now competes directly with firms such as Booz Allen and IBM. At the same time, SBIR awards are becoming more competitive in general and much more difficult to acquire for companies with limited commercialization records.

[38]Primary sources for this case study are the meeting with Dr. Hoffman, and a review of the Danya International website (http://www.danya.com) and related company documents.

CORE CAPABILITIES

Danya has developed broad competencies in program management, communications, monitoring and evaluation, training and technical assistance, and information solutions and services. Most of the company's revenue comes from government contracts.

Dr. Hoffman said that Danya's strategy was to use SBIR to develop new products and services, and then to find ways to commercialize them. However, the latter had provided to be an extremely difficult challenge. Danya had tried a number of strategies and had put significant resources into commercialization. Danya did have one significant commercial success, according to Dr. Hoffman. The company licensed its Living in Balance curriculum for publication by Hazelden, a publisher of health and education materials with a particular emphasis on support for addiction recovery.[39] This offering was very successful, with more than $4 million sold.

However, this success has not been replicated despite ongoing efforts to commercialize. Danya invested in new sales channels, and in an extensive overhaul of the website to encourage e-commerce, but none of this was very successful. At one point, Danya bought an existing website focused on autism, according to Dr. Hoffman, but the company soon determined that generating substantial sales would require a very significant upfront investment, and decided that this investment would be too risky. Danya then tried an ad-based model providing free resources, but this too failed to generate sufficient market traction. In addition, Danya worked with some interested associations to provide materials to their members, but this too failed to generate sufficient scale to be viable, again experiencing what Dr. Hoffman terms a "glut of free materials" in the market.

Dr. Hoffman believes that there are fundamental difficulties which essentially preclude commercialization of educational and support materials in the health care sector: competition from free sources is simply too great, particularly as other parts of the government (e.g., the Centers for Disease Control and Prevention) continue to publish high-quality resources at no cost to the user. The Substance Abuse and Mental Health Services Administration (SAMSA) is another major Federal source of free-to-the-user materials.[40] Thus while many SBIR projects are successful in terms of delivering as promised, they face an insurmountable barrier to commercial success.

In some cases, these materials can be sold if they meet detailed and specific federal requirements, but Dr. Hoffman noted that this has not been the case for Danya products. He also observed that being a federal contractor (such as Danya) can make it difficult to commercialize products. Not only are personnel attuned to the needs and rhythms of federal agencies rather than the market, but also there are significant compliance costs to federal contracting that require company

[39]See http://www.hazelden.org/web/public/storerecovery.page.

[40]See http://www.samhsa.gov/.

resources that could otherwise be devoted to commercial activities, and at the same time indirect costs can be used for writing further proposals, but cannot be used for sales and marketing. So it is not surprising that few small- to mid-sized federal contractors are also commercially successful.

Overall, Dr. Hoffman concluded that even generating substantial take-up when materials are provided free was a problem. Unless a product was adopted by a large organization, it was simply not feasible to expect that it would generate traction among users. In its early years, Danya developed a curriculum around phases of treatment for substance abuse. This approach was picked up by SAMHSA as a model, and was also now widely used in other countries. For example, it had been incorporated into legislation in Bulgaria. However, although the model was innovative there was no defensible IP (Danya has no U.S. patents on file), so in the long run Danya's own products did not benefit from substantial additional take-up.

Dr. Hoffman noted that a further core challenge was the need to develop a comprehensive product line if sales and marketing expenses were to be recouped.

Program Management

Danya has extensive experience managing large, complex multi-year programs for the federal government. It develops a custom management system for each program that emphasizes accountability and impact as the basis for program sustainability. Danya augments its cadre of experienced program managers with understanding of its program areas; competence in communications, monitoring, training, and IT; and knowledge of emerging methodologies that improve project outcomes.

Communications

Danya develops research-driven communications strategies to motivate behavior change (primarily around health) in target audiences. Potential barriers to behavior change can include infrastructure, geography, level of education, economic status, language, and culture.

Danya's methodology is an end-to-end marketing-based solution involving developing a segmentation, identifying messaging to target key segments, identifying multiple channels to deliver the message, and finally developing metrics that allow ongoing improvement of the overall communication strategy.

Monitoring and Evaluation

Designing data collection and monitoring into program implementation, Danya facilitates both ongoing and overall evaluation of program impact. The data collected through a mix of remote instrumentation, surveys, and interviews

is evaluated to improve program performance. Resulting findings are used to improve program performance and are integrated with findings from other programs to identify best practices and model processes.

Training and Technical Assistance

Danya has a strong capacity for training and technical assistance. Danya develops curricula to build local capacity. Danya delivers this content through a broad range of delivery methods. It can manage the meetings, materials, evaluations, and logistics of face-to-face training both domestically and internationally. With the rise of the Internet, Danya has also developed extensive competence providing online training through webcasts, e-briefings, distance learning, and collaborative portals.

Information Technology Solutions and Services

Danya is committed to using technology as a basis for its communications, monitoring, and training activities. The company develops content (e.g., websites, interactive databases, e-learning modules, dashboards, 3D animation, and interactive games) and uses a broad range of technologies to deliver and monitor this content (e.g., mobile phones, the Internet, radio, television, and traditional publishing). Maintaining these technical capabilities is crucial to Danya's continued success.

SBIR

Danya International has received support from SBIR. Overall, the company has received 70 Phase I awards and 33 Phase IIs, starting in 1997 and concluding in 2010, providing a total of $45 million in SBIR funding.[41]

In fact, during the early stage of the company, SBIR funding around public health communications from National Institute on Drug Abuse (NIDA) was a crucial source of support for the first year of Danya's existence. Dr. Hoffman said that even after winning initial awards in its first year, Danya experienced a serious liquidity problem, and that the acquisitions of three Phase II awards constituted a major turning point for the company. Overall, SBIR provided critical funding to grow the company to acquire the skills needed to expand the company as a government contractor.

Danya also leveraged its SBIR awards effectively in some cases. For example, SBIR awards on HIV and STD prevention for youth translated into a major long-term contract worth about $13 million annually (under a small business set-aside). This was recently broken into a series of small contracts, and

[41]NIH RePORTER awards database, accessed December 10, 2014.

although Danya did win the health communications component, this is worth only $1.7 million annually.

Similarly, Danya leveraged its expertise to experiment with work in development, and opened an office in East Africa. Once again, though, while the project itself was reasonably successful, this effort to diversify has yet to succeed to get to sufficient scale.

Danya is, according to Dr. Hoffman, now effectively blocked from further SBIR grants at NIH because it has not successfully commercialized previous awards.

RECOMMENDATIONS

Dr. Hoffman had a number of suggestions and recommendations for the program:

- Focus on fewer larger projects. Scale is so critical to commercial success that efforts should be focused on projects that may get to scale. Currently, the SBIR program is not designed to address this issue. He welcomed the eligibility of venture-funded companies as another source of commercial discipline for SBIR firms.
- Bias toward science. At the same time that SBIR has become much more competitive and selective, the selection process has tilted further toward science rather than commerce. Commercialization reviews at NIH are "fairly generic," not a careful return on investment (ROI) analysis of the potential for a product. This helped Danya acquire a considerable number of awards but in the long term the company might have benefited from more rigorous commercial review.
- Investment in sales and marketing. SBIR awards need to include more commercial activities. Even great products need marketing: Danya's autism products are highly reviewed, but an extensive outreach campaign for example through Google would cost $100,000, and all of that would be unallowable under SBIR awards.
- Program managers. Program managers generally come from research programs, and although they encourage commercialization they add little value toward it. A different kind of manager, or additional support, would be helpful.

GMS Biotech[42]

Meeting with
Dr. Michael Hogan, CSO and Co- founder
September 30, 2014

GMS Biotech (formerly trading as Genomics USA[43]) is a privately held business headquartered in Austin, Texas, with laboratories in Tucson, Arizona. Co-founded in 2004 by Drs. Krishna Jayaraman and Michael Hogan, the company owns technology to support scalable, high throughput microarray technology for testing bio-samples for Human Leukocyte Antigens (HLA).

This GMS Biotech technology turns high-resolution DNA analysis into a benchtop test that can be performed with simple equipment and little training. The technology is protected by multiple patents.

In addition, GMS Biotech has—with SBIR funding—developed a novel "Raw Sample Genotyping" technology that allows raw blood or buccal swabs and saliva or dried blood spots to be genotyped directly without the need for DNA purification. This eliminates both DNA purification and DNA quantitation from the sample preparation workflow."[44]

Dr. Hogan described the company's technology as potentially engaging multiple markets and opportunities. Initially, the company aims to sell into ASHI-certified[45] transplant center labs while undertaking the FDA 510k certification process. Once that is completed, the company expects HLA testing to become a core component of personalized medicine with HLA analysis enabling custom design of vaccines, antimicrobial treatments, and therapies for autoimmune diseases.

In a success story published on the NIH website, the company noted that beyond organ transplantation and vaccine response, there is now very strong evidence that personal variation in the HLA genes is also directly related to personal variation in the risk of viral infection; the risk of inflammatory joint disease; drug sensitivity such as Abacavir in HIV-infected patients. Some experts argue that HLA testing should be performed as part of routine childhood and adult vaccination, and for that reason, HLA-testing could become the first complex genetic test to be given routinely at birth, as part of the standard neonatal screening panel. The HLA-Chip product was developed, from its inception, to meet

[42]Primary sources for this case study are a meeting with Dr. Michael Hogan and a review of the GMS Biotech website (http://www.gmsbiotech.com), the legacy Genomics USA website (http://www.gencomicsusa.com), and related company documents.

[43]In July 2010, Genomics USA rebranded itself as GMS Biotech.

[44]NIH Self-Reported Success Stories, http:// http://archives.nih.gov/asites/SBIR/08-19-2015/statistics/self-reported-success.html/.

[45]The ASHI certification is owned and managed by the American Society for Histocompatibility and Immunogenetics (which despite its name is an international organization). The European Federation for Immunogenetics performs a similar function, but has fewer members.

such large-scale clinical and public health needs, and consequently, we view the entire 12,000 test per day neonatal screening market to be a realistic sales goal within the next 5 years."[46]

The technology provides potentially substantial time and cost savings. The company claims that pre-test DNA processing can cost as much in time and labor as the genetic test itself, and that its technology offers savings on the order of 80 percent of cost and 50 percent of time.

To date, the company has depended primarily on SBIR funding to support development of its microchip technology. It received SBIR funding to initiate FDA's 510(k) premarket approval process in 2009, and hopes to have a micro-array testing product in the market by 2016. According to Dr. Hogan the current phase of FDA testing should be completed for the first products by the mid-2016.

Dr. Hogan noted that market strategy had evolved to focus on ASHI-certified transplant center labs. These labs (he noted that the overall number shifts but is about 4,000 worldwide) meet a strict international standard for their operations, which is independent of FDA certification. This market is therefore not as dependent on FDA certification and processes, and substantial sales can occur before FDA certification is complete.

In addition to SBIR funding, external investment has come from a variety of sources, including the Arizona Technology Investor Forum, an organization for angel investors.

TECHNOLOGY

HLAs are a set of genes that encode for the proteins responsible for control of the immune system in humans. At present, HLA testing is predominantly limited to identifying recipients that are likely to be successful matches for organ transplants. However, HLAs figure importantly in triggering the immune response to both disease and cancer and in the process of certain autoimmune diseases. Given the importance of HLA in understanding the human disease process, HLA testing will likely become an important element in the development of individually customized medicine.

Unfortunately, current techniques are complicated—most require DNA purification of samples as an intermediate step—and consequently do not scale well at a reasonable cost.

GMS Biotech has developed a microarray technology for detecting variations in the HLA genetic sequence. Although other HLA-based microarray tests do exist, Dr. Hogan noted that these are research tools not suited for clinical or public health screening. GMS Biotech technology in contrast provides a high-resolution, low-cost micro-array platform for performing HLA DNA testing at scale.

[46]NIH, "SBIR and STTR Success Story for Genomics USA," 5/12/2011. http://grants1.nih.gov/grants/funding/sbir_successes/3140.htm, accessed August 29, 2014.

PRODUCTS

Using SBIR funding, GMS Biotech is developing products based on its HLA microchip technology plus associated sample image analysis tools, which together support population-scale HLA-typing.

GMS Biotech HLA Microarray

A DNA microarray is a collection of DNA spots attached to a solid surface. Each DNA spot contains a small amount of a DNA sequence called probes. In the presence of a target DNA sequence, the spot luminesces; the more light produced, the higher the concentration of the target string. Light sensors detect the variation in bioluminescence.

GMS Biotech specific products targeting the transplant market include EZMatch™—a microarray supporting identification of possible solid organ and bone marrow transplant candidates—and EZScreen™—a microarray enabling identification of specific donor antibodies that may cause rejection. This is a highly sensitive native state antibody screening and monitoring assay for the accurate detection of Donor Specific Antibodies (DSA), for use both before and after a transplant, and is expected to be much more cost-effective than current approaches. EZScreen™ is currently in development, and is expected be available for ASHI lab use in late 2016.

SBIR has provided $9.2 million in funding to support development of the GMS Biotech core probe technology and the development of microarrays. In addition to HLA, GMS Biotech has developed microarray technologies both for determining the progression and therapeutic response for different patients with HIV/AIDS and also for performing blood typing.

Software Tools

GMS Biotech offers a software visualization tool called "Ricimer™"—which is a Data Analysis Software package—to interpret information captured from the microarray. The output for an entire microarray can be viewed with color coding, indicating the intensity of photoluminescence for each probe in the microarray. The software interprets the pattern, providing the HLA type of a sample even to an operator with minimal training.

PATENTS AND OTHER INTELLECTUAL PROPERTY

GMS Biotech owns five patents on the core microarray sensing technology and its scaled application to HLA typing. (See Table E-8.)

TABLE E-8 GMS Biotech Patents

Patent Number	Patent	Year
8,771,951	Methods for PCR and HLA typing using raw blood	2014
8,575,325	Population scale HLA-typing and uses thereof	2013
8,183,360	Population scale HLA-typing and uses thereof	2012
7,667,026	Population scale HLA-typing and uses thereof	2010
7,354,710	Methods and devices based upon a novel form of nucleic acid duplex on a surface	2008

SOURCE: U.S. Patent and Trademark Office. Accessed August 15, 2014.

FUNDING

Since 2004, GMS Biotech has relied mostly on SBIR and other grants to support its research. It has also received sporadic equity investments.

Non-Dilutive Grants

Between 2004 and 2015, SBIR funded six projects with GMS Biotech. GMS Biotech received 14 awards amounting to $9.20 million from HHS to develop scalable microarray technology for performing HLA typing.

