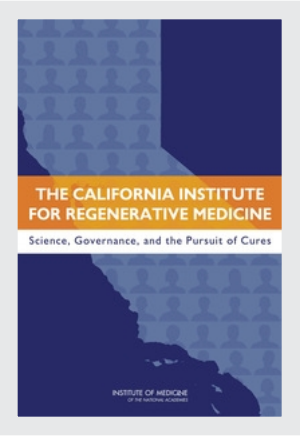


The California Institute for Regenerative Medicine: Science, Governance, and the Pursuit of Cures

DETAILS

216 pages | 6 x 9 | HARDBACK
ISBN 978-0-309-38402-5 | DOI 10.17226/13523

AUTHORS

Committee on a Review of the California Institute for Regenerative Medicine; Board on Health Sciences Policy; Institute of Medicine

THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Science, Governance, and the Pursuit of Cures

Committee on a Review of the
California Institute for Regenerative Medicine

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. 2267 between the National Academy of Sciences and the California Institute for Regenerative Medicine. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number-13: 978-0-309-26590-4
International Standard Book Number-10: 0-309-26590-8

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Suggested citation: IOM (Institute of Medicine). 2013. *The California Institute for Regenerative Medicine: Science, governance, and the pursuit of cures*. Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON A REVIEW OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

HAROLD T. SHAPIRO (*Chair*), President Emeritus, Professor of Economics and Public Affairs, the Woodrow Wilson School of Public and International Affairs, Princeton University, New Jersey

TERRY MAGNUSON (*Vice Chair*), Vice Dean for Research, School of Medicine, S.G. Kenan Professor and Chair, Department of Genetics, University of North Carolina at Chapel Hill

RICHARD R. BEHRINGER, Professor, Department of Genetics, the University of Texas MD Anderson Cancer Center, Houston

REBECCA S. EISENBERG, Robert and Barbara Luciano Professor, School of Law, University of Michigan, Ann Arbor

INSOO HYUN, Associate Professor, Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, Ohio

GARY A. KORETZKY, Francis C. Wood Professor, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

CATO T. LAURENCIN, Albert and Wilda Van Dusen Distinguished Professor of Orthopaedic Surgery; Professor of Chemical, Materials and Biomolecular Engineering; Chief Executive Officer, Connecticut Institute for Clinical and Translational Science; and Director, Institute for Regenerative Engineering, University of Connecticut, Farmington

AARON D. LEVINE, Assistant Professor, School of Public Policy, Georgia Institute of Technology, Atlanta

MICHAEL H. MAY, Chief Executive Officer, Center for Commercialization of Regenerative Medicine, Toronto, Canada

CHERYL A. MOORE, Executive Vice President and Chief Operating Officer, Howard Hughes Medical Institute, Chevy Chase, Maryland

STUART H. ORKIN, David G. Nathan Professor of Pediatrics; Chair, Department of Pediatric Oncology, Dana-Farber Cancer Institute; and Investigator, Howard Hughes Medical Institute, Harvard Medical School, Boston, Massachusetts

ALLEN M. SPIEGEL, Marilyn and Stanley M. Katz Dean, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York

SHARON TERRY, President and Chief Executive Officer, Genetic Alliance, Washington, DC

Consultant

RALPH SNYDERMAN, Chancellor Emeritus for Health Affairs; and James B. Duke Professor, School of Medicine, Duke University, Durham, North Carolina

IOM Staff

ADRIENNE STITH BUTLER, Senior Program Officer
JING XI, Research Associate
THELMA L. COX, Senior Program Assistant
DONNA RANDALL, Administrative Assistant
LORA K. TAYLOR, Financial Associate
ANDREW M. POPE, Director, Board on Health Sciences Policy

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 Research Council'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 deliberative process. We wish to thank the following individuals for their review of this report:

Laurence Baker, Stanford University
Christopher H. Colecchi, Broadview Ventures, Inc.
James Fossett, University of Albany
Joseph G. Hacia, University of Southern California
Zach Hall, Retired
Mark S. Humayun, University of Southern California
Edison Liu, The Jackson Laboratory
Mary Majumder, Baylor College of Medicine
Robert M. Nerem, Georgia Institute of Technology
Mahendra Rao, National Institutes of Health
David Resnick, Nixon Peabody
Janet Rossant, University of Toronto

William A. Sahlman, Harvard Business School
Bernard Seigel, Genetics Policy Institute
Nancy S. Wexler, Columbia University

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the report's conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Ellen Wright Clayton,** Vanderbilt University, and **Huda Akil,** University of Michigan. Appointed by the National Research Council and the Institute of Medicine, 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.

Preface

The energetic, imaginative, and committed coalition of California citizens and others responsible for the passage of Proposition 71 in the 2004 general election produced a social innovation. Although state initiatives in research and development are not new, this initiative, in both scope and design, broke new ground. In essence, the voters of California expressed a strong desire to move ahead in the field of regenerative medicine, including research using human embryonic stem cells, despite the ongoing near paralysis of the federal government in aspects of this arena. In the globalized world of biomedical research, they grasped the possibility that by building on California's already strong and deep biomedical research and biotechnology community and by structuring a distinctive model of finance, they could not only dramatically advance the field of regenerative medicine, but also establish California as one of the worldwide hubs in this promising area of biomedical research and development. At the time, this was also a courageous initiative given that certain aspects of regenerative medicine, especially work using embryonic stem cells derived from human embryos, were highly controversial in ethical terms. It is worth remembering that in 2004, there had been little demonstration of the potential for reprogramming somatic cells to bring them to a pluripotent state.

The California Institute for Regenerative Medicine (CIRM) was the organization charged with responsibility for thoughtfully expending the $3 billion set aside by voters through the passage of Proposition 71 to advance critical aspects of the field of regenerative medicine in California. Indeed, one of the Institute's principal aims was to help create in California an international hub of research and development in regenerative medicine. It

is the committee's judgment that overall, CIRM has done a very good job of initially establishing and then updating the strategic plans that have set priorities for and guided its programs, and of taking advantage of its guaranteed flow of $300 million per year for 10 years to establish a sustainable position in regenerative medicine for California. The challenge of moving its research programs closer to the clinic and California's large biotechnology sector is certainly on CIRM's agenda, but substantial achievements in this arena remain to be made.