Equity Investments

GMS Biotech has sporadically received equity funding from both corporate and individual investors. It has not been a major source of support for operations. Most recently, in June 2013, GMS Biotech offered $3.29 million in equity; it raised $1.2 million in seed funding from a group of 24 early-stage investors.[47]

Prior to that, in May 2006, GMS Biotech received $200,000 from Quantrx Biomedical—a developer of genomics-based diagnostic products—in exchange for 144,000 in shares (roughly 10 percent of the shares then outstanding). In January 2007, Quantrx provided GMS Biotech an additional $200,000 through an 8 percent promissory note. QuantRx was interested in acquiring GMSBiotech and had presented a term-sheet, however, QuantRx could not raise sufficient capital and the acquisition was not completed. Quantrx sued GMS Biotech to recover the loan capital. In May 2013, both parties agreed to a monthly payment plan

[47]Genomics USA, Form D, Notice of Exempt Offering of Securities, (June 11, 2013), http://www.sec.gov/Archives/edgar/data/1577606/000157760613000001/xslFormDX01/primary_doc.xml.

stretching over the next 18 months.[48] In 2014 GMS Biotech had paid in full any remaining outstanding payments owed to Quantrx under the agreement.

SBIR

Dr. Hogan said that SBIR was critical for the progress made at GMS Biotech: "We would never have made it otherwise." All of the company's initial R&D was based on SBIR, funding that continued through Phase IIB. The company only sought series A funding after that research was completed.

In looking at grant funding more generally, Dr. Hogan is a strong supporter of the gated approach that underpins SBIR. He believed that current practice at NIH of funding large multi-year RO1 awards for academic investigators would be much improved by the adoption of such a gated, milestone-based approach. Early high-risk work could be funded initially with subsequent implementation and testing funded only after initial milestones were met. He believed that the traditional RO1 structure had made NIH too conservative, as large investments were being made at a very early stage in the process. He noted a recent RO1 for $10 million at NCI as an example of the decision pressures incurred in the traditional approach.

Dr. Hogan said that Phase I awards (with the possible exception of the AT program at NAIAD) were still too small, and that he would prefer to see NIH fund fewer, larger Phase I awards. He believed this was necessary to attract higher quality proposals given the risks incurred in revealing IP during the application process. An average of $200,000 per award or even $300,000 per award would be appropriate.

Dr. Hogan was concerned about the likelihood that potential competitors would see proprietary information in the course of review. However, he noted that he "preferred competitors to incompetents."

To improve the quality of reviewed applications, Dr. Hogan said that he thought NIH should explore the adoption of a white paper approach that could draw on the experience at NSF and the Department of Energy (DoE).

Dr. Hogan noted that the quality of reviews and management were both excellent at DARPA, which did an excellent job of organizing and vetting high-tech advanced ideas. At NIH, the quality of management varied. His experience with staff at NCI, NIAID, and NHLBI was very positive: in general they took personal ownership of projects and uses study sections as expert consultants whose reviews could be folded in the program manager's understanding of programmatic needs, which they would then present strongly to the Institute's governing Council.

[48]Quantrx Biomedical Corporation, FORM 10-K/A, (December 31, 2011), Minority Investments, http://www.sec.gov/Archives/edgar/data/820608/000141588912001711/qtxb10ka12312011.htm; Quantrx Biomedical Corporation, FORM 10-Q, (March 31, 2014), Legal Proceedings, http://www.sec.gov/Archives/edgar/data/820608/000141588914001649/qtxb10qa_march312014.htm.

This approach reflects Dr. Hogan' strong belief that the "study section reviewers should not be king—they should be viewed as important high level consultants, not decision-makers." On the other hand, he noted that the lack of a time limit on the program manager positions meant that programs could get stuck in specific technological tracks and that there were also risks of the emergence of an old boy's network of persistent winners.

The Phase IIB program is in Dr. Hogan's view an excellent idea. He noted that the valley of death is a large and growing problem, and that such a program is critical given the absence of other NIH funding and declining interest in early-stage investments from venture capitalists and large pharmaceutical companies. In the current environment, he believes it is extremely difficult to attract outside funding if the company did not have a product ready to sell: it was not necessary to have substantial sales, but some sales did have to be at least imminent.

However, Dr. Hogan believes that at least on the personnel side, the 10-page proposals required for Phase IIB are little better than polite fiction: Phase IIB does not fund any commercial or marketing personnel, but these are of course absolutely necessary for a commercial venture which is what Phase IIB is designed to help fund. He recommended that either NIH or Congress consider changing these limitations to permit a more realistic approach, in which some limited amount of Phase IIB funding—perhaps 30 percent—could be used for commercial activities. He thought this could be a transformative change for Phase IIB companies: Phase IIB should not just be funding for FDA review but also for the shift toward commercial activities.

Dr. Hogan also observes that Phase IIB did not provide sufficient funding to complete FDA review. Although $3 million was not insignificant, it was still considerably less than required to meet the program's goals (he estimated that completion of FDA review would cost about $6-9 million). Currently, Phase IIB provided enough money to enter the regulatory structure, hire consultants, put quality systems in place, and begin to pay for the start of studies. He therefore recommended that the maximum size of Phase IIB awards should be increased to $5 million, and should permit funding of business personnel to perform functions mandated by the required business plan.

Dr. Hogan also noted that the timeframe of the Phase IIB is somewhat unrealistic: moving from the end of Phase II to marketing a product (as a medical device or a drug) in 3 years would be extremely fast track to get market. He suggested that perhaps NIH should add optional additional years of support. It should also expand allowances for indirect costs.

Lpath Therapeutics, Inc.: SBIR Case Study[49]

Meeting with
Dr. Roger Sabbadini, Founder
June 17, 2014
San Diego, California

Over the past 10 years, bioactive lipids have been implicated in numerous disease processes. This new field, called lipidomics, examines how, within biological systems, lipids provide signaling pathways between various biological processes. Bioactive lipids have a crucial role in the regulation of a wide range of important cellular phenomena such as cell growth, death, senescence, adhesion, migration, and inflammation.[50]

Lpath, Inc. is a publicly traded company (NASDAQ: LPTN) headquartered in San Diego, California. Founder Professor Roger Sabbadini spun Lpath out of San Diego State University in 1997. Lpath is developing monoclonal antibody based therapeutics that neutralize bioactive lipids involved in regulating a whole range of disease processes such as cancer, cardiovascular disease, diabetes, neurological disorders, immune function, pain, and inflammation. At present Lpath has one product candidate in clinical trials and several in pre-clinical evaluation.

Researchers believe there are at least 1,000 bioactive lipids in the human body that become dysregulated in disease and can be potential drug targets. As important to the long-term success of Lpath as its product pipeline is the ImmuneY2™ drug-discovery engine. Having defined a target lipid, Lpath uses the ImmuneY2™ process to develop antibody product candidates for that lipid.

Lpath did not accept venture capital, as many biotech companies do, to fund its clinical trials. Instead, it has paid for the Phase 1b/2a trials of its lead product candidates by selling exclusive rights to pharmaceutical companies such as Pfizer and Merck-Serono and by raising additional capital through the sale of stock on the public markets. In addition to developing and patenting its own technical capabilities, Lpath has acquired patents to enhance its own capabilities.

Lpath outsources manufacturing and clinical development activities to contract research organizations and contract manufacturing organizations. Retaining such third-party specialists is common within the biotech industry.

Lpath leases an 11,960-square-foot laboratory and office facility in San Diego, California. It currently has 15 employees, of which 10 have advanced degrees.

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[49]Primary sources for this case study are the meeting with Dr. Roger Sabbadini and a review of the Lpath, Inc. website (http://www.lapth.com) and related company documents and SEC filings.

[50]Yusuf Hannun and Lina Obeid, "Principles of Bioactive Lipid Signaling: Lessons from Sphingolipids," *Nature Reviews Molecular Cell Biology* 9:139-150 (February 2008).

EVOLUTION OF RELATIONSHIP WITH SAN DIEGO STATE UNIVERSITY (SDSU)

SDSU let Dr. Sabbadini incubate a company on campus in an academic lab, renting academic lab space at above market rate to ensure that there was no question of university subsidies for Lpath activities. The company also reimbursed the university for Dr. Sabbadini's time and fully supported all the work of graduate students engaged in company projects. It was designed in part as a biotech incubator, training students in academic and applied science related to biotech. Some students got joint MBAs.

As a faculty member, Dr. Sabbadini was required to assign all IP to SDSU. However, after 2 years of waiting, it became clear that SDSU had no intention of filing any patents related to the work, and SDSU eventually reassigned the rights back to Dr. Sabbadini. He started the company immediately, using $7,000 of his own money to file the first patent.

Dr. Sabbadini has remained engaged in academia at SDSU, where he has excellent relationships with the administration; a number of the students have also become Lpath employees. The company's first spinoff (Vaxiion) is run by a former PhD/MBA student, Matt Giacalone, who received his degrees at SDSU under company sponsorship.

TECHNOLOGY

Lpath describes its ImmuneY2™ technology platform as a crucial part of its business strategy. ImmuneY2™ is a series of proprietary processes developed by the company to allow development of other monoclonal antibody therapeutics for any given bioactive lipid.

PRODUCTS

Currently Lpath has three products in its pipeline. One began passage through the FDA's regulatory process and early clinical development is being conducted under an approved Investigational New Drug (IND) designation for clinical trials. Two other products have already completed Phase 2 clinical trials.

iSONEP™

iSONEP™ is the lead product in Lpath's product portfolio. It is a humanized monoclonal antibody (mAb) effective against sphingosine-1-phosphate (S1P) and formulated for use in the treatment of eye disease. iSONEP™ is administered by intravitreal injection and has demonstrated multiple mechanisms of action relevant to diseases of the eye. Potential applications include "wet" age-related macular degeneration (wet AMD), dry AMD, diabetic retinopathy, and glaucoma-related surgery.

In 2009, Lpath completed a Phase 1 clinical trial for iSONEP™, which showed that all patients in the trial could tolerate it. Positive biological effects were also observed, with the most common being regression of the disease process that leads to degeneration of the macula.

Large pharmaceutical companies were apparently impressed. "In December 2010, Lpath entered into an agreement with Pfizer" to provide an "exclusive option for a worldwide license to develop and commercialize iSONEP."[51] Under the agreement, Pfizer provided Lpath with an upfront payment of $14.0 million and agreed to fund the costs of the planned Phase 2a clinical trials, bringing additional Pfizer's payments to Lpath of $23.0 million for the co-development of iSONEP.

Through SBIR, Lpath received $4.70 million in funding to develop the iSONEP™ monoclonal antibody to neutralize the S1P lipid for ocular indications and it is the results of this funding that led to the completion of the Phase 1 safety trial in wet-AMD patients and the resulting Pfizer deal. The Pfizer supported trial was a multicenter, Phase 2 "Nexus" clinical trial evaluating iSONEP™ in patients with wet AMD patients who had not responded adequately to existing anti-vascular endothelial growth factor (VEGF) therapies including Lucentis®, Avastin® and Eylea, The Nexus Trial was a prospective, randomized, double-masked, positive control, Phase 2 clinical trial conducted in the United States that enrolled 158 patients with wet AMD. All enrolled patients had been sub-responsive to treatment with anti-VEGF drugs, and had received at least three previous injections of an anti-VEGF drug. Nexus study patients each received four intravitreal injections over the 90-day dosing period. There were approximately 39 patients in each of the four treatment arms. The pre-specified primary endpoint of the study was mean change in best corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) from Day 0 to Day 120. At day 120, patients who received intravitreal injections of (i) 4.0 mg iSONEP alone lost a mean of 3.17 letters on the ETDRS, (ii) a combination of 0.5 mg iSONEP and anti-VEGF therapy gained a mean of 4.22 letters, (iii) a combination of 4.0 mg iSONEP and anti-VEGF therapy gained a mean of 3.63 letters, and (iv) an anti-VEGF therapy alone gained a mean of 4.34 letters.

BCVA and anatomical endpoints were collected throughout the 9-month period. The data collected suggests that in this study iSONEP was safe and well tolerated across all dose levels when administered alone or in combination with anti-VEGF therapy. Thus, patients in this trial did not show any statistically significant improvement in visual acuity when treated with iSONEP as an adjunctive or monotherapy. Full study results will be presented during the Retina Subspecialty Days in conjunction with the American Academy of Ophthalmology in Las Vegas, Nevada, in November 2015.

[51] PR Newswire, http://www.prnewswire.com/news-releases/lpath-provides-update-on-plans-for-isonep-option-226956521.html.

ASONEP™

Between 2008 and 2010, ASONEP™ was the lead product in Lpath's product pipeline. Like iSONEP™, it is a humanized monoclonal antibody (mAb) effective against sphingosine-1-phosphate (S1P), but it has a systemic formulation designed to target S1P's role in the cancer.

Like iSONEP™, ASONEP™ was developed in collaboration with a large pharmaceutical company as a partner after demonstrating preclinical efficacy with SBIR support from the National Cancer Institute. In October 2008, Lpath entered into a licensing agreement with Merck-Serono to develop and commercialize ASONEP™. Lpath provided Merck-Serono exclusive worldwide rights to ASONEP™ across all non-ocular indications. In early 2010, Lpath completed a Phase 1 clinical trial in which ASONEP™ was shown to be well tolerated at all dose levels. Moreover, more than half the patients that completed the treatment showed positive biological effects.

Even though the technical partners at Merck-Serono remained highly positive about Lpath and about the partnership, changes at a more senior level undermined the relationship. Problems arose before Phase 2 clinical trials focused on cancer. Senior management at Merck-Serono was faced with budgetary difficulties as more internal projects than expected had come successfully through initial clinical trials and hence required more funding than anticipated. As a result, funding for external partnerships was reduced and the Lpath agreement unraveled.

Merck-Serono sought to renegotiate the terms to reduce its commitment, but the Board of Lpath rejected this offer. The Board contains a number of financial investors who preferred for Lpath to retain all rights to what was seen as exciting technology; as a result, Lpath had to develop several new capabilities of its own—for example, hiring an entire group of oncology researchers. Merck relinquished all rights to the ASONEP™ development program. Lpath received $17.0 million from Merck-Serono over the course of the licensing agreement. Lpath is collaborating with researchers at various medical research institutions and with continued SBIR support undertook a small Phase 2 study for ASONEP™ in the treatment of renal cell carcinoma in patients who have failed up to three standard-of-care treatments such as mTOR and/or VEGF tyrosine kinase receptor inhibitors. This trial recently completed enrollment of 40 mRCC patients (37 net). There was some evidence of biological activity in some patients with progression free survival (PFS) as the primary efficacy endpoint as 14 of 40 patients (~35 percent) showed PFS at 4 months, 8 of whom were progression-free for at least 6 months, of which 3 patients remain progression-free for over 20 months. Four patients exhibited partial responses (PR) at some point during the study.

Lpath has received $4.26 million in funding from SBIR and the National Cancer Institute to develop ASONEP™, a monoclonal antibody to neutralize the S1P lipid for cancer indications.

Lpathomab™

Lysophosphatidic acid is a bioactive lipid that plays a major role in cancer-cell growth and metastasis in a broad range of tumor types. It has also been linked to neuropathic pain, traumatic brain injury, and pulmonary fibrosis. Lpathomab™ neutralizes lysophosphatidic acid.

Lpath has developed methods to reliably produce this antibody for clinical trials. Lpathomab™ received Investigational New Drug (IND) designation in mid-2015. The first cohort of subjects have been dosed in the Phase 1 clinical study with Lpathomab™. This is a double-blind, placebo-controlled, single ascending dose study designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of Lpathomab in healthy volunteers. The study also aims to establish a maximum tolerated dose for future clinical studies in patients with neuropathic pain. Lpathomab is an antibody targeting lysophosphatidic acid, or LPA, a bioactive lipid that has been characterized in the scientific literature as playing a key role in nerve injury and neuropathic pain. Lpath's preclinical studies showed strong *in vivo* results with Lpathomab in several different pain models, which suggest that LPA may be an attractive target across a variety of chronic pain conditions, including diabetic peripheral neuropathy, post-herpetic neuralgia, chemotherapy-induced neuropathic pain and pain associated with lumbosacral radiculopathy. Other preclinical studies have also demonstrated the potential for Lpathomab as a treatment for traumatic brain injury.

Lpath is looking for a partner to defray the cost of commercializing Lpathomab™.

Lpath has received $0.51 million in funding from SBIR to develop Lpathomab™ as a therapeutic treatment for traumatic brain injury and diabetic nerve damage.

Other Indications

Lpath also has a pair of other products named Altepan™ and Nextomabs against various other bioactive lipid targets. Altepan™ targets a class of cysteinyl leukotrienes involved in asthma and inflammation. Altepan is is being studied in models of inflammatory bowel disease, respiratory disease, and inflammation. These therapeutic antibodies are in the research stage, and although mentioned on the website they are not reported as material in any financial filings made by the company.

PATENTS AND OTHER INTELLECTUAL PROPERTY

For a small company, Lpath has invested substantially in its patent estate and believes that this portfolio "will provide broad, commercially significant coverage

of antibodies, receptors, enzymes, or other moieties that bind to a lysolipid . . . for diagnostic, therapeutic, or screening purposes."[52]

In its most recent SEC filings, the company reports 55 U.S. patents and patents pending and 141 patents and patents pending internationally. Lpath has received 16 U.S. patents covering the development of its iSONEP™, ASONEP™, and Lpathomab™ products. Also, when Ataigin Technologies, Inc. bankrupted, Lpath acquired eight of its patents related to cancer diagnostics.[53]

FUNDING

Since 2004, Lpath has utilized various sources of funding, totaling roughly $74 million. SBIR has provided $10.2 million, the public markets an additional $26.0 million, licensing agreements $37.0 million, and royalties $0.4 million.

Non-Dilutive Grants

Between 2004 and 2014, NIH funded 11 SBIR projects with Lpath, providing 16 awards amounting to $10.2 million to develop monoclonal antibodies for neutralizing bioactive lipids. These covered 11 projects including three Phase II awards and one bridge commercialization award.[54]

Equity Investment

Lpath, Inc. was founded in September 1997 as Medlyte Diagnostics, Inc. Management changed the name to Medlyte, Inc. in July 2001 and to Lpath Therapeutics, Inc. in July 2004. Dr. Sabbadini said that early-stage research and company development was mostly about proving the technology and thus creating a clear path to commercialization. Once that stage was completed, the company could become a real business venture rather than an idea or concept, and should, he believed, be run by professional management. In 2005, Dr. Sabbadini gave up the management role and hired Scott Pancoast, a Harvard MBA, as CEO and president. Gary Atkinson is Lpath's current chief executive.

Shortly after, Lpath successfully engineered a reverse merger that allowed it to merge into a shell company with a NASDAQ listing. This in turn allowed the company direct access to capital markets which it has utilized five times, raising a total of $40-50 million starting in 2008.[55]

[52]"Patent Portfolio," http://www.Lpath.com/about-Lpath/patents/.
[53]U.S. Patent and Trademark Office, accessed June 27, 2014.
[54]NIH RePORTER, accessed June 27, 2014.
[55]LPATH INC (LPTN) SPO, http://www.nasdaq.com/markets/spos/company/Lpath-inc-417990-55184.

LPATH AND SBIR

Dr. Sabbadini has extensive experience with SBIR, both as a grantee and as a member of study sections for both SBIR and RO1 awards. He offered a number of observations with regard to the program at NIH.

SBIR was a critical source of funding during the company's early years when little funding was available. SBIR truly helped Lpath bridge the valley of death when it was not possible to get outside financing or corporate partnerships. Lpath proved that it was possible to make real steps forward with relatively small amounts of money.

After access to capital markets became available, SBIR was used for different purposes. Although Lpath was very successful at tapping capital markets, some projects were seen as simply too risky by the investment community: for example, work on traumatic brain injury (TBI). There have been more failures in this area than almost any other biomedical problem, but it is a huge potential market where there are no FDA-approved products. In most cases, investment money is also "herd money," and investors will not fund such a high-risk proposition. Neither will big pharmaceutical companies for the same reason. And although small biotech companies like Lpath can take the chance on a risky activity, investors like to share the risk, because they prefer a clear path where there are already products in the market. SBIR funding shares the risk and provides not just the risk share but also the peer review and the validation that NIH is funding the project.

Dr. Sabbadini used SBIR to pursue TBI in part because there was resistance to using internal funding for such a speculative project. He said that the recent NINDS grant funded the most exciting project he had ever worked on, with the most long-term potential for commercial success.

Overall, Dr. Sabbadini was a strong supporter for the NIH SBIR program: "I love the SBIR program—would still review and support it even if I never got another SBIR. It is critical to innovation in this country; without SBIR lots of innovation would die on the vine." He also offered two recommendations for improving the program:

More flexibility in the application process. Dr. Sabbadini said that the application process is onerous, dysfunctional, and stifling, and applicants are punished for minor errors. One Lpath application was rejected because one word in an import data field was in lower not upper case. Another revised application was rejected for using a font of the original, amended application which had since been disallowed in the interim. While the revised application was submitted well in advance of the grant deadline, the error was identified only after the grant deadline had passed. Administrative review should be used to fix minor errors, not reject small companies because of them.

NCI Phase II Bridge awards. Dr. Sabbadini believes that other institutes should follow NCI's example. He now sits as reviewer on bridge awards. He also participates in partnering conferences which link up awardees with pharmaceutical companies and venture capital. His experience is that these are very effective.

NOVA Research Company[56]

Meeting with
Paul Young, Executive Vice-President and Co-Founder
January 23, 2014
Bethesda, Maryland

NOVA Research Company (NOVA) is a privately held woman-owned small business headquartered in Silver Spring, Maryland. NOVA was founded in 1986 by Ms. Peggy Young, a research biochemist with a strong marketing background, and her husband, Mr. Paul Young. The company provides research support services to a broad range of government, industry, not-for-profit, and university research organizations. Of particular importance to NOVA as clients are NIH and the Centers for Disease Control and Prevention (CDC).

According to Mr. Young, the company's first major client in 1987 was the National Institute on Drug Abuse (NIDA), for whom NOVA served as national data coordination and evaluation center on a multidisciplinary research project focused on HIV/AIDS. The project—focusing on prevention in hard-to-reach populations—started with 6 grantees and later expanded to 24 grantees. A subsequent NIDA contract focused on community-oriented HIV/AIDS prevention interventions across 61 sites. These projects were large and complex. They required a broad spectrum of services, including design of questionnaires, quantitative (survey) and qualitative (interview) data collection, data management and analysis, and training for interviewers.

NOVA found that there were inadequate electronic tools available to support this effort (which occurred early in the era of laptops). At that time (late 1980s) interviewers typically used paper-and-pencil questionnaires, because interviews took place in the field and laptops were generally bulky to carry or not available. NOVA adapted a touch screen for use with desktops and laptops, and this was used to generate self-interview electronic records for interviewees who were not computer literate or comfortable with keyboards.

These interviews probed in very sensitive areas related to drugs used, sexual behavior, and other personal topics. NOVA found through analysis of answers that responses were biased by gender and other factors; researchers also found that using computer-generated audio prompts instead of live interviewers generated more truthful responses.

In order to communicate activities across 64 sites, NOVA developed communications capacities, including a quasi-journal through which new researchers could publish material that was peer-reviewed by senior researchers on the projects. NOVA also developed the capacity to run a considerable number of

[56]Primary sources for this case study are the meeting with Mr. Young and a review of the NOVA Research website and related company documents.

meetings, which included semi-annual all-team meetings as well as numerous subgroup meetings.

With demand for better electronic tools generated (and guaranteed) by long-term (5-year) federal contracts, NOVA was well positioned to seek SBIR funding for developing what eventually became the Questionnaire Development System (QDS™) survey design, data collection, and data management system (http://www.novaresearch.com/QDS/).

Initially focused on health research among special populations—women and children at risk for HIV/AIDS, and substance abusers as examples—NOVA has broadened its emphasis to include research in the behavioral sciences, software tool development to support survey research studies and evaluations, and community outreach and information dissemination.

SERVICE OFFERING

NOVA now provides a complete set of professional services to clinical, biomedical, and behavioral scientists. It supports their research programs, which in turn generate scientific findings, as well as field programs that test those findings. It offers IT services for survey design and implementation in all modes of questionnaire administration to systematically collect and analyze data related to research programs and field tests. And, finally, if research findings warrant, then NOVA provides services for marketing/communications and organizational meetings and conferences necessary to publish and promote findings both for professional advancement (as scientists) and public awareness (as policy makers).

NOVA provides services in five broad but related categories:

- Research and Research Support Services
- Program Planning and Evaluation
- Health Information Technology
- Health and Scientific Communications
- Meetings, Conferences, and Exhibits

Research and Research Support Services

NOVA Research Company provides a complete range of support services to help researchers undertake research studies. These services include developing initial research protocols, performing research, collecting data, performing analyses, developing findings, and disseminating results.

NOVA can manage, monitor, and/or analyze data for an organization's research; provide program management; and conduct project evaluations as part of its services. Basic data services include database design, implementation, and maintenance; survey instrument design and implementation using NOVA's

SBIR-developed QDS software suite or custom programming; data collection in multiple modes of survey administration; and data processing and analysis.

Examples include applied research such as an NIH R01 grant to develop and validate an adolescent-appropriate screening instrument for HIV/STD risk, and research program support as in the case of data collection and analysis through interviews and surveys of community intervention programs to reduce cancer burden among underserved and minority populations.

Program Planning and Evaluation

NOVA also partners to implement and evaluate programs. Again, NOVA provides assistance at any stage in development, implementation, monitoring, and evaluation of program impact. NOVA can design program protocols, conduct program implementation, monitor research client/patient accruals, perform data collection processes, and monitor adherence to protocols. Evaluation includes planning, metric selection, focus group and survey administration, and preparation of findings and recommendations.

Examples of NOVA's experience as program manager to test research findings include NIDA's Five-City Women's Health Research Study contract to pilot the National AIDS Prevention Model and the National AIDS Demonstration Research Project to evaluate efficacy of research-based community interventions to reduce risky behaviors for HIV transmission.

Health Information Technology

Over its 28 years of operation, NOVA has developed and expanded its capabilities in data management, processing, and analysis. Some of the technology within NOVA's Health Information Technology offering—for example, survey instrument development and administration using its QDS—has been funded and developed through SBIR grants.

QDS is NOVA's primary product generated via the SBIR program. Funded through a series of awards (see SBIR Funding section below) that advanced the technology, QDS development was driven by the need for better tools for NOVA's internal project support operations. QDS was developed and is maintained and enhanced/updated by a small in-house information technology and research staff at NOVA.

Today, QDS is used worldwide to help researchers design, implement, and deploy complex questionnaires related to health information topics, although it can be used for any type of survey topic. It is used extensively by the CDC HIV/AIDS Behavioral Surveillance Branch, which maintains QDS capabilities in each of the 50 states plus Washington, DC, and Puerto Rico, for HIV/AIDS risk behavior monitoring. While NIH itself was an early supporter, it undertakes relatively low levels of in-house research: most NIH-funded re-

search is conducted by university- and hospital-based researchers, many of whom use QDS.

According to Mr. Young, QDS is used today by about 3,000 researchers worldwide with about 13,000 QDS modules having been sold. Many medical research institutions maintain multiple users—University of California, San Francisco, for example, currently has about 60 registered users. This extensive reach results, in Mr. Young's view, from a combination of advanced features, ease of use for complex research surveys, and low cost. The latter is especially noteworthy: in a world of per-seat annual fees, NOVA sells its various QDS modules outright to researchers, who are free to use them indefinitely—one license per user/computer—in an unlimited manner. Mr. Young noted that the average cost of a QDS package is about $2,500, which compares very favorably with competing packages (e.g., its closest competitor from The Netherlands, which charges approximately $25,000).

QDS is designed to allow easy transition to new languages and has, as a result, been used widely in non-English environments, including Russian, Chinese, Polish, Vietnamese, and Korean as well as all European languages.

With further SBIR funding, NOVA recently implemented a web-based survey option, which can be used in conjunction with all other QDS modules, and which should, according to Mr. Young, allow it to maintain market share in the face of new market entrants from outside the medical sector (such as Qualtrics and Survey Monkey). Sales remain dominated by word-of-mouth marketing, although NOVA has tried a modest amount of marketing at selected health conferences.

Examples of NOVA's technological support include its work for the National HIV/AIDS Behavioral Surveillance Survey (NHBS), a CDC study to understand behaviors in populations at high risk of HIV infection, such as men who have sex with men, injection drug users, and high-risk heterosexuals. For the NHBS, NOVA programmed and tested the English and Spanish versions of the data collection software as well as provided training and administrative and technical support.

Health and Scientific Communications

NOVA provides clinical, biomedical, and behavioral scientists with assistance in the writing, editing, graphic design, layout, production, and distribution of their findings. NOVA has specialist teams for both health and science communications who understand how to communicate technical findings effectively to both public and professional audiences.

In September 2012, NOVA was selected to work with the NIH Office of Communications and Public Liaison (OCPL) to collect information to develop strategies and messages for improving stakeholder understanding of NIH's mission, goals, and accomplishments. NOVA used a mixed-mode of qualitative interviews and quantitative surveys using QDS to collect information about a variety

of important audiences, including the general public, the interested public, the media, advocacy organizations, the grantee researcher community, and federal partners. Based on analysis of the various types of data collected, NOVA prepared recommended strategies, tactics, and tools for OCPL to use with each audience.

Meetings, Conferences, and Exhibits

NOVA provides staff to manage government and nongovernment meetings and conferences. In addition to site selection, NOVA can organize the entire logistics of a meeting. Since its founding in 1986, NOVA has managed more than 1,000 conferences for its clients, ranging in size from 10 to 1,500 participants. Using its in-house graphic designers, NOVA can produce exhibits or posters for individual scientists to display at conferences.

For example, since 1993 NOVA has supported the prestigious President's Cancer Panel, holding meetings around the country and internationally to examine barriers and make recommendations to improve our National Cancer Program. In 2011, for the Center to Reduce Cancer Health Disparities, NOVA provided all pre-meeting, onsite, and post-meeting logistics (including a web-based participant registration and pre-meeting information site) for the Center's national meeting to discuss and promote methods to reduce the unequal burden of cancer across different segments of our society.

CLIENTS

NOVA's client list is a broad cross-section of the government; academic; and, to a lesser extent, commercial organizations undertaking clinical, biomedical, and behavioral research (see Table E-9).