Despite its demonstrable achievements to date, as well as the largely positive independent reports covering various aspects of its operations, no one would claim that CIRM is a perfect organization or that it should adhere slavishly to its initial form of organization, set of regulations, or pattern of priorities. The field of regenerative medicine has advanced rapidly since November 2004, and CIRM itself has seen the need to alter its activities and approaches in some areas. The committee believes the same should be true of its governance structure, some of its administrative practices, and its use of external perspectives on strategic scientific priorities and on the evaluation of other key policies, such as intellectual property, to ensure that they continue to encourage the development and deployment of new treatments. Experience has shown that Proposition 71 can, in partnership with the California Legislature and the governor, be amended in a manner that would optimize CIRM's functionality and best serve the interests of the citizens of California.

In this report, the committee has endeavored to evaluate various aspects of CIRM's programs and experiences with the aim of acknowledging both its successes and remaining challenges. The committee also has considered the lessons of CIRM's experience for other states, or even the federal government, that might wish to use CIRM's experience to inform some of their initiatives.

Finally, we wish to thank our colleagues on the committee for their tireless devotion to this task. We also wish to express our appreciation to CIRM for its openness and responsiveness to the committee's many requests for information during the course of this study.

Harold T. Shapiro, *Chair*
Terry Magnuson, *Vice Chair*
Committee on a Review of the California
Institute for Regenerative Medicine

Acknowledgments

Several individuals and organizations made important contributions to the study committee's process and to this report. The committee wishes to thank these individuals, but recognizes that attempts to identify all and acknowledge their contributions would require more space than is available in this brief section.

To begin, the committee would like to thank the sponsor of this study. Funds for the committee's work were provided by the California Institute for Regenerative Medicine (CIRM). The committee thanks Lynn Harwell, who served as project officer, and CIRM staff for their assistance during the study process.

The committee gratefully acknowledges the contributions of the many individuals who assisted in the conduct of this study. The perspectives of many individuals and organizations were valuable in understanding CIRM and its work. The committee thanks those who provided important oral testimony at its open workshops. Appendix A lists these individuals and their affiliations. As part of its review, the committee also visited three sites that receive CIRM funding to gather information about the role of that support in their work. In addition, many individuals with knowledge of CIRM, as well as analogous programs in other states, participated in interviews with committee members (see Appendix A). The committee also received written testimony through several questionnaires targeting various stakeholder groups. The committee greatly appreciates the time, effort, and information provided by all of these knowledgeable and dedicated individuals.

Contents

Acronyms

CCR5	C-C chemokine receptor type 5
CEO	chief executive officer
CFO	chief financial officer
CIRM	California Institute for Regenerative Medicine
CPRIT	Cancer Prevention Research Institute of Texas
CRADA	cooperative research and development agreement
CTRC	clinical translational research center
CTSA	Clinical and Translational Science Award
EAP	External Advisory Panel
FDA	Food and Drug Administration
FTE	full-time equivalent
GSP	gross state domestic product
GWG	Grants Working Group
hES	human embryonic stem (cell)
HHS	Department of Health and Human Services
ICOC	Independent Citizens Oversight Committee
IND	Investigational New Drug
IOM	Institute of Medicine
iPS	induced pluripotent stem (cell)
IRB	institutional review board

ISSCR	International Society for Stem Cell Research
MSCRF	Maryland Stem Cell Research Fund
NACD	National Association of Corporate Directors
NAS	National Academy of Sciences
NCSL	National Conference of State Legislatures
NGA	National Governors Association
NIH	National Institutes of Health
NRC	National Research Council
NYSTEM	New York State Stem Cell Science Research Fund
OTA	Office of Technology Assessment
R&D	research and development
RFA	request for applications
RNAi	ribonucleic acid interference
SAB	Scientific Advisory Board
SVP	senior vice president
SWG	Standards Working Group
TGR	The Guttmacher Report
UCLA	University of California, Los Angeles
UCSD	University of California, San Diego
UCSF	University of California, San Francisco

Summary[1]

ABSTRACT

The California Institute for Regenerative Medicine (CIRM) was created in 2005 by The California Stem Cell Research and Cures Act (Proposition 71) to distribute $3 billion in state funds for stem cell research. The passage of Proposition 71 by the voters of California occurred at a time when federal funding for research involving human embryonic stem cells was uncertain, given the ethical questions raised by such research. During its initial period of operations, CIRM has successfully and thoughtfully provided more than $1.3 billion in awards to 59 California institutions, consistent with its stated mission. As it transitions to a broadened portfolio of grants to stimulate progress toward its translational goals, the Institute should obtain cohesive, longitudinal, and integrated advice; restructure its grant application review process; and enhance industry representation in aspects of its operations. CIRM's unique governance structure, while useful in its initial stages, might diminish its effectiveness moving forward. The committee recommends specific steps to enhance CIRM's organization and management, as well as its scientific policies and processes, as it transitions to the critical next stages of its research and development program.

[1]This summary does not include references. Citations for the findings presented in the summary appear in the subsequent report chapters.

Proposition 71 (The California Stem Cell Research and Cures Act) was adopted by the voters of California on November 2, 2004, to provide substantial state support for a comprehensive in-state stem cell research program. The California Institute for Regenerative Medicine (CIRM) was created in 2005 to carry out this program. The act established a distinctive model of both finance and governance for CIRM. The Institute itself was to be governed by an Independent Citizens Oversight Committee (ICOC) and was to be financed through the issuance of long-term general obligation bonds of the State of California. CIRM was charged by Proposition 71 with determining the most effective means of distributing $3 billion in state funds for stem cell research and research on regenerative medicine more broadly over at least 10 years. Its principal aims are to accelerate certain critical aspects of the science of regenerative medicine and its translation into treatments for a spectrum of currently intractable human diseases.

Research on stem cells is an important area of biomedical research because of the promise it holds for developing new and more effective treatments for a wide variety of diseases. However, the past 15 years has seen continuing uncertainty regarding the federal government's willingness to fund research using human embryonic stem (hES) cells. Given that the federal government has traditionally been the largest source of funding for biomedical research outside of industry and the largest funder of basic research, some believed that the United States was forgoing an important opportunity to be a pioneer in developing the basic research necessary to produce critical new clinical applications. It was in this context that a broad group of California-based scientists, leaders in higher education in the state, disease advocates, and others mounted the Proposition 71 initiative. The aim of this initiative was to fill the gap created by fluctuating and uncertain federal policies, thereby helping both to develop new clinical modalities and to create a leadership position for California in this critical area of biomedicine. It is worth remembering that in 2004, there had been little demonstration of the potential for reprogramming somatic cells to bring them to a pluripotent state.