In the past 10 years, while participating in trade missions with the Department of Commerce, NOVA has expanded its business activities internationally. Representative international clients are Max-Planck-Institut für Biochemie (Germany), Niigata University (Japan), Universidad Nacional Autónoma de México (Mexico), University of Cape Town (South Africa), Groote Schuur Hospital (South Africa), Instituto de Salud Carlos III (Spain), London School of Hygiene and Tropical Medicine (UK), and The Whittington Hospital Trust (UK). Unlike NOVA's domestic clientele, its international business has few government clients and is mostly academic and commercial.

SBIR FUNDING

Between 1994 and 2007, NOVA Research Company received 13 Phase I and Phase II SBIR grants from HHS for various technology-related projects. In total, SBIR funding has amounted to $5.78 million, $1.51 million in Phase I and $4.27 million in Phase II.

TABLE E-9 Representative Domestic Clients for NOVA Research Company

Government	Academic	Commercial
Centers for Disease Control and Prevention	Columbia University	Institute for Community Research
— 5 Centers within CDC	Duke University	M.D. Anderson Cancer Center
National Institutes of Health	Emory University	Massachusetts General Hospital
— 6 Institutes within NIH and the Office of the Director	Johns Hopkins University	New York Presbyterian Hospital
National Cancer Institute	Mount Sinai School of Medicine	RAND Corporation
— 20 Offices and Programs within NCI, including the Office of the Director	University of California, Los Angeles	Sinai Urban Health Institute
Health Resources and Services Administration	University of California, San Francisco	
U.S. Department of Education	University of Connecticut	
	University of Illinois	
	University of Texas	
	Yale University	

SOURCE: NOVA Research Company.

NOVA used much of its SBIR funding to build a software product for managing surveys. NOVA offers the QDS as a means to facilitate design, deployment, and warehousing of survey data generated by researchers.

Using QDS, a research program manager can produce all materials needed to administer a questionnaire, in multiple modes of administration (Computer-Assisted Personal Interview, Audio Computer-Assisted Self-Interview, paper/pencil, and web) from a single set of specifications and manage all data generated by those materials in a single Warehouse Manager module.

NOVA offers QDS modules for between $300 and $500 per user per computer depending on the module type. With the exception of a book on methodologies for research on drug abuse in Hispanic communities, QDS is the only product offering in the NOVA business model. However, NOVA currently is developing an educational game under SBIR contract to inform children about clinical trials, which eventually will be provided free on an NIH-maintained website and sold as an educational game foundation for other health topics.

SBIR

Although NOVA has received what it views as important support from NIH, its experience with CDC SBIR awards has been different. Unlike NIH, where awards are determined largely by priority scores from peer-review panels, the primary driver of awards at CDC is, in Mr. Young's view, the numerous layers of prioritization, starting with the sponsoring office and continuing up to the level of CDC itself. In effect, he believes that this ensures that regardless of technical merit (assuming that applications receive an acceptable priority score), awards are made based almost entirely on agency need. Thus, even though NOVA has worked closely with CDC in the past, and its recent proposal received an acceptable priority score from the NIH review panel, it did not fit the needs profile that was eventually determined by CDC.

More broadly, the SBIR program at NIH has, in Mr. Young's view, changed substantially over the years. There has been a shift at many Institutes away from projects that are behaviorally focused and toward medical devices and applied biomedical research. Funding is more oriented today toward biomedical product-oriented research firms. Despite the substantial and ongoing impact on research of the awards made to NOVA, Mr. Young does not believe that any of the NOVA proposals would be funded in today's research climate. By his analysis less than 10 percent of NIH SBIR funding goes to behavioral and information technology support topics.

Mr. Young noted that his primary contact is with the SBIR topic manager and is related to seeking further feedback on proposals. NOVA has found that resubmission is now more or less expected for every application, and, hence, feedback is especially important.

Mr. Young also observed that reviewers often seem to lack a deep commercialization awareness. This is an area where review could be strengthened, although in his view the selection process generally seems fair and appropriate. (He participated as a peer reviewer on an SBIR review panel in the 1990s, although he noted that the focus on PhD reviewers today means that he is not likely to be asked again.)

Sanaria, Inc.[57]

Meeting with
Dr. Stephen L. Hoffman, CEO and co-founder
January 29, 2015
Rockville, Maryland

Sanaria, Inc. is a private company founded in 2003 by Stephen Hoffman and Kim Lee Sim. The company is commercializing whole-parasite sporozoite vaccines that confer long-lasting protection against *Plasmodium falciparum*, the malaria parasite responsible for more than 95 percent of malaria-associated severe illness and death worldwide. Sanaria is headquartered in Rockville, Maryland.

Dr. Hoffman founded the company after a substantial clinical career and a period as senior vice president for biologics at Celera Genomics. This followed 21 years in the U.S. Navy, where he had worked on tropical disease programs. He founded Sanaria after determining that the approaches to development of cancer vaccines and other immunotherapeutics he wanted to pursue would not fit with Celera's priorities, and when he came to the conclusion that there was an approach to a malaria vaccine that would work.

Dr. Hoffman had at about this time come to the conclusion that the research data he and colleagues had generated in the 1990s and that they had published in the first half of 2002 included the technical basis for an effective vaccine against malaria and possibly against other infectious diseases as well. More than half the vaccines currently in use are based on a weakened (attenuated) form of the micro-organism that causes the disease. Indeed, since the 1960s, researchers have known that attenuated *Plasmodium falciparum* parasites provide immunity to malaria. However, because of the requirement of producing the parasites in mosquitoes, development of a vaccine that met regulatory standards had not seemed possible.

Discussions with senior staff at NIAID indicated that a SBIR would likely be the most effective way to approach NIH funding to address the numerous existing obstacles between the theory and the practical implementation of this approach. Dr. Hoffman was also able to utilize the experience of his wife, Dr. Kim Lee Sim, who had successfully utilized NIH SBIR awards at EntreMed, Inc., to fund anti-angiogenesis (Endostatin and Angiostatin) and malaria vaccine (PfEBA-175) R&D.

From the outset Sanaria took a scientific approach quite different from that of other entities working in this space: its primary focus was high-level efficacy, while the ease of vaccine delivery was initially a secondary objective. This contrasted with strategies espoused by many major drug companies (e.g., GSK, Sanofi) as well as the Gates Foundation, who considered ease of delivery as important as efficacy.

[57]Primary sources for this case study are the meeting with Dr. Hoffman, and a review of the Sanaria website (http://www.sanaria.com) and related company documents.

The initial awards from NIH came from NIAID, where Phase I awards were, according to Dr. Hoffman, running at about $600,000 during 2 years. Dr. Hoffman filed his first NIH applications in August 2002, immediately after leaving Celera. Funding from the first grant came in July 2003, and provided the initial seed money through which to found the company and rent 800 square feet of space. A positive response to two more Phase I grant proposals allowed the company to hire its first two research associates in August 2003. The company's first facilities were located in a rundown strip mall in Rockville, which was gradually upgraded to enable to FDA compliant manufacture of pre-clinical quantities of the PfSPZ vaccine.

Sanaria currently employs approximately 50 people at its Maryland facilities. This facility, which includes a clinical manufacturing facility (CMF) was opened in 2007 with funding from the Bill and Melinda Gates Foundation; as the company now plans to scale vaccine production, Sanaria is looking for investors to expand these facilities to reach its goal of producing 2 million regimens of PfSPZ vaccine in the year after licensure.[58]

Sanaria has received substantial recognition for this important work. Recently, in 2013 it received the Montgomery County Emerging Business of the Year award. In 2014, the Sanaria® PfSPZ Malaria Vaccine won the 2014 Vaccine Industry Excellence Award for "Best Prophylactic Vaccine." Other competitors for this award included major biopharmaceutical companies such as Sanofi Pasteur, GSK, and Novartis.[59]

Sanaria maintains research relationships with a broad range of government, corporate, and nonprofit organizations including, but not limited to, multiple branches of NIH/NIAID, the Naval Medical Research Center, the Walter Reed Army Institute of Research, the Military Infectious Disease Research Program (MIDRP), the Centers for Disease Control, the National Institute of Standards and Technology, the University of Maryland Baltimore, the University of Tübingen, Swiss Tropical Public Health Institute, Radboud University Medical Center, Leiden University Medical Center, the PATH-Malaria Vaccine Initiative, the Ifakara Health Institute, University of Bamako, Ministry of Health Equatorial Guinea, the Kenya Medical Research Institute, and the Kintampo Health Research Center.

[58]"Addressing A Global Imperative: Malaria Eradication through Vaccination," https://sbir.nih.gov/statistics/success-stories/sanaria.

[59]"Sanaria wins Very Zanders Award," http://www.choosemontgomerymd.com/features/sanaria-named-verl-zanders-emerging-company-of-the-year-by-mccc#.VMTv2P7F_94; Sanaria PfSPZ Malaria Vaccine Wins 2014 Vaccine Industry Excellence Award for "Best Prophylactic Vaccine," http://www.vaccinenation.org/2014/04/04/sanaria-pfspz-malaria-vaccine-wins-2014-vaccine-industry-excellence-award-best-prophylactic-vaccine/.

A NEW BUSINESS MODEL FOR FUNDING CLINICAL RESEARCH

Dr. Hoffman pointed out that a malaria vaccine, and in particular the kind of path-breaking vaccine developed by Sanaria, faced difficult business challenges. To begin with, large pharmaceutical companies are in general not especially interested in vaccines: they prefer solutions that involve the delivery of multiple doses of medication over a long period of time. Moreover, the vast majority of end users are poor people in poor countries, where margins are thin and delivery is difficult.

In addition, according to Dr. Hoffman, there is no precedent for the technical solutions developed by Sanaria—there are no previous examples of successful vaccines for diseases caused by eukaryotic pathogens and utilizing live attenuated organisms. This requires preservation and storage in vapor phase liquid nitrogen, again, no precedent. The delivery system is direct venous injection (DVI), a safe, easy and painless procedure, again, no precedent. This increased the apparent risk of the project substantially. The amount of funding needed to complete and deliver the solution is now also much larger than venture firms can provide—he estimated that eventually the company and its partners would need to raise approximately $400 million; more than half that amount has been raised.

From a business perspective, Sanaria has three distinct challenges. First, it needs to continue to improve the technology underpinning its solution and to develop sufficient manufacturing capabilities so that it can address its initial markets. This is the area where continuing SBIR funding has underpinned success in the past and will continue to be needed in the future.

Second, the company needs to fund clinical trials in a variety of settings. Here it is pioneering an innovative approach in which it provides support for entities seeking to trial its technology, but without providing the bulk of funding. Sanaria simply provides the vaccines, while others raise money to pay for the trials (see below).

This approach has been very successful. A wide range of partners in the United States, Africa, Asia, and Europe are currently undertaking clinical trials with Sanaria. These in turn have been undertaken by a number of different stakeholders, including African governments, energy companies, nonprofit foundations, universities and research labs, and private companies (see Table E-10). This includes the first clinical trials in Africa sponsored by African governments. Recently a path-breaking agreement was signed by Marathon Oil, Noble Energy, and AMPCO and the government of Equatorial Guinea to completely fund clinical trials of Sanaria's PfSPZ vaccines through Phase 3 clinical trials through $48.5 million in support. In each case, the sponsor is responsible for funding the actual trial. Sanaria raises the much more modest amounts needed to pay for the vaccine itself. It currently has trials under way in the United States, Europe, and Africa.

Because Sanaria directly manufactures its own vaccines, clinical trials are not delayed by manufacturing bottlenecks, which Dr. Hoffman regards as a significant competitive advantage.

TABLE E-10 PfSPZ Vaccine Consortium

Location	Collaborative and Funding Partners	Funders
USA	NMRC, DoD	Military Infectious Disease Research Program (MIDRP)
	WRAIR, DoD	U.S. Navy Advanced Medical Development Program
	VRC, NIAID, NIH	USAMMDA
	LMIV, NIAID, NIH	DMID, NIAID, NIH
	University of Maryland Baltimore, CVD	PATH MVI (BMGF)
		Marathon Oil Company
	Centers for Disease Control and Prevention	AMPCO, Noble Energy
	Medical Care Development International	
EUROPE		
Switzerland	Swiss TPH	Swiss State Secretariat for Education, Research and Innovation; R. Geigy Foundation
Germany	University of Tübingen	German Centre for Infection Research
The Netherlands	Radboud University Medical Center (RUMC)	Top Institute Pharma
	Leiden University Medical Center	
Spain	ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clinic – Universitat de Barcelona, Barcelona	CRESIB, Spanish Government
UK	Jenner Institute, Oxford University	The Wellcome Trust
AFRICA		
Tanzania	Ifakara Health Institute (IHI)	Tanzanian Commission on Science and Technology (COSTECH)
Equatorial Guinea	Ministry of Health and Social Welfare	Government of Equatoria Guinea, EG LNG
Kenya	Kenya Medical Research Institute; Wellcome Trust Laboratories; Centre for Research in Therapeutic Sciences (CREATES)	
Gabon	Centre de Récherches Medicales de Lambaréné	

continued

TABLE E-10 Continued

Location	Collaborative and Funding Partners	Funders
Mozambique	Manhica Center	
Ghana	Kintampo Health Research Center	Ghana Ministry of Health
Mali	University of Bamako (MRTC)	
Burkina Faso	Centre National de Recherche et de Formation sur le Paludisme (CNRFP)	
ASIA		
Indonesia	Eljkman-Oxford Clinical Research Unit (EOCRU), Jakarta	

SOURCE: Sanaria, Inc.

Third, the company will need to raise money to reach scale, which will involve building entirely new manufacturing facilities, automating some aspects of the manufacturing process, and most likely expanding internationally. This will require substantial investment, and the company has been in discussions with investment banks and other large-scale investors on a preliminary basis.

Thus, as Dr. Hoffman observed, the traditional paradigm of SBIR use does not apply to Sanaria. There is no direct linear path between Phase I, Phase II, and commercialization. Yet he also noted that if the company is successful, then SBIR will have played a critical role in addressing one of the most significant diseases in the developing world—a globally transformative impact which, aside from immediate disease-related benefits, is likely to boost the gross national product (GNP) of poor countries significantly every year.

As a result, Sanaria has developed a new model for funding clinical trials. It is partnering with a wide range of organizations (See Table E-10).

Markets for Sanaria

Dr. Hoffman sees two core markets for Sanaria's malaria vaccine. Sanaria is focusing on the "traveler" market—visitors from richer countries entering malarial regions. These include business people, military, government workers, and nonprofits, as well as companies with substantial operations in these areas. He regards this market as lower-volume/high margin and estimates that the overall market is worth at least $1 billion annually.

In parallel with its efforts to license the vaccine for travelers and military, the company is focusing on licensing the vaccine for use in geographically focused, mass administration campaigns in malaria endemic areas to halt transmission

of the infection and eliminate the malaria-causing parasites. This will be a high volume/low margin market in less developed countries where malaria is endemic.