CHARGE TO THE COMMITTEE AND STUDY APPROACH

At the request of CIRM, the Institute of Medicine (IOM) convened the Committee on a Review of the California Institute for Regenerative Medicine in 2011 to critically review the Institute and produce a report including recommendations for how CIRM could improve its performance. The committee's statement of task is presented in Box S-1.

The committee was not asked to assess the wisdom of the California voters in passing Proposition 71. However, many of the detailed provisions of Proposition 71 directly impact aspects of CIRM's operations that the

BOX S-1
Statement of Task

The California Institute for Regenerative Medicine (CIRM) asked the Institute of Medicine (IOM) to convene a committee to produce a report providing an independent assessment of CIRM's programs, operations, strategies, and performance since 2005. Specifically, the committee was charged with addressing the following questions:

- **CIRM's initial processes—**What can be learned from the history and process of building consensus in the public and scientific communities to support the inception and work of CIRM?
- **CIRM's programmatic and scientific scope—**Does CIRM have the portfolio of projects and grant opportunities necessary to meet its scientific goals? How can CIRM improve upon its existing array of programs? What additional programs and initiatives are recommended to meet its goals? What impacts have been seen from international agreements? Does CIRM's scientific strategic plan address the range of relevant issues in regenerative medicine within CIRM's mandated scope of work?
- **CIRM's organizational and management systems—**Are the internal organizational and management systems (in particular the board and working group structures and operations, the peer review system, the conflict of interest guidelines, and the grants management system) effective in working toward the Institute's scientific goals? Are the systems that are in place scientifically and ethically valid and rigorous? Do they achieve the level of transparency and the level of stakeholder and scientific community involvement needed to meet the Institute's public responsibilities and scientific goals?
- **CIRM's funding model—**Has the funding model for CIRM had an impact on the work of the Institute? What are the advantages of CIRM's model for covering long-term costs of medical research? Could aspects of this funding model serve as a paradigm for other states or countries? What has been the economic impact of CIRM's research and facilities awards and grants?
- **CIRM's intellectual property policies—**What are the strengths and weaknesses of CIRM's policy for sharing revenue generated by intellectual property? How does this model compare to the model governing federally supported research?

The principal objective of this review was to ensure that all aspects of CIRM's operations are functioning at peak performance. The committee was asked to provide recommendations regarding short-, medium-, and long-term actions that could improve the performance of CIRM.

committee was asked to evaluate in its charge. The committee was also not asked to rigorously evaluate the details of CIRM's scientific contributions, specific grant awards, or impact on the field of regenerative medicine. This report evaluates some of the unique aspects of CIRM's origins, governance structure, and scientific and intellectual property policies. The report is intended to help CIRM consider the best path forward for achieving its mission.

CIRM'S ORIGINS AND TRANSITION

CIRM is in many ways a bold social innovation. CIRM's existence is the result of the work, initiative, commitment, and imagination of a broad, diverse, and evolving group of dedicated citizens, scientists, university leadership, disease advocacy organizations, and some members of the California Legislature. CIRM differs from many other competitive scientific research programs in its innovative funding model, which provides for a stable source of funding for research in regenerative medicine over 10 years, financed by the issuance of general obligation bonds of the State of California. This approach transfers the financing burden of current research funding from current to future tax revenues. In these respects CIRM is both a creative supplement to the more traditional sources of biomedical research funding in the United States and an innovative initiative designed to further strengthen California's biotechnology efforts.

Estimating the long-term economic impact of investments in a particular set of biomedical research activities is a complex task that requires at the very least considerable time and experience with various treatments and/or cures that result from those investments. In the short term, CIRM's expenditures are supporting approximately 3,400 jobs, and its innovative efforts have also attracted substantial additional private and institutional resources to this research arena in California. CIRM's long-term impact on such critical aspects of the California economy as state tax revenues and health care costs beyond the shorter-term and temporary impact of its direct expenditures cannot be reliably estimated at this point in CIRM's history.

Because the funding provided by Proposition 71 is limited to the $3 billion initially authorized, it is now critical for CIRM to continue to develop its plans for taking fullest advantage of its achievements in order to help support a sustainable future in which its funding circumstances could be quite different. The committee believes that in this process, it will be important for CIRM to increase industry inputs and share with the public any plans to obtain private-sector support for its ongoing activities and how any such arrangements might affect its continuing public obligations, including those related to CIRM-funded intellectual property, as well as its obligations as laid out in its access plans.

Recommendation 2-1.*[2] *Develop a Sustainability Platform. **CIRM should work with its current and future partners and those who have been substantial recipients of CIRM support to develop and present to the public its plans for sustaining the momentum of its achievements as it moves beyond its first decade of operations.**

Any such plan should address such key strategic areas as how CIRM intends to obtain funding after bond proceeds have been spent, how the venture philanthropy fund proposed in the 2012 Strategic Plan will interface with CIRM, and impacts of any new funding models on the role and structure of the ICOC.[3]

GOVERNANCE OF CIRM

Assembling the broad coalition of citizens and institutions that were united in their enthusiasm for stem cell research, but had somewhat different perspectives, had implications not only for the design of Proposition 71 but also for CIRM's ongoing programs and operations. While CIRM's restrictions on amending the administrative structure established in Proposition 71 had the advantage of protecting the Institute's ongoing operations from outside interference in an ethically controversial arena, they also made it difficult to modify the organization's structure in response to experience and/or changing circumstances. Moreover, these protections, whatever their benefits, appear to some to shield CIRM from the normal accountability mechanisms in place for state agencies. In assessing the governance of CIRM, the committee considered issues of operations versus oversight, the ICOC and working group structure, and conflict of interest definitions and policies.

Operations Versus Oversight

Proposition 71 established the 29-member ICOC as the governing board of CIRM and created three large working groups—a 19-member Scientific and Medical Accountability Standards Working Group, a 23-member Scientific and Medical Research Funding Working Group (Grants Working Group), and an 11-member Scientific and Medical Facilities Working Group—to provide guidance to the ICOC. The CIRM president serves as the Institute's chief executive officer, but the ICOC board chair has significant operational responsibilities in addition to managing the ICOC itself.

[2]The committee's recommendations are numbered according to the chapter of the main text in which they appear.

[3]See main body of the report for the full text of this recommendation.