THE SANARIA VACCINE

Sanaria is working to solve a major development problem. One-half of the world's population lives in areas at risk for transmission of malaria. Approximately 200,000,000 cases of malaria occur annually with about 600,000 deaths. In the period 1965-1990, all other things being equal, the economies of countries afflicted with intensive malaria grew 1.3 percent less per person per year. Furthermore, a 10 percent reduction in malaria incidence has been shown to be associated with 0.3 percent higher growth.[60]

Since the 1970s, researchers have known that humans could be immunized using attenuated whole-parasite sporozoites, an immature form of the *Plasmodium* parasite. However, because the parasites do not survive outside mosquitoes and because attenuation using irradiation blocks the parasite's ability to reproduce, vaccination required exposing volunteers to bites by up to 1,000 mosquitoes carrying the attenuated parasite.[61]

Sanaria has overcome these problems and has developed a vaccine based on the sporozoites of the *P. falciparum* parasite. Sanaria makes its vaccine by irradiating aseptic (bacteria free) mosquitoes that have fed on malaria-infected blood and removing their salivary glands manually. The vaccine is stored cryogenically in the vapor phase of liquid nitrogen. Although originally intended for dermal or subcutaneous injection, clinical trials showed that the vaccine did not generate sufficiently strong immunological responses when administered this way. This is primarily because the vaccine parasites must reach the liver to initiate the next stage of development, and this is best achieved by DVI injection, not injection in the skin.[62]

In 2011, Sanaria initiated a clinical trial of multiple doses (two to five over the course of the trial) administered by DVI through a standard temporary DVI catheter. Volunteers were subsequently exposed to malaria. Of the six volunteers receiving five doses of the PfSPZ vaccine, none developed malaria, and of the nine volunteers who received four doses, only three developed malaria. Among

[60]John Luke Gallup, Jeffrey Sachs, "The Economic Burden of Malaria," *American Journal of Tropical Medicine and Hygiene*, Supplement, Volume 64, no. 1, http://www.ncbi.nlm.nih.gov/books/NBK2624/.

[61]Donald McNeil, "The Soul of a New Vaccine," *The New York Times*, December 11, 2007, http://www.nytimes.com/2007/12/11/health/research/11mala.html?pagewanted=all.

[62]Donald McNeil, "A Malaria Vaccine Works, With Limits," *The New York Times*, August 12, 2013, http://www.nytimes.com/2013/08/13/health/a-malaria-vaccine-works-with-limits.html?_r=1&; Epstein, et. al. "Live Attenuated Malaria Vaccine Designed to Protect Through Hepatic CD8-T Cell Immunity," *Science* Volume 334, no. 6055 (October 28, 2011), 475-80, http://www.ncbi.nlm.nih.gov/pubmed/21903775?dopt=Abstract; Declan Butler, "Zapped Malaria Parasite Raises Vaccine Hopes," *Nature* (August 8, 2013) http://www.sanaria.com/pdf/Nature2013.pdf.

the controls, 11 of 12 volunteers developed malaria, as did 16 of 17 volunteers receiving low-dosage vaccination.[63]

As an effective means of immunizing people with an FDA-compliant vaccine, the PfSPZ Vaccine is an important step forward.

In addition to enabling additional clinical trials, SBIR funding is being used to establish ways to improve the vaccine. Because radiation disrupts the parasite's ability to reproduce in the liver, Sanaria is using SBIR funding to investigate genetic attenuation that does not render the parasite sterile. By increasing the amount of active parasites in the body, this could reduce the number of doses required and even eliminate the need for intravenous injection. Sanaria is also investigating ways to scale production of the PfSPZ vaccine. Other potential lines of research include revising the protocol for cryogenically storing the sporozoites.

Challenges

Sanaria is attempting to develop the first highly effective vaccine against a eukaryotic organism. The vaccine will also be the first vaccine composed of a live attenuated eukaryotic organism. This would therefore represent a substantial technical breakthrough, and preliminary results from safety and efficacy clinical trials indicate that the vaccine is both safe and effective at three to five doses per vaccinee. According to Dr. Hoffman, not only are there no vaccines against eukaryotic organisms, there are no major research programs addressing using eukaryotic organisms as vaccines at the major pharmaceutical companies.

However, major challenges do remain. The vaccine is designed to be stored and deployed in cold storage provided through liquid nitrogen technology. Although this does not require electricity to provide constant cooling, it does add some challenges to distribution. Dr. Hoffman notes that other products have been delivered successfully in developing countries using this technology, and does not regard it is a substantial problem, and in fact considers it an advantage for mass administration campaigns.

The parasites are also currently extracted from mosquitos manually. Dr. Hoffman said that each technician can remove about 200 pairs of salivary glands per hour, and that on this basis the current manual approach has adequate capacity for all clinical trials and for initial sales. However, he acknowledged that once the company ramps up sales, it will need to switch to a more automated manufacturing process. Again, though, he said this did not present major technical challenges; it was simply engineering and investment. Perhaps most exciting is that an SBIR grant is now funding the development of methods to produce the sporozoites without mosquitoes.

[63]Nailing Padmanabhan, "Investigational Malaria Vaccine Found Safe and Effective," http://www.niaid.nih.gov/news/newsreleases/2013/Pages/PfSPZ.aspx; "Experimental PfSPZ Vaccine in Adults Without Malaria," https://www.clinicaltrials.gov/ct2/show/record/NCT01441167?term=sanaria&rank=15; Seder et. al. p. 1359.

There have also been questions about the likelihood that the market will accept vaccines that require injection by DVI. Dr. Hoffman observed that the needles used are extremely small and are largely pain free, and also that more than 20 million people have their blood drawn every month in the United States alone. He believes the benefits of the vaccine will so clearly outweigh the administration innovation that this too will not be a substantial problem.

The most substantial challenge will be to raise the large sums of money needed to move the vaccine into mass production. This will cost tens of millions of dollars, but Dr. Hoffman is confident that once a finalized immunization regimen has been established in the upcoming clinical trials, much more funding will become available.

PRODUCTS

In creating its vaccine, Sanaria has developed capabilities to manufacture and assay malaria parasites and mosquitoes in a highly regulated, cGMP-compliant environment. Sanaria offers these parasites, mosquitoes, and assay services to the general research community to advance malaria research.

Reagents and Antibodies

In developing its vaccine, Sanaria has successfully developed techniques for isolating and preserving the *P. falciparum* parasite across its different life stages. Sanaria offers these different forms of purified, vialed, and cryopreserved for laboratory research. Sanaria can provide the parasite either in attenuated or non-attenuated form. Sanaria also offers a broad range of purified recombinant proteins and antibodies related to the *P. falciparum* parasite that are used in its assays to detect antibodies against the different stages of the parasite.

Mosquitoes

To produce FDA Good Manufacturing Practice (GMP) compliant vaccines from the salivary gland of mosquitoes, Sanaria has bred mosquitoes free of bacteria. Sanaria offers these aseptic mosquitoes either infected with *P. falciparum* or not for research and other work by biomedical scientists.

Services

Although most of Sanaria's research has focused on *P. falciparum* and *Plasmodium vivax* as the principal vectors for malaria transmission, over 100 other varieties of *Plasmodium* exist which infect humans, other mammals, reptiles, and birds. Sanaria can produce reagents and assays customized to these different varieties of *Plasmodium*.

TABLE E-11 Sanaria Inc. Assigned Patents

Patent Number	Patent	Year
8,992,944	Purified Plasmodium and vaccine composition – methods of using in Sanaria® PfSPZ Vaccine	2015
8,821,896	Purified Plasmodium and vaccine composition – methods of using in Sanaria® PfSPZ CVac	2014
8,802,919	Apparatuses and methods for the production of haematophagous organisms and parasites suitable for vaccine production – composition of matter claims for aseptic sporozoites and mosquitoes	2014
8,367,810	Purified Plasmodium and vaccine compositions – methods of manufacture	2013
8,043,625	Purified Plasmodium and vaccine compositions – composition of matter claims for purified SPZ	2011
7,229,627	Apparatuses and methods for the production of haematophagous organisms and parasites suitable for vaccine production – methods of manufacture	2007

SOURCE: U.S. Patent and Trademark Office. Accessed June 27, 2014.

PATENTS AND OTHER INTELLECTUAL PROPERTY

Sanaria is the assignee for the U.S. patents shown in Table E-11. These patents cover the actual materials used to make the vaccine, so Dr. Hoffman sees the company as well protected in this area.

Sanaria also publishes it work in leading peer-reviewed journals. The results of the first two clinical trials of PfSPZ Vaccine were published as research articles in the prestigious journal *Science*.

FUNDING

Non-Dilutive Funding

Between 2003 and 2015, SBIR funded 30 projects with Sanaria (18 Phase I and 12 Phase II). Sanaria has received 67 annual SBIR awards amounting to nearly $40.5 million from the Department of Health and Human Services (HHS). Including future years the number increases to $46.2 million. In addition Sanaria received $1.9 million in ARRA supplements against two of the Phase II awards in 2011. Of this amount, 42 percent targeted research on vaccine development, 22 percent on vaccine manufacture, 20 percent on vaccine delivery, and 13 percent on vaccine storage. In total, Sanaria has received approximately $200 mil-

TABLE E-12 Sanaria Sources of Non-dilutive Funding

Organization	Amount	Year
The Gates Foundation	$32.3 million	2006, 2010
TI Pharma	$23.6 million	2008
Congressional Allocation – Army	$4.1 million	2005
Joint Warfighter Program – Army	$3.9 million	2014
Joint Warfighter Program – Army	$7.6 million	2015
Advanced Medical Development – Navy	$3.5 million	2015
Government of Equatorial Guinea and 3 Energy Companies	$48.5 million	2015

SOURCE: Sanaria Inc.

lion directly or indirectly since it was founded.[64] Other non-dilutive funding are shown in Table E-12.[65]

Sanaria has also been innovative in raising capital, even using an only partially successful crowdsourcing campaign on Indiegogo to raise $45,000 in funding to develop a robot to automate mosquito dissection and scale vaccine production.[66]

Equity Funding

To date, Sanaria has received no significant equity investment. Following its recent successful clinical trials, senior management has indicated that it may partially fund upcoming trials through investments. It is focusing on socially conscious investors and possibly an initial public offering.[67]

Operations

Sanaria generates significant income from the sale of aseptic mosquitoes, reagents, including sporozoites, and various services to the malaria research

[64]"Addressing a Global Imperative: Malaria Eradication through Vaccination," https://sbir.nih.gov/statistics/success-stories/sanaria.

[65]Steve Berberich, "$29.3M Gates Grant Boosts Sanaria," *Washington Business Journal*, December 15, 2006, http://www.sanaria.com/pdf/Press-7-Gazette-Gates_grant_12-15-06.pdf; Neil Adler, "Sanaria Gets $4M in Gov't Funds for Malaria Vaccine," *Washington Business Journal*, June 6, 2005, http://www.bizjournals.com/washington/stories/2005/06/06/story7.html.

[66]"Malaria Vaccine Robot – Robot vs. Mosquito Sanaria – SporoBot," Set goal of $250K on May 6, 2014; closed campaigne at ~$45K on June 5, 2014, https://www.indiegogo.com/projects/malaria-vaccine-robot-robot-vs-mosquito-sanaria-sporobot#home.

[67]Bill Flook, "With the World Watching, Sanaria Maps Out its Future," *Washington Business Journal*, August 30, 2013; http://www.bizjournals.com/washington/blog/techflash/2013/08/with-the-world-watching-sanaria-maps.html?page=all.

community. This has been dwarfed by government and foundation support for Sanaria's work.

SBIR AND SANARIA

According to Dr. Hoffman, "SBIR is the lifeblood of the company." Competitive SBIR awards allowed the company to develop every single aspect of its manufacturing process. Dr. Hoffman said that while the Gates Foundation had been a generous funder of the company, it would never have given money to develop the technology in the first place. SBIR funding was the only conceivable way in which the company could have been founded and the technology perfected to the point of successful clinical trials. In fact, SBIR was the primary reason the company was not formed as a nonprofit entity, as these are not permitted to receive SBIR funding.

Dr. Hoffman was emphatic about the importance of SBIR for Sanaria and also more generally for small innovative companies. He said that without SBIR there was no possible source of funding for the work done by Sanaria: that private sector funding would—for reasons described earlier in this case study—never fund high-risk investments in areas where potential rewards were both uncertain and likely to be much lower than for chronic diseases. And within the government, SBIR provided the only source of funding for private companies to engage in high-risk, high-reward research. He noted that Dr. Anthony Fauci, director of NAIAD, had specifically advised Sanaria to work through SBIR as the only likely initial source of funding from NIH.

SBIR funding had both supported the initial founding of Sanaria, paying the salaries of the founding staff, and had consistently paid for much of the technology development, manufacturing capacity, and preparation for clinical trials.

Sanaria has had a range of SBIR awards. These include:

- Phase I awards at NIAID, which can be as high as $300,000/year for 2 years.
- Phase II awards, which can be as high as $1 million/year for 3 years. The initial Phase I award, which was converted to Phase II award from NIAID eventually reached $9 million.
- American Recovery and Reinvestment Act (ARRA)-derived supplementary funding.

SBIR RECOMMENDATIONS

Dr. Hoffman said that in his view—and as a recipient of many kinds of awards at NIH—SBIR was far more effective than RO1 grants in delivering new approaches that could make a real difference. Accordingly, he believed that NIH should add considerably more funding to the SBIR program, beyond the amounts mandated by Congress.

Proposal review panels (e.g. study sections) were a real challenge for NIH, Dr. Hoffman observed. They often included academic scientists who did not have an extensive understanding of translational research. On the other hand, some of these scientists were also potential competitors, and Sanaria had in several instances asked for specific reviewers to be removed from panels addressing its proposals. Overall, the quality of reviews—and especially of business reviews—was quite variable.

Dr. Hoffman strongly supported any changes that would allow proposers to add a rebuttal to draft reviews prepared by the lead reviewer. He believed this would substantially improve the overall quality of review, at minimal cost to NIH. He felt this might also help to address reviews that went outside the expertise of the reviewer. For example, a recent review of a very successful Phase I effort modifying an oral typhoid fever vaccine for use with anthrax had been rejected in part because the lead reviewer said that the government did not need an anthrax vaccine.

Dr. Hoffman also observed that in the past reviews did not arrive in time to be able to resubmit the grant in the next cycle (4 months from the previous submission). However, in the last year NIAID has actually been getting reviews back in time for a re-submission. He urged NIH to continue to adjust its schedules to ensure that debriefings arrived in time for resubmission to occur on the next deadline, 4 months after the previous deadline.

Finally, Dr. Hoffman is concerned that the quality of staff working for companies on SBIR awards will suffer because the maximum permitted salaries have declined recently and are now well below market levels. Although there are good reasons to prevent excessive payments, it does seem that allowing the market to work will in almost all cases be more efficient, and there is now a real danger that senior researchers will simply be priced out of working on SBIR grants.

Stratatech Corporation: SBIR Case Study[68]

Meeting with
Dr. Barbara Allen-Hoffman, CEO and Founder
April 8, 2015

Stratatech Corporation is a private company founded in 2000 by B. Lynn Allen-Hoffmann. The company is developing novel skin regeneration and repair products for therapeutic use, drawing on what Dr. Allen-Hoffmann described as a serendipitous discovery in her lab at the University of Wisconsin that offered entirely new technical opportunities in cell-based therapy for human skin replacement and treatment of complex skin defects.

Working together with the University of Wisconsin and the Wisconsin Advanced Research Foundation (WARF), Dr. Allen-Hoffmann used an STTR award to begin the transition from university lab to the private sector. In conjunction with WARF, she determined that a small private biotechnology company was the appropriate legal structure to house the work, and provided access to the SBIR program.

Stratatech started operations in a small space provided by Mirus Corporation, another small spin-off of the university located in the University Research Park in Madison, Wisconsin. The company soon started to attract angel funding, which Dr. Allen-Hoffmann attributes to the understandable nature of the technology for skin replacement. While business advisors recommended that she avoid applying for grants due to the lengthy time required to generate the application and administer the grants if awarded, Dr. Allen-Hoffmann decided that the best path to funding lay through the SBIR/STTR programs.

Based on the discovery of a human keratinocyte cell line, NIKS® cells, that produces tissue nearly identical to human skin, Stratatech has used the cells as a platform technology for the development of a pipeline of cell-based products. Stratatech is developing StrataGraft® as it's flagship product based on the core technology. StrataGraft® is a living skin-tissue therapeutic for the treatment of severe burns and other complex skin defects, the use of which may reduce or possibly avoid the need for painful skin harvest and transplantation (autografting). The ExpressGraft™ lineage is comprised of skin tissues that have been genetically enhanced to encourage wound closure by providing elevated levels of human wound healing or antimicrobial factors that may be underrepresented in some wound environments. Both the core technology, Stratagraft®, and the world's first genetically enhanced human skin, Expressgraft™, are being evaluated in late-stage and early-stage clinical trials, respectively. The late-stage clinical development supporting the StrataGraft® product is in part funded by a

[68]Primary sources for this case study are the meeting with Barbara-Allen Hoffman April 9 2015 and a review of the Avanti website (http://www.acousticmed.com) and related company documents.

$247 million contract with Biomedical Advanced Research and Development Authority (BARDA) awarded in September 2015. Results to date have supported the safety and initial efficacy of the company's flagship product, StrataGraft®.

By late 2013, Stratatech had thirty-eight full-time employees and expected to add ten to twenty additional employees over the next 5 years. Currently, the company has approximately 50 full-time employees. It has research relationships with various universities and research institutions including the University of Wisconsin-Madison, Wake Forest University, The Arizona Burn Center, the U.S. Army Institute of Surgical Research, Harvard Medical School, and an unnamed Fortune 200 consumer products company.[69] However, even with a large support contract in hand from HHS/BARDA and continuing support from NIH, funding for later stage clinical trials and manufacturing infrastructure remains an ongoing challenge. Dr. Allen-Hoffmann observed that there had been no new products available for burn patients in decades, in large part because the market was perceived as too small to interest large biomedical companies. In 2012, StrataGraft® received orphan drug designation from the FDA to expedite treatment for severely burned patients.

TECHNOLOGY

Unlike other cultured human cell lines, the NIKS® progenitor line at the heart of Stratatech's core technology is a consistent source of pathogen-free, non-tumor-producing, long-lived adult keratinocyte progenitor cells. Keratinocytes are the cells that make up approximately 90 percent of the outer layer of human skin known as the epidermis. The value of the NIKS® cell line lies in its ability to regenerate the epidermal component within a fully stratified human skin tissue. The resulting multi-layered tissue has the physical strength and biological characteristics of intact human skin. When handled appropriately, this cell line grows new human skin and—as important—ceases growth when these cells abut neighboring mature skin cells. The NIKS® cell line can be utilized indefinitely to produce cultured skin, avoiding the costly need to recreate and requalify new cell lines that restricts other technologies.

Having a well characterized, pathogen-free, continuous source of epidermal progenitor cells serves as a foundation for the company's products and allows Stratatech to pursue strategies to improve the cell line's performance genetically. Stratatech is introducing new genetic characteristics without using viral vectors or other delivery technologies that could impart unwanted safety risks to the transgenic tissue and, most importantly, the patient. This approach supports the creation of custom cell-based therapeutics with enhanced antimicrobial properties and improved vascular function and that may lead to faster healing.

[69] "Company Profile: Stratatech," http://inwisconsin.com/insource-newsletter/Stratatech-company-profile/.

PRODUCTS

StrataGraft® and the ExpressGraft™ line of genetically enhanced tissues are the principal products under development from the NIKS® cell line. Currently, the company has created six ExpressGraft™ pipeline products, each genetically augmented to address the underlying pathophysiology of complex skin defects. All pipeline products have been successfully developed from hypothesis to completed cGMP manufactured master cell banks with support from the SBIR/STTR Program.

StrataGraft® Regenerative Skin Tissue

Each year in the United States, about 40,000 hospitalizations occur for burns.[70] At present, patients with severe burns must endure autografting, a procedure requiring the harvest of healthy skin from another part of the body for transplantation to the site of the wound. StrataGraft® tissue has the potential to provide a safe, effective, and less painful alternative that avoids the creation of donor site wounds.

StrataGraft® skin tissue is a cellular therapeutic for use as a treatment for severe burns and other complex skin defects. It mimics natural human skin, with both dermal and fully-differentiated epidermal layers. StrataGraft® skin tissue is easily sutured to a wound bed, provides barrier function, and is anticipated to serve as a source of factors promoting the natural skin regeneration process.

In October 2014, StrataGraft® completed a Phase Ib clinical trial in patients with deep partial-thickness burns. By 90 days after treatment, 27 of 28 patients achieved complete wound closure after a single application of StrataGraft® tissue. By this time, no StrataGraft® DNA was detectable, confirming regeneration of the patients' own skin.

If successful, StrataGraft® could revolutionize treatment for burns by providing an alternative to autografting and its associated donor site pain, infection risk, and possible poor cosmetic outcome. These advantages may lead to shorter hospital stays and reduced after-care costs.

ExpressGraft™ Genetically Enhanced Regenerated Tissue

Approximately 50 million surgeries occur annually in the United States, each requiring some form of wound closure.[71] Stratatech is developing genetically enhanced tissues that produce elevated levels of natural wound healing and antimicrobial factors. Delivered as skin grafts, ExpressGrafts™ create a

[70]American Burn Association, "Burn Incidence and Treatment in the United States: 2013 Fact Sheet," http://www.ameriburn.org/resources_factsheet.php.

[71]CDC FastStats, http://www.cdc.gov/nchs/fastats/insurg.htm.

controlled wound microenvironment in which to fight infection or promote vascularization while accelerating healing.

In one ExpressGraft™ product, the NIKS® cell line has been genetically modified to produce higher levels of cathelicidin, a peptide with antimicrobial properties that plays an active role in wound healing. These tissues produce 140-fold greater levels of cathelicidin protein *in vitro*, and in an *in vivo* animal wound model showed a 100-fold reduction in the presence of a multidrug-resistant strain of *Acinetobacter baumannii.*

Clinical development of ExpressGraft™ will start in 2015 with a Phase I/II trial focused on non-healing diabetic foot ulcers. An IND was submitted to the FDA in spring 2015 and received clearance from CBER to enter a first-in-human safety trial. Dr. Allen-Hoffmann observed that this project has been supported from "hypothesis to translation into the clinic" by NIH through the STTR and SBIR programs.

StrataTest® Human Skin Research Model

Many of today's animal- and cell-based toxicity testing models are burdened by significant accuracy, reproducibility, cost, and ethical concerns. The European Union, for example, has banned the sale of animal-tested cosmetic and consumer products.

Based on the NIKS® cell line, StrataTest® is a human skin model for *in vitro* consumer product testing, drug discovery and toxicity screening. Like StrataGraft®, StrataTest® tissue is composed of both epidermal and dermal layers, and displays the same physical, chemical and histological characteristics of human skin, enabling better prediction of *in vivo* biological responses than monolayer skin culture technologies.

Dr. Allen-Hoffmann said that while StrataTest® has shown considerable technical promise and the company regularly fields inquiries from larger potential customers, the decision was made to focus efforts on the therapeutic flagship StrataGraft® product and the ExpressGraft™ pipeline of products for the time being.

Other Potential Products

Other ExpressGraft™ potential products are in the pipeline. Like the cathelicidin-expressing variant of ExpressGraft™, some product candidates produce elevated levels of other naturally-produced human wound healing factors. For example, one proposed product expresses VEGF, a protein that plays a central role in blood vessel growth (angiogenesis). Because many chronic wounds are associated with insufficient tissue oxygenation, boosting local levels of VEGF may improve wound healing and closure. Clinical development will target the need for underserved markets in chronic, non-healing ulcers.

Additional potential products target different classes of skin trauma. For example, by creating tissues that express Interleukin-12 (IL-12), a human anticancer protein, Stratatech hopes to develop a product that surgeons could apply after surgical excision of solid skin tumors. Locally produced IL-12 from the genetically modified tissue could facilitate the patient's own immune surveillance of residual tumor cells remaining after the surgery, reducing the potential for recurrence.

PATENTS AND OTHER INTELLECTUAL PROPERTY

Stratatech is the assignee for 20 issued patents listed in Table E-13.

TABLE E-13 Stratatech Assigned Patents

Patent Number	Patent	Year Issued
9,163,076	Human skin equivalents expressing exogenous polypetides	2015
8,992,997	Dried and irradiated skin equivalents for ready use	2015
8,808,685	Method of treatment using organotypically cultured skin tissue comprising NIKS® cells that express exogenous HIF-1.alpha.	2014
8,790,636	Human skin equivalents expressing exogenous polypeptides	2014
8,685,463	Dried and irradiated skin equivalents for ready use	2014
8,580,314	Dried and irradiated skin equivalents for ready use	2013
8,092,531	Human skin equivalents expressing exogenous polypeptides	2012
7,988,959	Method of treatment using organotypically cultured skin tissue comprising NIKS® cells that express exogenous HIF-1a	2011
7,955,790	Skin substitutes with improved barrier function	2011
7,915,042	Keratinocytes expressing exogenous angiogenic growth factors	2011
7,888,496	Kit for species specific DNA detection	2011
7,807,148	Organotypically cultured skin tissue comprising NIKS® cells that express exogenous HIF-1a	2010
7,674,291	Human skin equivalents expressing exogenous polypeptides	2010
7,541,188	Skin substitutes and uses thereof	2009
7,501,238	Skin Substitutes for irritancy testing	2009
7,498,167	Keratinocytes expressing exogenous angiogenic growth factors	2009
7,462,448	Species specific DNA detection	2008
7,407,805	Skin substitutes with improved barrier function	2008
6,974,697	Skin substitutes with improved barrier function	2005
6,846,675	Skin substitutes and uses thereof	2005

SOURCE: U.S. Patent and Trademark Office.

FUNDING

Stratatech Corporation has received grant support from SBIR (mostly from NIH but also from DoD), other grants from non-SBIR sources, a major contract from HHS's Biomedical Advanced Research and Development Authority (BARDA), and investment from independent investors.

Non-Dilutive Grants

Between 2001 and 2013, SBIR funded 21 projects with Stratatech. From 2001 to 2003, it received Phase I SBIR awards from four NIH centers—National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of General Medical Sciences, National Cancer Institute, and National Institute of Environmental Health Sciences—followed in 2004 by the first Phase II award from NIGMS. Subsequently, Stratatech also received awards from NIDDK and NIA.

STTR grants funded three projects aimed at completing the scientific work that, according to Dr. Allen-Hoffmann, needed to be done within her lab at the University of Wisconsin because that provided access to otherwise unaffordable equipment.

Stratatech has also applied for and received Fast Track awards from NIH. Dr. Allen-Hoffmann observed that these had been especially helpful as they reduced the time from initial idea to clinical trials by many months. One Fast Track provided by NIDDK is supporting Phase I clinical trials for an anti-infective human skin tissue that can be used to treat ulcerated skins from diabetic skin ulcers.

Stratatech has received grants from other sources to support commercialization of its StrataGraft® product. In July 2013, Stratatech received a grant for up to $47.2 million from BARDA. The award supports the preclinical, clinical, regulatory, and technology development activities needed to complete FDA approval for StrataGraft®. Also, the contract funds manufacturing process development and scale-up to enable large-scale production in case of a mass casualty event.[72] In September 2015 Stratatech received a second BARDA contract through Project BioShield that replaced the first contract. This most recent BARDA contract enables expansion of the company's clinical program to include pediatric patients and aging adults and positions StrataGraft for use under a pre-Emergency Use Authorization, provided the clinical findings support continued development of the product. Importantly, the new BARDA contract included the procurement of StrataGraft by the U.S. government in the event of a mass casualty caused by a natural disaster or an act of terrorism.

In 2010 the Defense Department's Armed Forces Institute of Regenerative Medicine (operating in conjunction with Wake Forest University) funded the

[72]Stratatech, "Stratatech Awarded BARDA Contract Valued up to $47.2 Million for Advanced Development of StrataGraft® Skin Tissue for Thermal Burns," Press Release, July 31, 2013, accessed at http://www.stratatechcorp.com/news/20130731.php.

proof of concept Phase IIB clinical trial of StrataGraft®. In 2015 Stratatech received approval from the FDA to continue with a Phase 3 clinical trial, based on results from the Phase IIB. The Phase 3 trial will start in early 2016, to be funded by BARDA's Project BioShield.

Equity Funding and Operations

Stratatech has received ongoing support from Wisconsin's angel investor community and from the Wisconsin Advanced Research Foundation. For example, in May 2010 it announced $3.0 million in funding comprised of convertible notes from its current investors.

Strategic Partnership

In 2010 Stratatech entered into a collaborative agreement with a Fortune 200 consumer products company to develop an advanced skin care product. Dr. Allen-Hoffmann said that the objective was to develop the capability to provide testing kits for skin care products. The announced goal was to use extracts from the NIKS cell line to prevent wounds or ulceration by enhancing the resiliency of compromised or susceptible skin.

SBIR/STTR AT STRATATECH

Dr. Allen-Hoffmann stressed that the SBIR/STTR program at NIH had provided absolutely critical funding for Stratatech. She said that she had no doubt that her company and its associated products would not be in existence without SBIR/STTR funding. She also observed that the funding was especially important for a woman-owned company: other sources of capital were, in her view, even more inaccessible for a woman-owned small high-tech firm than they were for small high-tech firms in general.

In her view, STTR was particularly important. Some of the initial work—such as work on genetically enhanced tissues—had to be completed in the university lab as necessary equipment was not available at the University Research Park. Once Stratatech was established as a functioning company and the basic research had been completed, other sources of funding became more available.

Today, academic institutions continue to view STTR more favorably than SBIR, particularly with regard to issues related to the allegiance of faculty. University departments take a different view of projects where more of the work and most of the PI's time is committed to the university as opposed to the private sector. Dr. Allen-Hoffmann observed that despite some changes, tenure decision committees were still very conservative about the activities of junior faculty outside academia, and STTR provided an important mechanism for helping to resolve that tension.