In some cases, the allocation of responsibility for important management functions is split between the president and the board chair.

The committee recognizes that CIRM's current governance structure, as designed under Proposition 71, may have been appropriate at the start of the endeavor and contributed to its early success. Now that CIRM is a more mature organization, however, it would benefit from a clear and appropriate separation of duties, with the board being responsible primarily for independent oversight and strategy and staff for the implementation of the board's policies. The current structure of the ICOC impedes independent oversight because it relies on the ICOC to function as both overseer and executer.

The committee believes good governance requires that the board delegate more authority and responsibility for day-to-day affairs to the president and senior management. The Little Hoover Commission recommended that CIRM and the legislature eliminate overlapping authority between the chair and president and improve the clarity and accountability of each. This recommendation was echoed by the External Advisory Panel, which called for clarity in the division of roles and responsibilities between these two positions, particularly with respect to strategic direction, policies, international partnerships, funding decisions, public communications, and oversight.

Recommendation 3-1. Separate Operations from Oversight. **The board should focus on strategic planning, oversee financial performance and legal compliance, assess the performance of the president and the board, and develop a plan for transitioning CIRM to sustainability. The board should oversee senior management but should not be involved in day-to-day management. The chair and the board should delegate day-to-day management responsibilities to the president. Each of the three working groups should report to management rather than to the ICOC.**

Board and Working Group Structure

The predominance of direct stakeholders—defined as individuals with a direct stake in the process and outcomes of CIRM's activities that arises outside of their service to the Institute—in the composition of the ICOC compromises its independence beyond the entanglement of operations and oversight. Board members who have personal and professional interests in the activities of CIRM that go beyond the interests of the general public undoubtedly bring considerable energy and commitment to the tasks before them, but they may also introduce bias into the board's decisions that compromises its stewardship over CIRM as a public institution. The board's

composition should be modified to include a majority of members who are independent in the sense of having no direct personal or professional interest that might compete or conflict with the interests of CIRM and the people of California in ways that might bias their decisions (see also the discussion of conflict of interest below).

The working groups currently report to the chair. The committee believes they should report to CIRM senior management, with the ICOC being reserved to perform its responsibilities for high-level and independent strategic oversight. Thus, it is important that the chair and other ICOC members not serve on the working groups. As board members on the working groups are replaced, the working groups should not lose the fundamental and critical perspective of disease advocates; instead, any board members of the working groups who are disease advocates should be replaced by an equal number of other disease advocates who are not board members. The committee's recommendation is intended to both redefine and expand the role of disease advocates.

Recommendation 3-2. Change the Composition and Structure of the Board and Working Groups. **CIRM should put systems in place to restructure the board to have a majority of independent members, without increasing the size of the board. It should include representatives of the diverse constituencies with interests in stem cell research, but no institution or organization should be guaranteed a seat on the board. Consideration should be given to adding members from the business community. The terms of board members should be staggered to balance fresh perspectives with continuity.**

The chair and other ICOC members should be prohibited from serving on the working groups. During the reconstitution of the working groups, the current level of representation of disease advocates should be maintained, such board members being replaced with other disease advocates who are not board members.

Conflict of Interest Definitions and Policies

The built-in allocation of ICOC board seats to university leadership, patient advocates, and members of the biotechnology industry, for example, ensured that a high percentage of those seats would be permanently occupied by persons with almost unavoidable, conflicts of interest, whether actual or perceived, between their roles as ICOC board members and their other, non-CIRM responsibilities. At the very least the perceived conflicts are one factor that has led some observers, perhaps unfairly, to continue to question the integrity and independence of some of CIRM's decisions. Such

conflicts, real or perceived, are inevitable given the provisions of Proposition 71 and were not addressed by Senate Bill 1064.[4] Conflict of interest is not misconduct, but bias that potentially skews the judgment of a board member in favor of interests that may be different from or narrower than the broader interests of the institution. Inherent conflicts arise from the interests of board members as employees of grantees and as representatives of disease advocacy organizations. The committee did not uncover or search for evidence of any inappropriate behavior by any ICOC board members. The point is that the board suffers from a wide range of perceived conflicts generated directly by the particular and unique governance requirements of Proposition 71. This threatens to undermine respect for ICOC decisions.

California law focuses primarily on financial conflicts of interest, but the committee believes that personal conflicts of interest arising from one's own or a family member's affliction with a particular disease or advocacy on behalf of a particular disease also can create bias for board members. Studies in psychology and behavioral economics show that conflict of interest leads to unconscious and unintentional "self-serving bias" and to a "bias blind spot" that prevents recognition of one's own bias. Bias distorts evaluation of evidence and assessment of what is fair.

The presence of conflicts of interest for individual board members would be less cause for concern if the board had more non-conflicted members. CIRM should address real and apparent conflicts of interest, including and beyond financial interests, built into its governance structure regardless of whether these conflicts have in theory been waived by the voters or excused under California law.

Recommendation 3-3. Revise Conflict of Interest Definitions and Policies. **CIRM should revise its definitions of conflict of interest to recognize conflicts arising from nonfinancial interests, such as the potential for conflict arising from an individual's interest in a specific disease, and should reassess its policies for managing conflict of interest in light of this broader definition.**

An important theme of the committee's governance recommendations is for CIRM to transition from the governance structure initially outlined in Proposition 71 to one the committee believes would better serve the interests of the citizens of California and the field of regenerative medicine. In assessing CIRM's current governance structure and proposals for reform, the committee did not limit considerations and recommendations to the boundaries imposed by Proposition 71. Instead, the committee worked to

[4]California Legislature (Sen. Bill No. 1064), approved by Governor September 30, 2010. Filed with Secretary of State on September 30, 2010.

develop recommendations that would best serve CIRM and the California taxpayers from this point forward. The committee fully appreciates the fact that even in the best of circumstances, such a transition, if carried out thoughtfully, must take place over time.

THE SCIENTIFIC PROGRAM

The ICOC adopted its first scientific strategic plan in December 2006. The goals during this initial phase were to develop appropriate laboratory facilities for stem cell research, to fund basic research in stem cell biology, to invest in programs focused directly on research on a broad range of diseases, and to establish a long-term foundation for California's leadership in stem cell research and development. In this first crucial period of operations, CIRM provided—in a remarkably expeditious and thoughtful manner—more than $1.3 billion in awards to 59 institutions. The focus of these awards was fully consistent with CIRM's stated mission and was important for building the infrastructure for stem cell research in California. Collaborations with funding partners and stem cell researchers in the United States and around the world have attracted tens of millions of dollars in matching funds for CIRM projects, and resulted in new levels of cooperation and funding in the field. It is clear that in this initial period, CIRM substantially enhanced California's position as one of the key international hubs of activity in regenerative medicine.

Two years after developing its initial strategic plan, CIRM moved to broaden its portfolio of grants to stimulate progress toward its translational goals. Over time, 14 disease team awards totaling $210 million were made. A subsequent evaluation of the progress of these teams in 2011 led to the termination of one of these grants. It is not possible to say at this stage whether the net cast by CIRM's disease teams is too wide or too narrow. What is clear is that the resources ultimately required to bring any one of these initiatives to the bedside far exceed those available from CIRM.

Evolution Past the Initial Phase

In 2012, CIRM developed a new strategic plan outlining 10 goals that build on and extend those efforts articulated in the 2006 plan. The new plan increases the priority of projects clearly focused on moving toward clinical trials for evidence of therapeutic benefit and the development of partnerships with both industry and other centers for research in regenerative medicine. These are the key objectives that, in part, reflect CIRM's response to the 2010 External Advisory Panel review. This shift is illustrated further by the July 26, 2012, announcement of an additional eight disease team awards totaling approximately $151 million. These teams are

expected either to have filed a request to begin clinical trials or to have completed a Phase 1/2 clinical trial within 4 years. The latest round of awards brings the number of disease teams to 22 and the total funding for this program to approximately $360 million. CIRM-supported late-stage research projects now address 37 different disease areas.

Given the pressure for CIRM to show progress in therapeutic applications within its limited time frame, the rapid transition to the disease teams and the stated goals of the 2012 strategic plan are understandable. Nonetheless, based on the consensus of both academic and industrial stem cell experts who provided comments to the committee, and given both the lengthy time frame generally required for development of new therapies and the high failure rate of clinical trials at Phase 1 or 2, the committee believes the translational goals enumerated in the 2012 strategic plan are unrealistic. Instead of focusing purely on quantitative measures, such as numbers of trials and disease areas, CIRM should also focus on fundamental biological mechanisms that ultimately determine the success or failure of a specific disease intervention and on the careful design of translational studies to make them maximally informative even in the absence of any demonstrable clinical benefit.

To guide its ongoing implementation of the 2012 strategic plan, CIRM proposes to create a Clinical Advisory Panel and Industry Advisory Board. Although the committee supports CIRM's intent to establish advisory boards, it recommends that one Scientific Advisory Board be established. Striking the proper balance in research across the portfolio of basic, translational, and clinical studies will require that CIRM solicit broad input in executing its strategic plan. The committee believes the proposed Scientific Advisory Board could serve an invaluable role in this process.

Recommendation 4-1. Establish a Scientific Advisory Board. **CIRM should establish a single Scientific Advisory Board comprising individuals with expertise in the scientific, clinical, ethical, industry, and regulatory aspects of stem cell biology and cell-based therapies. A single Scientific Advisory Board, as opposed to multiple advisory boards as proposed in the 2012 strategic plan, would provide cohesive, longitudinal, and integrated advice to the president regarding strategic priorities, which is lacking in the current CIRM organizational structure. The majority of the members of the Scientific Advisory Board should be external to California, appointed by and reporting to the CIRM president. Such an external board would be invaluable in vetting ideas for new Request for Applications (RFAs), suggesting RFAs that otherwise would not have been considered, and helping CIRM maintain an appropriate balance in its research portfolio. Input from this board would help CIRM make fundamental decisions about dealing with**

challenges that cut across particular diseases, decide which discoveries should progress toward the clinic, and determine how best to engage industry partners in developing new therapies. The board's reports and the president's response to those reports should be delivered to the ICOC and discussed in sessions open to the public.

Omitted Areas of Emphasis

CIRM made strategic decisions that resulted in the omission of some important areas of emphasis during its initial phase, areas that fall squarely within the CIRM mandate. For example, there is a lack of RFAs addressing the novel ethical and regulatory aspects of clinical applications of potential stem cell therapies. Most of CIRM's ethics and public policy spending has focused on intramural funding for public outreach and education and the internal development of technical, instrumental, and procedural policy frameworks for basic stem cell research.

Also lacking are proposals that would prepare academic institutions in California for collaboration with the private biotechnology or large pharmaceutical sectors. CIRM has engaged industry in a number of ways. However, CIRM's relatively small investment in industry projects (roughly 6 percent of its total budget) and the notable absence of industry representatives on most disease teams demonstrate the inadequate emphasis of CIRM's translational/development RFAs on what is needed to enable regulatory approval for cell-based therapies.

Recommendation 4-3. Fund Research and Training on Ethical and Regulatory Issues. **CIRM should sponsor training programs and workshops and offer new grant opportunities aimed specifically at identifying and addressing ethical and regulatory issues surrounding stem cell–based clinical trials research. CIRM should use the information resulting from these initiatives, together with current knowledge, to strengthen its ethical standards for CIRM-funded human subjects research based on sound empirical and theoretical grounds.**

Recommendation 4-4. Enhance Industry Representation in Key Aspects of CIRM Organization. **Industry representation on the ICOC, the Scientific Advisory Board, the Standards Working Group, and the Grants Working Group should be enhanced to leverage industry's expertise and resources in product development, manufacturing, and regulatory approval in support of the ultimate goal of bringing therapies to patients.**

Grant Review and Funding Process

The committee recognizes the magnitude of CIRM's successful effort to develop a grant management infrastructure within a remarkably short period of time following passage of Proposition 71. Given the complexity of this endeavor and the legislated limitation on staff size (initially no greater than 50 full-time equivalents), the overall success of this grant management infrastructure is impressive.

At the same time, CIRM's credibility requires that the grant review process be expert, transparent, and fair. The committee has considerable concern about the role of the ICOC with regard to management versus oversight of CIRM activities, particularly for the grant-making process. The ICOC may move applications from one tier to another before taking a final vote. Examination of ICOC records indicates that the shifting of applications from one tier to another does occur, including some for major programs with large budgets. As of October 22, 2012, 62 extraordinary petitions were heard by the ICOC, of which 20 (32 percent) were successfully funded. The committee is troubled by the extraordinary petition mechanism and suggests that this practice be eliminated.