Dr. Allen-Hoffmann said that Stratatech had participated in the Fast Track program in the early 2000s when working on developing cell-based ExpressGraft clones. The company feared that the Phase I-Phase II gap would kill the project. Fast Track had worked perfectly from the company's perspective. It had provided a seamless transition from Phase I to Phase II; in her view the company would have lost key people without it. Continuity of staffing remains a key issue for small companies.

RECOMMENDATIONS

Dr. Allen-Hoffmann observed that the SBIR program coordinators at each of the Institutes and Centers played a critical role. Although program officers in general have a strong commitment to the SBIR/STTR program, the SBIR program coordinators possess specific knowledge and can be extremely helpful in guiding investigators. She recommended that small companies make sure that they established contact with the program coordinators.

She also noted that the alignment between topics and awards had changed significantly over the past ten years. During her early years with the program, Dr. Allen-Hoffmann said that she was confident that a strong project would receive consideration and perhaps funding regardless of its connection to a topic described in the Omnibus Solicitation. That has changed over the years, and Stratatech now only applies for awards where there was a clear alignment between the topic and the proposal. In her view this was not a positive development for identifying and supporting innovation.

In addition, Dr. Allen-Hoffmann noted that contracting had become more complex because it was no longer possible to interact routinely with specific financial management officers at NIH. As a result, the advice received started to lack continuity. Continuity is especially important to a small firm trying to budget accurately.

Overall, Dr. Allen-Hoffmann said that she remains truly grateful for the support provided by the NIH SBIR/STTR program and that the technology could not have been developed without that support. The value of this program is immeasurable in helping patients and their families benefit from the world-class research conducted in the United States.

Targeson, Inc.: SBIR Case Study[73]

Meeting with
Jack DeFranco, CEO
June 18, 2014
San Diego, California

Targeson develops, manufactures, and markets acoustically active microspheres for the medical research market. Its research tools include ultrasound contrast agents for molecular imaging and targetable gene transfection agents.

Targeson was initially founded as a Limited Liability Corporation (LLC) based on the dissertation work of Joshua Rychak, PhD, at the University of Virginia, which was funded by a Phase I SBIR award. In 2009, Targeson, Inc. was formed as a merger of the assets of Targeson LLC and some key assets and technology from a previous company run by Mr. DeFranco. At the time of the merger Mr. DeFranco became President and CEO of Targeson, Inc. and established the company in San Diego.

Targeson provides targeted microspheres to the research community for use in animal models. Targeted microspheres are coated with molecules, called targeting ligands, that bind to another molecule of interest in the vascular system. Targeson offers microspheres that will target various types of vascular tissue markers, including angiogenic tissues (related to various cancers) and inflamed tissues (related to atherosclerosis and Crohn's disease).

TECHNOLOGY

Targeson's core platform technology is targeted microspheres. These microspheres are flexible, compressible, buoyant, have a high surface area to mass ratio, and are biocompatible—all characteristics to enable ultrasound imaging, gene transfection, and cell separation applications.

Microspheres are a mature technology when used to enhance image contrast in performing ultrasound imaging. Microspheres reflect sound waves much more efficiently than tissue and are used to heighten definition in blood perfusion studies. Targeson has augmented this technology by coating its microspheres with targeting molecules that adhere to receptors known to characterize particular markers in the endovasculature. This enables noninvasive visualization of intravascular disease structure with sonography. As an example, Targeson is producing imaging agents that target angiogenesis, the development of new blood vessels. Because angiogenic tissue is produced by cancer, researchers evaluating cancer

[73]Primary sources for this case study are the interview with Jack DeFranco and a review of the Targeson website http://www.targeson.com, and related company documents.

therapeutics in animal models can monitor tumor growth without sacrificing as many animals.[74]

Transfection is the deliberate introduction of nucleic acids and other genetic materials into cells. Targeson offers targeted microspheres as gene delivery vehicles for intravascular disease. Following injection into the bloodstream, transfection is enabled as microspheres attach to the target tissues—for example, the targeting ligands might attach to new blood vessel tissue. After sufficient microspheres have collected, the ultrasound technician initiates a pulse of sound waves. The acoustic waves cause the microspheres to disintegrate and deliver their genetic payload on target to the targeted tissue. This phenomenon, known as sonoporation, has been shown for the transfer of DNA and other macromolecules.[75]

PRODUCTS

Using SBIR funding, Targeson has improved both its imaging and transfection technologies. It offers these products as research tools for use in animal models.

Targeson, according to Mr. DeFranco, has had to reinvent itself as market and financing circumstances changed. It began as a company aiming to address the research ultrasound imaging market. However, as the preclinical market began to consolidate and financial market remained tight, Targeson shifted development into cell biology opportunities such as transfection and cell separation. This was possible because of the versatility of the microbubble platform.

Imaging Agents

Targeson offers three classes of imaging agents for medical research:

- Targeted Agents: Targeson's Visistar® line comes pre-loaded with widely used ligands already attached to the microsphere surface. Visistar Integrin and Visistar VEGFR2 target angiogenesis. Visistar VCAM1 and Visistar Selectin target inflammation.
- Labeling Agents: Targeson offers Targestar® SA that can accept any biotinylated ligand (such as an antibody or peptide[76]) on the microsphere's surface. Targestar provides a kit that explains how to attach the user's ligand of choice to the microsphere. Perfusion Agents: Targeson's

[74]Flordeliza Villanueva and William Wagner, "Ultrasound Molecular Imaging of Cardiovascular Disease," *Cardiovascular Medicine,* 2008, 5:S26-S32, http://www.readcube.com/articles/10.1038/ncpcardio1246.

[75]Joshua J. Rychak, et. al. "Analysis of In Vitro Transfection by Sonoporation Using Cationic and Neutral Microbubbles," *Ultrasound in Medicine and Biology,* Nov. 2010, 36(11):1907–1918. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996233/.

[76]Biotinylation is the covalent bonding of biotin to a protein, nucleic acid, or other molecule. In general, it does not affect the function of the bonded molecule.

Targestar-P and Targestar-P HF are intended for measurement of organ perfusion and microcirculatory blood flow.

Since 2007 Targeson has received $2.79 million from NIH SBIR awards to examine the use of microspheres for imaging different disease processes such as angiogenesis, inflammation, and acute myocardial syndromes. Related to a patent pending, Targeson also received SBIR funding to investigate the use of microspheres for optical imaging in the near infrared spectrum.

Transfection Agents

The Targeson product line offers a pair of microsphere products for cell transfection. Targesphere® is used for general purpose transfection. Targesphere SA offers the capability for the user to label the microsphere with biotinylated ligand for specific molecular targeted transfection. The genetic payload is coupled to the microsphere by incubation and activated using sonography. Since 2007 Targeson has received $1.63 million from SBIR to examine the use of microspheres for the transfective treatment of kidney disease.

In either transfection or imaging applications, the agent is injected into the animal and allowed to accumulate at the target site for 5-10 minutes. This allows clearance of any unbound agent, leaving only target-bound microspheres in the tissue which can then be activated or imaged with ultrasound.

According to Mr. DeFranco, Targeson currently has a database of more than 5,000 potential customers, including all the major pharmaceutical companies, all the larger contract research organizations, and many academics and academic laboratories. It has developed a web-based sales and marketing capability to serve its clients.

PATENTS AND OTHER INTELLECTUAL PROPERTY

Targeson's research has focused principally on the problem of targeting, transfection, and optical imaging using microspheres. Targeson has a patent pending for optical imaging.

Targeson owns over 20 patent families related to the use of microspheres. These patents were transferred to Targeson as part of the company's formation. They were previously owned by IMCOR Pharmaceuticals Inc. and Alliance Pharmaceutical Corp., both companies for which the current CEO of Targeson, Jack DeFranco, had worked.

FUNDING

Between 2010 and 2012, Targeson raised limited funds through individual investors and developing a strategic relationship with a Chinese pharmaceutical

company. In the absence of large equity or strategic investors, Targeson focused on producing and selling products for research use. However, Mr. DeFranco noted that all of these research products are relevant to Targeson's long-term goal of creating diagnostics for human use and that he anticipates that as the company grows, it will attract interest from a strategic partner for its technology.

Non-Dilutive Grants

Between 2007 and 2014, SBIR funded nine projects with Targeson. Targeson received 14 awards amounting to $4.25 million from the Department of Health and Human Services (HHS) to develop targeted microsphere technology for imaging and transfection applications.

TARGESON AND SBIR

Mr. DeFranco said that the SBIR program has been critical for Targeson. It provided initial support for the company's formation and since then had supported Targeson as it adjusted its tools and technologies to market realities.

Regarding major aspects of the program, Mr. DeFranco had few concerns. Broadly, he thought the program worked very well. He had comments about the NCI Bridge program, which offered $3 million over 3 years in support of clinical trials. He believed this was an important program given the difficulties in funding clinical trials, but also that it could be improved. In his experience, both venture firms and strategic investors did not see that the program met their needs. It required matching funds (minimum $1 million annually) be fully upfront committed before the award was made. Potential investors were reluctant to commit before the award was made. Targeson, for example, has an imaging agent for prostate cancer, but venture investors were apparently discouraged by Targeson's initial plans to apply for Bridge funding. Mr. DeFranco believed that take-up of these opportunities had, as a result of these difficulties, been low and strongly recommended that NIH find a way to make a preliminary commitment pending the completion of matching fund arrangements.

Mr. DeFranco was also a strong supporter of a new program at NHLBI—Science Moving towards Research Translation and Therapy (SMARTT). The program provides services for awards and seems particularly useful for SBIR companies. Available services include the following:

- Preclinical study planning and regulatory support
- Pharmacology and toxicology services
- Manufacturing of small molecules and non-biologics
- Manufacturing of biologics

Mr. DeFranco expected that SMARTT would be very helpful in connecting Targeson to the FDA and to support for toxicological studies via NHLBI's specialist contracts in the Research Triangle.

JULY 2015 UPDATE

Targeson has leveraged its imaging technology and recently progressed one of its ultrasound imaging agents into early preclinical developed. TS-07-009 as an ultrasound imaging diagnostic agent developed for the detection of the P-selectin adhesion molecule. P-selectin is a biomarker of myocardial ischemia in the context of Acute Coronary Syndrome. This progress was funded by Phase I and Phase II SBIR programs. In addition, Targeson received 2 non-monetary grants through the NIH/LARTA Commercial Assistance Program (CAP). These two grants led to obtaining a successful pre-IND meeting with the FDA for TS-07-009. This development may lead to interest from strategic and financial partners to move the product through clinical development. Targeson has applied and is eligible for the SMARTT program. Mr. DeFranco expects that, if awarded, it will be very helpful for the preclinical development of its lead clinical product TS-07-009.

Targeson was also issued its patent for the use of microspheres for optical imaging. It has also filed a patent application for the proprietary ligand used in TS-07-009.

TissueTech, Inc. and Bio-Tissue Inc.[77]

Meeting with
Dr. Scheffer Tseng, CEO
January 21, 2015

TissueTech, Inc. is a private company founded in 1997 by Amy Tseng and Scheffer Tseng. The company is developing amniotic tissue-based products to use in ophthalmology, optometry, orthopedics, and wound care. TissueTech is headquartered in Doral, Florida, where it recently opened a 10,000-square-foot state-of-the-art biotechnology manufacturing clean room. The company is part of a broader corporate structure that also includes two wholly-owned companies, Bio-Tissue Inc. and Amniox Medical Inc., through which it commercializes its technology in different markets (for the purposes of this case study, the group is collectively described as "TissueTech").

Dr. Tseng said that he had been moved to start TissueTech by the need to bring new techniques to many more people. While an employee of the University of Miami in the mid-late 1990s, he developed new tissue-based approaches for ocular surface problems in humans. This technology was in its infancy at the time, and the university had no interest in pursuing the technology through its technology transfer office. Ownership of the technology was returned to Dr. Tseng.

There was at the time demand from doctors for his innovative tissues, but he was concerned about liability issues and also wanted to see whether it might be possible to scale the technology sufficiently to provide services to many more patients. This led to the formation of the first company and to Dr. Tseng's decision to leave his Chair at the University of Miami in 2001. The company was formed with one part-time employee, based on a personal bank loan.

The company was initially challenged just to break even. According to Dr. Tseng, it faced difficulties because there were as yet no FDA regulations governing its products and potential products; so no reimbursement was available for its products from Medicare or the Centers for Medicare and Medicaid Services (formerly the Healthcare Financing Administration). And the company itself was still learning to operate effectively.

Dr. Tseng identified a number of key turning points in the path that led to the company's current annual revenues of about $55 million in 2015.

In 2001, the FDA initially issued guidance in relation to human cell products (HCP). This specifically noted that amniotic use in eyes was not to be included under the guidance. TissueTech discussed this issue at length with FDA, which eventually reversed its ruling and agreed that TissueTech products should be included under HCP guidance. This was, according to Dr. Tseng, a key change

[77]Primary sources for this case study are the meeting with Dr. Scheffer Tseng, and a review of the Bio-Tech and Amniox Medical websites (http://www.bio-tissue.com and http://www.amnioxmedical.com) and related company documents. TissueTech does not have its own website.

which made it possible to consider this could be the basis for a sustainable and even growing business.

In the same year, Dr. Tseng decided to leave his full-time position at the university, backed by the remaining 2 years of NIH RO1 grant support which moved with him out of the university.

The company was then confronted with a core strategic decision: whether to remain a pure R&D company, develop by licensing and manufacturing for other companies, or become a vertically integrated company which included sales activities directly to doctors and hospitals. Experts consulted at this time unanimously recommended that the company remain focused on R&D and avoid sales, as the latter was likely to be too expensive and risky. TissueTech in the end, however, decided to take on the additional risk. Dr. Tseng said that the key factor in the decision had been the need for direct feedback from patients to improve the product. He was clear that the profits were initially of limited interest—the company was focused on improving its products and finding customers.

Today, the company employs almost 40 direct full-time sales representatives in ophthalmology and an additional 15 representatives working on wound care. Overall the company has almost 225 employees and operates several facilities.

In 2013, the company received $10 million in the form of a private investment from two equity investors, which was used to expand the sales force and to support expansion into lines of business, notably wounds and orthopedic procedures, as well as international expansion. The investors are providing an additional $15 million in 2015 for further expansion.

The company is now working to move the product line to a biologics base. This is both costly and time-consuming, but will, according to Dr. Tseng, provide long-term protection against potential competitors. He predicts average annual growth of 30 percent of revenues in the coming years. Amniotic membrane has demonstrated capacity to enhance wound healing and tissue regeneration.

The core innovation owned by TissueTech is a cryogenic method called CryoTek™, which preserves this regenerative capacity of the amniotic membrane for long-term storage. Unlike other methods, the CryoTek™ process maintains the tissue in a hydrated (if frozen) state. This improves retention of the functional and structural integrity of the tissue and improves outcomes when used to heal wounds.

TissueTech is using amniotic tissues preserved using CryoTek™ to develop treatments for the ocular, orthopedic, and wound care markets. It is productizing this technology through two wholly-owned subsidiaries, Bio-Tissue, Inc. and Amniox Medical, Inc.

Bio-Tissue develops amniotic membrane–based products to treat ocular surface disorders and now provides three products based on this amniotic membrane technology: AmnioGraft®, an ocular transplantation graft; AmnioGuard®, a glaucoma shunt tube graft; and PROKERA®, a range of corneal bandage devices. Both PROKERA® and AmnioGuard® are in clinical trials to measure efficacy.

Amniox Medical, Inc. was founded in 2011 in Atlanta, Georgia, by Amy Tseng, Scheffer Tseng, and Aaron Smith to develop amniotic membrane–based products to accelerate wound healing. Amniox Medical has two products: CLARIX®, a general surgical wound covering or barrier, and NEOX®, a wound covering for dermal ulcers and other defects. Both CLARIX® and NEOX® are in clinical trials to measure efficacy.

Bio-Tissue employs more than 150 people. Much of this expansion occurred in 2013 following TissueTech's Series A funding. The company's workforce is diverse with about 80 percent drawn from minorities, and in 2014 Bio-Tissue received the annual Top Minority Business Award from the Greater Miami Chamber of Commerce awarded.[78] In 2015, the company received the Tibbetts Award from Small Business Administration/NIH for their successful commercialization of their innovative technology.

TissueTech maintains research relationships with institutions such as Bascom Palmer Eye Institute, the New York Eye and Ear Institute, Walter Reed National Medical Center, and Columbia University.

PRODUCTS—BIO-TISSUE

CryoTek™

Amniotic membrane has various innate regenerative properties that can be preserved and transplanted to other environments. Amniotic membranes have also been shown to have multiple clinical uses for ocular disorders, open wounds, skin burns, and leg ulcers. Numerous studies have shown the capacity of amniotic membranes to promote healing with minimal inflammation and scarring, similar to the healing processes seen in fetal tissues.[79]

Although desirable, the use of fresh amniotic membrane tissue for clinical applications is both impractical in a clinical setting and can pose a serious risk of disease. The CryoTek™ process is designed to enable long-term, safe storage of amniotic tissues, because it permits human placenta from a caesarian section to be stored for up to a year at -80°C prior to processing. The frozen placenta gradually thaws over 24 hours and is cleaned of blood clots using phosphate buffered solution (PBS). The amniotic membrane is separated by blunt dissection and rinsed with PBS until all blood discoloration disappears. The membrane is cut and packaged in a pouch containing medium and glycerol before storage

[78]"Top Entrepreneurial Awards," https://www.miamichamber.com/events/awards-programs/top-entrepreneurial-awards.

[79]For example, M. R. Kesting, et. al., "The Role of Allogenic Amniotic Membrane in Burn Treatment," *Journal of Burn Care Resources*, Vol. 29, 907 (2008); J. P. Bennett et. al., "Treatment of Chronic Ulceration of the Legs with Human Amnion," *Lancet* 1, 1153 (1980); or H. S. Dua, et al., "The Amniotic Membrane in Ophthalmology." *Survey of Ophthalmology* Vol. 49, 51 (2004).

at -80°C for up to 2 years. All TissueTech placental materials are harvested and prepared according to FDA regulation for Good Tissue Practices.

Most techniques for preserving amniotic membranes—dehydration and lyophilization, for example—substantially affect the characteristics of the membrane. With SBIR funding, TissueTech compared fresh and amniotic membranes preserved using CryoTek™. TissueTech found that there was no difference in the histological or biochemical features between the two sample types. Furthermore, although total protein and albumin levels were lower in cryogenically preserved tissues, the levels of hyaluronic acid (HA), heavy chain hyaluronic acid (HC-HA), and other anti-inflammatory, regenerative factors were similar.[80]

Ocular Inflammation—PROKERA®

The PROKERA® family of corneal bandages is designed to treat and heal a broad variety of inflammatory eye disease. By introducing amniotic membrane preserved using the CryoTek™ process, the ocular surface is exposed to a fetal microenvironment, which reduces inflammation, pain, and scarring of the eye. Depending on the intensity of the infection, the ophthalmologist can select from three contact lens–like devices, PROKERA Slim®, PROKERA®, and PROKERA Plus®. Each carries a different load of amniotic material. With local anesthetic, the device is inserted over the diseased eye and left in place for 24 hours.

In collaboration with Walter Reed National Medical Center, TissueTech is undertaking a study to demonstrate the effect of PROKERA® on corneal healing in terms of pain, visual recovery, and corneal clarity following photorefractive keratectomy, a common eye surgery used to improve nearsightedness, farsightedness, and astigmatism.[81] TissueTech used 23 percent of its SBIR funding in the development of its PROKERA® product line.

Ocular Transplantation Graft—AmnioGraft®

Inflammatory surface diseases of the eye are painful, lead to scaring, and can result in vision loss. AmnioGraft® is a biologic ocular transplantation graft used by eye doctors to treat ocular surface disorders. Indications include a variety of conditions such as keratitis, corneal ulcers, SPK, pterygium, conjunctivochalasis (CCh) dry eye, and Stevens-Johnson Syndrome. Surgical application of the amniotic tissues preserved in AmnioGraft® promotes regenerative healing of

[80]Ek Kia Tan, et. al., "Structural and Biological Comparison of Cryopreserved and Fresh Amniotic Membrane Tissues," *Journal of Biomaterials and Tissue Engineering*, Vol. 4, 2014, pp. 379-388. http://www.amnioxmedical.com/2ec733a07c_sites/www.amnioxmedical.com/files/PUBLISHED_Comparison_between_Cryopreserved_and_Fresh_Amniotic_Membrane.pdf.

[81]Samantha Rogers, "Sutureless Cryopreserved Amniotic Membrane Graft (ProKera) and Wound Healing After Photorefractive Keratectomy," https://clinicaltrials.gov/ct2/show/NCT00915759?term=prokera.

the ocular surface. TissueTech used about 30 percent of its SBIR funding in the development of the AmnioGraft® product.

Ocular Glaucoma Drainage Graft—AmnioGuard®

For many cases of glaucoma, surgeons install drainage devices to manage intraocular pressure. AmnioGuard® is a biologic glaucoma shunt tube graft used to cover and position tube shunts from glaucoma drainage devices. Because of its high tensile strength and because it does not require hydration, AmnioGuard® is easy to handle and suture during surgery. TissueTech used 21 percent of its SBIR funding in the development of the AmnioGraft® product. The company received an NIH SBIR grant to support conducting a prospective randomized control study to compare AmnioGuard® to pericardium to protect the glaucoma drainage shunt tube.

Facial Cleanser—Cliradex®

Cliradex® is a lid, lash, and face cleanser that helps manage symptoms associated with blepharitis, meibomian gland dysfunction (MGD), rosacea, dry eye, demodex, chalazia, and other lid margin diseases. Cliradex® is derived from Tea Tree Oil, which has a demonstrated effect as a cleanser on such diseases. Research by TissueTech isolated Terpinen-4-ol as the most active ingredient against demodex mites believed to cause many of these conditions.[82] TissueTech used 24 percent of its SBIR funding in the development of the Cliradex® product. Cliradex is the only Bio-Tissue product not based on CryoTek®. The company has received an NIH SBIR grant to conduct Phase I FDA safety study using Cliradex® for treating demodex mite infestation in patients with blepharoconjunctivitis.

PRODUCTS—AMNIOX MEDICAL

Amniox Medical is using cryogenically preserved amniotic tissues to improve healing of wounds created by surgery or disease. Because of its products' capacities to improve outcomes in various podiatric interventions, the company recently received the American Podiatric Medical Association Seal of Approval in recognition of its products' value as part of a podiatric wound care regimen.[83]

[82]Sean Tighe, et. al., "Terpinen-4-ol is the Most Active Ingredient of Tea Tree Oil to Kill Demodex Mites," *Translational Vision, Science and Technology*, Vol. 2, No. 7 (November 2013), 2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860352/.

[83]"AMNIOX® Medical's NEOX® and CLARIX® Product Lines Receive American Podiatric Medical Association (APMA) Seal of Approval," *BusinessWire*, July 24, 2014, http://www.businesswire.com/news/home/20140724005070/en/AMNIOX%C2%AE-Medical%E2%80%99s-NEOX%C2%AE-CLARIX%C2%AE-Product-Lines-Receive#.VL7SGdLF_Tq.

Wound Covering—CLARIX®

CLARIX® is a surgical covering, wrap, or barrier. CLARIX® modulates a wound environment, emulating the environment seen *in utero* and stimulating a fetal healing process. Case studies on the Amniox Medical website show CLARIX® being used for aftercare following a bunionectomy, repair of the peroneal tendon, and surgery for MTP joint pain.

Ulcer Covering—Neox®

NEOX® is a wound covering for dermal ulcers and defects. Case studies on the Amniox Medical website show NEOX® used to promote healing of various types of diabetic ulcers and a wound to the ankle. A significant application of NEOX® is on hard-to-heal ulcers on the feet and lower extremities for diabetics. *Podiatry Today* recognized NEOX® as one the top 10 podiatric innovations of 2012.[84]

PATENTS AND OTHER INTELLECTUAL PROPERTY

TissueTech is the assignee for the U.S. patents listed in Table E-14.

FUNDING

TissueTech has received support from both SBIR funding and private investors. NIH has also funded Dr. Tseng directly through the RO1 grant program.

Non-Dilutive Grants

Between 2003 and 2014, SBIR funded 10 projects with TissueTech. TissueTech received 17 SBIR awards amounting to nearly $5.50 million from the Department of Health and Human Services (HHS).

NIH grant support has been and remains critical to TissueTech's programs. The company started on the basis of an RO1 which continues today and has provided direct research support for Dr. Tseng for more than 30 years, on a continuous basis.

Soon after its formation, the company started to win SBIR awards at NIH. This funding was especially important, according to Dr. Tseng, during the early 2000s when the company was still small and had very limited resources. At the time, SBIR funding paid for almost all of the development costs for TissueTech products. The company used a small amount of angel funding to provide a cushion, while operating to a considerable extent on the basis of SBIR funding.

[84]Brian McCurdy, "The Top Ten Innovations in Podiatry," *Podiatry Today*, Vol. 25, No. 8 (August 2012), http://www.podiatrytoday.com/top-10-innovations-podiatry.

TABLE E-14 TissueTech Patents

Patent Number	Patent	Year
8,865,233	Compositions and methods for treating Demodex infestations	2014
8,865,232	Method for treating ocular Demodex	2014
8,460,714	Purified amniotic membrane compositions and methods of use	2013
8,455,015	Compositions and methods for treating Demodex infestations	2013
8,455,009	Amniotic membrane preparations and purified compositions and anti-inflammation methods	2013
8,440,240	Method for treating ocular demodex	2013
8,440,235	Amniotic membrane preparations and purified compositions and therapy for scar reversal and inhibition	2013
8,153,162	Purified amniotic membrane compositions and methods of use	2012
8,128,968	Compositions and methods for treating Demodex infestations	2012
7,824,671	Retinal pigment epithelial cell cultures on amniotic membrane and transplantation	2010
7,494,802	Amniotic membrane covering for a tissue surface and devices facilitating fastening of membranes	2009

SOURCE: U.S. Patent and Trademark Office

In 2001, the company brought its first FDA-approved products to market. Immediately after, CMS approved its products as reimbursable for Medicare and Medicaid, and private sector companies followed. Cash flow from product sales started to ease direct dependence on SBIR, but the company still largely relied on SBIR to fund the development of additional products. SBIR funding has since been used to develop two additional products.

The second additional product, PROKERA®, was approved as a Type II medical device, which had the effect of providing additional barriers to entry for potential customers. CMS then approved reimbursements for products approved under the new regulatory approach.

Equity Funding

In addition to grants from NIH, TissueTech has received Series A investment from a pair of venture funds.[85] (See Table E-15.)

[85]https://www.crunchbase.com/organization/tissuetech.

TABLE E-15 Equity investments in TissueTech

Investment Round	Amount	Cumulative	Date	Investors
Series B	$15.0M	$15.0M	6/15/2015	River Cities Capital Funds, Ballast Point Ventures
Series A2	$1.4M	$11.4M	10/15/2013	River Cities Capital Funds, Ballast Point Ventures
Series A1	$10.0M	$10.0M	8/22/2013	River Cities Capital Funds, Ballast Point Ventures

SOURCE: Crunchbase Equity Investment Database. Accessed February 14, 2015.

Operations

Although TissueTech does not generate income from operations, TissueTech's subsidiary, Bio-Tissue, has shipped more than 200,000 units of amniotic membrane–based products and enabled over 150,000 transplants. Since 2007, its compound annual ground rate is 35 percent. DoD has proven a reliable customer with nearly $300,000 in procurement from Bio-Tissue between 2007 and 2014.[86]

ROLE OF SBIR

Dr. Tseng said that SBIR was critical for the period when the company was newly established. It would not have been possible to build a successful company without SBIR, which funded the technical development and hence allowed all commercial revenue to be used to fund commercial expansion. SBIR had also funded the subsequent development of the technology and would continue to be an important supporter as the company moved toward a biologics base for its technology.

Since its inception, TissueTech had spent 20 percent of top-line revenues on R&D. Originally, almost all of this was funded through SBIR. Today, with much expanded revenues, the share of SBIR in overall R&D expenditures is declining—in 2014, it was about 20 percent of the total: SBIR contributed about $1 million in 2014, while TissueTech invested an additional $5 million.

Dr. Tseng observed that the company had successfully developed one product for each of its SBIR-supported lines of research. Today, the company is receiving SBIR funding for its work on cell-based solutions. It planned to be the first biologics company in ophthalmology.

[86]"Bio-Tissue Announces 35% Compound Growth," January 28, 2014, http://www.healio.com/optometry/business-of-optometry/news/online/%7B522a7d5d-c425-4c9a-a74d-cebd699e8f70%7D/bio-tissue-announces-35-compound-growth; "2013 Government Contracts Awarded," http://www.governmentcontractswon.com/department/defense/bio-tissue-965469885.asp?yr=13.

SBIR RECOMMENDATIONS

Dr. Tseng said that his main concern was about bridge funding while the company took a product through the FDA regulatory pathway. This was of declining importance for his own company, which now had other resources available for this purpose, but he believed it would be a critical problem for other companies.

Currently, SBIR funding was available for Phase I clinical trials, and it was just possible—if resources were used very carefully—to use SBIR Phase II awards to complete Phase 2 clinical trials. However, in most cases that was not possible—and many companies faced huge challenges in finding that funding.

Appendix F

Glossary

BARDA—The Biomedical Advanced Research and Development Authority

Bridge awards—matching funds Phase IIB program operated by the National Cancer Institute and other ICs

CSR—Center for Scientific Review

ERNSIT—NHLBI report on *Enhancing the Return on the NHLBI SBIR/STTR Investment Team*

FOA—funding opportunity announcement

ICs—Institutes and Centers

NCAI—NIH Centers for Accelerated Innovation

NCI—National Cancer Institute

NHLBI—National Heart, Lung, and Blood Institute

Phase IIB awards—Funding of up to $1 million annually, for up to 3 years, primarily for regulation-related activities

REACH—NHLBI Phase 0 program (Research Evaluation and Commercialization Hubs)

SRG—scientific review group

SRO—scientific review officer

Appendix G

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