Given that membership of the ICOC includes individuals who have vested interests in which diseases are supported by grants and who represent institutions that stand to benefit greatly from grant-making decisions, it is not surprising that, even if no actions have been taken as a result of these interests, many in the community feel that irreconcilable conflicts exist. The committee believes these inherent and perceived conflicts diminish the credibility of the ICOC and therefore decrease its potential to be effective as a transparent, impartial body.

Recommendation 4-2. Restructure the Grant Review and Funding Process. **CIRM should restructure the grant review and funding process to separate oversight and strategic planning from day-to-day operations. The ICOC should remain responsible for oversight and articulation of an overall strategic plan. However, grant management, funding recommendations, and grant administration should be the responsibility of the CIRM scientific staff, reporting to the president. This restructuring would help mitigate concerns related to conflicts of interest and would also put the review and funding process in the hands of those best equipped to make those decisions.**

The committee recommends several changes pertaining to the development and approval of RFAs, composition of the Grants Working

Group, reordering of rankings by CIRM staff, notification of applicants, and process for making final decisions.[5]

INTELLECTUAL PROPERTY POLICIES

Intellectual property is a policy tool for motivating investments in innovation. CIRM has devoted considerable attention to the development of its intellectual property policies, repeatedly drafting and revising them in response to wide-ranging feedback from various stakeholders.

The argument for intellectual property rights differs for inventions developed with public funds and those funded privately. When the public bears the cost and risk of the research and development that yields an invention, it is arguable whether the public should not have to pay again for the same invention through higher prices as a result of the exclusionary rights conferred by patents. Often, however, substantial further private investment is necessary after government funding ceases, especially when the recipient of the latter funding is a research institution that is not in the business of translating new scientific discoveries into commercial products.

The Bayh-Dole Act of 1980 has been particularly influential in setting the ground rules for patenting of inventions by universities. While the intellectual property policies of CIRM follow the broad contours of the Bayh-Dole regime, there are some differences.

Consistent with the approach of the Bayh-Dole Act,[6] Proposition 71 appears to assign a significant role to contracts as a mechanism for implementing CIRM's intellectual property policies by binding grantees to its terms.[7] In practice, however, CIRM has instead used regulations to govern intellectual property for CIRM-funded research results. By their terms, these regulations bind not only CIRM grantees and loan recipients but also their collaborators and licensees, and even third parties who subsequently acquire rights from them.[8] Some flexibility is built into the regulations, but this flexibility also creates uncertainty as to how the regulations will be applied in the future. In addition, CIRM's intellectual property poli-

[5]See main body of the report for full text of this recommendation.

[6]35 U.S.C. § 202(c).

[7]Proposition 71 divides responsibility for CIRM's intellectual property policies among the ICOC, which is assigned to "establish policies regarding intellectual property rights arising from research funded by the institute"; the chairperson, whose responsibilities include "to lead negotiations for intellectual property agreements, policies, and contract terms"; and the president, whose responsibilities include "to manage and execute all intellectual property agreements and any other contracts pertaining to the institute or research it funds." Codified at California Health and Safety Code § 125290.40.

[8]California Health and Safety Code § 125290.40(j); interview with Scott Tocher and Elona Baum, January 24, 2012.

cies apply to a broader range of research outcomes than is covered by the Bayh-Dole Act.

Moreover, CIRM's intellectual property regulations, unlike Bayh-Dole, call for revenue sharing, with provisions designed to generate direct financial returns to the state treasury. Perhaps the most controversial aspect of CIRM's intellectual property provisions is the requirement that grantees and their exclusive licensees submit to CIRM "access plans" that will afford access to any drug resulting from CIRM-funded research to "Californians who have no other means to purchase the drug."[9] Federal law and other state-funded stem cell programs have no comparable provisions. Uncertainty about how the system will work could make industry cautious about licensing and investing in CIRM-funded inventions, especially if they have the option of turning to other sponsors that do not impose similar requirements.

CIRM holds "march-in rights" that allow it to enter into license agreements on behalf of a grantee or its exclusive licensee with respect to a CIRM-funded invention under three circumstances: (1) the grantee, collaborator, or exclusive licensee is failing to exercise reasonable efforts to achieve practical application of the invention; (2) the grantee, collaborator, or exclusive licensee has failed to submit or comply with an access plan; or (3) the grantee, collaborator, or exclusive licensee has unreasonably failed to use a CIRM-funded invention to alleviate a public health emergency declared by the governor.[10]

Overall, CIRM's intellectual property policies reflect a reasonable effort to balance conflicting interests of different constituencies, each with a legitimate stake in these policies. The actual impact of the policies may not be clear for many years, but the concerns of stakeholders are already apparent. Some of the more contested provisions attempt to address competing views by giving CIRM discretion over implementation, but this flexibility cuts two ways: it allows for adaptation to particular circumstances, but it also creates uncertainty and risk for potential developers of commercial products. CIRM might reduce some of the uncertainty arising from the unfamiliarity of its policies by modifying those policies to conform more closely to the more familiar Bayh-Dole approach. Departures from the Bayh-Dole approach may put CIRM-funded invention at a growing disadvantage in the future as funding from other states and the federal government yield competing candidates for commercial development that are available for licensing on more favorable terms.

[9]California Health and Safety Code § 125290.80; 17 California Code of Regulations § 100607.

[10]17 California Code of Regulations § 100610(b).

Recommendation 5-1. Incorporate Future Enforcement of Intellectual Property Policies in the Sustainability Platform. **As part of the plan maximizing the continued impact of CIRM's many achievements (see Recommendation 2-1), CIRM should propose regulations that specify who will have the power and authority to assert and enforce in the future rights retained by the state in CIRM-funded intellectual property. CIRM should seek to clarify which state agencies and actors will be responsible for the exercise of discretion currently allocated to CIRM and the ICOC over future determinations on issues regarding march-in rights, access plans, and revenue-sharing rights that might arise years after CIRM's initial funding period has passed. As it has done in the past, CIRM should provide ample opportunity for public comment on proposed changes to its intellectual property policies that pertain to transition planning.**

Recommendation 5-2. Consider Harmonizing Intellectual Property Policies with Policies of Bayh-Dole Act. **As other sources of funding for stem cell research become available and as the field of regenerative medicine advances from the laboratory to the clinic, the ICOC should reconsider whether its goal of developing cures would be better served by harmonizing CIRM's intellectual property policies wherever possible with the more familiar policies of the Bayh-Dole Act.**

CONCLUSION

The creation of CIRM resulted from the initiative, imagination, and hard work of a broad group of stakeholders in California. In its initial years, CIRM has been highly effective in building an impressive research portfolio. The Institute's governance structure is, however, unusual in important respects that the committee believes could diminish its effectiveness going forward. While the profile of the ICOC was understandably designed to include representatives from a broad range of those most concerned and most knowledgeable regarding the future of regenerative medicine, its members were also the constituencies expected to benefit most directly and immediately from CIRM's grants. The committee believes that CIRM and the taxpayers of California would be better served going forward by a structure and processes whereby the role of the ICOC would remain focused on broad oversight and strategic planning rather than involvement in day-to-day management issues.

The committee has offered several recommendations for CIRM and the transition to its next stage of operations. As discussed above, the committee did not limit its recommendations to the boundaries imposed by Proposition 71. In the committee's view, some recommendations (2-1, 4-1, 4-3,

and 5-1) can be carried out by CIRM without legislative action. For others (3-1, 3-2, 3-3, 4-2, 4-4, and 5-2), CIRM may be able to make modest moves in line with the recommendations, but it may need to work with the state legislature in order to fully implement them. The committee is aware that its recommendations come at a time when CIRM may well be faced with pressing challenges resulting from the expiration of Proposition 71 funding and/or dynamic changes in the field of regenerative medicine. The committee hopes its recommendations will be considered not only now, but also in the future as decisions are made.

1

Introduction and Context

On November 2, 2004, Proposition 71[1] (The California Stem Cell Research and Cures Act, reproduced in Appendix C) was adopted by the voters of California. Its purpose was to provide substantial state support for a comprehensive in-state stem cell research program or, more broadly speaking, to make a significant investment in biomedical research within the field of regenerative medicine in California. Proposition 71 also amended the state constitution to provide freedom to conduct pluripotent and progenitor stem cell research and established a distinctive model of both governance and long-term finance for this publicly financed activity in biomedical research.[2] In 2005, the California Institute for Regenerative Medicine (CIRM), charged by Proposition 71 with determining the most effective means of distributing $3 billion in state funds for stem cell research over at least 10 years, was created and began its operations. CIRM's principal aims were to accelerate certain critical aspects of the science of regenerative medicine, emphasizing pluripotent stem cell and progenitor cell research and other vital medical technologies, and its translation into the treatment of a spectrum of currently intractable human diseases. In addition, CIRM sought to establish California as one of the world's

[1]California Stem Cell Research and Cures Initiative, Proposition 71 (2004) (codified at California Health and Safety Codes § 125291.10-125291.85).

[2]In September 2002, California had enacted a law to permit research involving human embryonic stem cells. California Health and Safety Codes § 123440, 24185, 12115-7, 125300-320.

principal hubs in this area of biomedicine.[3] Under the terms of Proposition 71, the Institute was to be governed by an Independent Citizens Oversight Committee (ICOC).

In both its formation and its ongoing operations, CIRM has sought advice from a wide range of sources and has been the subject of a series of external evaluations. During the initial campaign for Proposition 71, the California Research and Cures Coalition, comprising the principal advocates for Proposition 71, consulted from time to time with the National Academy of Sciences (NAS) and the Institute of Medicine (IOM), as well as others, as they designed the proposition's details. Once established, CIRM again consulted the NAS and IOM for help in establishing the initial set of ethical guidelines for its research program (IOM, 2005). In addition, a number of studies have been commissioned to assess the potential economic impact of CIRM's activities. One such study, by the Analysis Group (Baker and Deal, 2004), preceded the Institute's establishment, and two others (an update by the Analysis Group [Baker and Deal, 2008] and an independent study by Jose Alberro [2011]) were completed more recently. In 2009, California's Little Hoover Commission, responding to a suggestion by two California legislators, undertook an evaluation of CIRM's governance structure, its conflict of interest policies, and its responsibilities in the area of accountability.[4] The Commission issued a report suggesting some significant changes in these areas, only a few of which CIRM adopted (LHC, 2009).[5] In addition, every 2 years, as required by California law, CIRM must report on the quality of its system of internal control. In 2012, as required under Senate Bill (SB) 1064[6] (2010, also reproduced in Appendix D), which amended certain provisions of Proposition 71, CIRM underwent an independent performance review aimed at evaluating its administrative procedures and its compliance with various responsibilities as laid out in both Proposition 71 and SB 1064 (Moss Adams, LLP, 2012). Finally, in 2010 CIRM convened a broad-based External Advisory Panel (EAP) comprising a distinguished international group of scientists, industry representatives, and global health leaders to assess the broad nature of

[3]Operations were delayed for more than a year by various legal challenges to Proposition 71, but the courts of California ruled decisively against these challenges. During this delay, CIRM initiated its operations through financing provided by private philanthropy and a loan from the State of California.

[4]The Little Hoover Commission is an independent state oversight agency whose mission is to investigate state government operations with the aim of promoting efficiency, economy, and improved service. The Commission selects its own agenda in deciding which government operations it wishes to study.

[5]CIRM'S response to the Little Hoover Commission's report (CIRM, 2012).

[6]California Legislature (Sen. Bill No. 1064), approved by Governor September 30, 2010. Filed with Secretary of State on September 30, 2010.

CIRM's scientific program and future plans (EAP, 2010). The EAP's report encouraged CIRM to continue its programs, but with a sharper emphasis on moving research in regenerative medicine toward clinical applications. Reports resulting from these various reviews have in general been highly positive, although, as noted above, the Little Hoover Commission made a series of recommendations, some echoed in the recent performance review (Moss Adams, LLP, 2012), regarding more efficient/effective governance and administration.

STATEMENT OF TASK AND STUDY APPROACH

In 2010, as CIRM approached the midpoint of its 10-year state funding horizon, it asked the IOM to provide an independent assessment of the process through which it was established and of its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies. The IOM Committee on a Review of the California Institute for Regenerative Medicine, comprising experts in developmental biology, stem cell research, research administration, bioethics, economics, business administration, finance, program evaluation, intellectual property, consumer perspectives, and policy, was assembled in 2011 to critically review the Institute and produce a report containing recommendations for ways in which it could improve its performance. The committee's statement of task is presented in Box 1-1.

The committee used several methods for data collection. First, it held five meetings and hosted three public meetings (one in Washington, DC, and two in California) to gather information on topics related to the study charge and to hear stakeholder perspectives on the operations of CIRM. The committee also received an extensive set of documents from CIRM describing its history, structure, operations, and policies; reviewed previous reports, detailed above, evaluating various aspects of the Institute; and gathered information through several questionnaires.[7] In addition, committee members visited three institutions that receive CIRM funding for facilities, research, and training to review some of the facilities funded by CIRM, to speak with both CIRM-funded investigators and the leaders of these institutions, and to learn firsthand about the CIRM-funded work being conducted.[8] The study methods are described more fully in Appendix A.

The purpose of this report is to present the committee's assessment of CIRM's organization, policies, and performance. The committee's find-

[7]The committee wishes to acknowledge the assistance of CIRM staff in expeditiously assembling a great deal of information for this study.

[8]The institutions visited were the University of California, San Francisco; Stanford University; and the University of California, Davis.

BOX 1-1
Statement of Task

The California Institute for Regenerative Medicine (CIRM) asked the Institute of Medicine (IOM) to convene a committee to produce a report providing an independent assessment of CIRM's programs, operations, strategies, and performance since 2005. Specifically, the committee was charged with addressing the following questions:

- **CIRM's initial processes—**What can be learned from the history and process of building consensus in the public and scientific communities to support the inception and work of CIRM?
- **CIRM's programmatic and scientific scope—**Does CIRM have the portfolio of projects and grant opportunities necessary to meet its scientific goals? How can CIRM improve upon its existing array of programs? What additional programs and initiatives are recommended to meet its goals? What impacts have been seen from international agreements? Does CIRM's scientific strategic plan address the range of relevant issues in regenerative medicine within CIRM's mandated scope of work?
- **CIRM's organizational and management systems—**Are the internal organizational and management systems (in particular the board and working group structures and operations, the peer review system, the conflict of interest guidelines, and the grants management system) effective in working toward the Institute's scientific goals? Are the systems that are in place scientifically and ethically valid and rigorous? Do they achieve the level of transparency and the level of stakeholder and scientific community involvement needed to meet the Institute's public responsibilities and scientific goals?
- **CIRM's funding model—**Has the funding model for CIRM had an impact on the work of the Institute? What are the advantages of CIRM's model for covering long-term costs of medical research? Could aspects of this funding model serve as a paradigm for other states or countries? What has been the economic impact of CIRM's research and facilities awards and grants?
- **CIRM's intellectual property policies—**What are the strengths and weaknesses of CIRM's policy for sharing revenue generated by intellectual property? How does this model compare to the model governing federally supported research?

The principal objective of this review was to ensure that all aspects of CIRM's operations are functioning at peak performance. The committee was asked to provide recommendations regarding short-, medium-, and long-term actions that could improve the performance of CIRM.

ings, conclusions, and recommendations are intended to address particular aspects of CIRM's operations and to assist the Institute in its future planning. Additional audiences for the report include other entities that fund biomedical research, policy makers, researchers, and the public.

It is important to be clear that this committee was not asked to assess the wisdom of the California voters in passing Proposition 71. However, many of the detailed provisions of Proposition 71 directly impact aspects of CIRM's operations that the committee was asked to evaluate in its statement of task. For example, Proposition 71 details certain aspects of CIRM's management and governance structure, as well as its funding model. The committee was not charged with rigorously evaluating the details of CIRM's scientific contributions, specific grant awards, or its impact on the field of regenerative medicine; however, the committee did examine CIRM's overall scientific priorities and the quality of the processes instituted to guide its funding priorities and decisions. In summary, the conclusions expressed throughout this report address some of the unique aspects of CIRM's beginnings, governance structure, policies, and ongoing efforts. The report considers the vitality and success of the important dimensions of the Institute's activities and presents the committee's assessment of whether this is a useful model for others to consider. Finally, the report is intended to help CIRM consider the best path forward as it works to meet its obligations to the citizens of California and the field of regenerative medicine. The remainder of this chapter briefly reviews the character and potential of stem cell research and the controversy that provides the historical context for the creation of CIRM.

CHARACTER AND POTENTIAL OF STEM CELL RESEARCH

Research on stem cells remains an important area of biomedical research because of its anticipated potential to yield new and more effective treatments for a wide variety of diseases. Stem cells have the critical characteristic that they can self-renew and also differentiate into a variety of specialized cell types (The National Academies, 2009; NIH, 2010). There are two major types of stem cells—adult and embryonic. Adult stem cells, sometimes referred to as "tissue-specific" or "somatic," generally are thought to have more limited developmental potential—for example, giving rise only to cells within a particular tissue or organ. Human embryonic stem (hES) cells are pluripotent cells derived from the inner cells of the 3- to 5-day-old embryo (the blastocyst), which give rise to the entire body of the human organism (Thomson et al., 1998) and retain the potential to differentiate into almost all types of cells (ISSCR, 2011). More recently, scientists have been able to reprogram differentiated adult cells into cells that closely resemble hES cells (Takahashi and Yamanaka, 2006; Takahashi et al.,

2007); however, the full therapeutic and scientific potential of these induced pluripotent stem (iPS) cells requires continued exploration (Robinton and Daley, 2012). Both hES and iPS cells are often referred to as pluripotent stem cells because they have, in principle, the capability to give rise to all adult tissues.

The ability of these different types of stem cells to self-renew and differentiate into more mature cell types is the foundation of the regenerative medicine field, providing hope for repairing or supplementing a patient's damaged tissue (Robinton and Daley, 2012). Furthermore, stem cell therapy, if successfully developed, could potentially treat diseases, such as Parkinson's disease, type 1 diabetes, and spinal cord injury, for which current forms of therapy are less than adequate, and although even more challenging, could potentially be used in treatment of other serious diseases that historically have had poor outcomes, such as Alzheimer's disease, stroke, and some types of cancer. Another use of stem cells is to help test and develop new drugs (Grskovic et al., 2011). Because pluripotent stem cells can differentiate into a variety of differentiated cell types, drug testing can be performed on these cells before clinical trials are conducted on human subjects, making it possible to test the drugs' effectiveness and adverse effects more efficiently, particularly in patient-specific stem cell lines (Yu and Thomson, 2010). Pluripotent stem cells (both hES and iPS) derived from patients with specific diseases have also proved useful in studying disease pathogenesis. This has been clearly demonstrated for "cell-autonomous" diseases such as long QT syndrome, in which cardiomyocytes differentiated from patient-specific pluripotent stem cells display the abnormal electrophysiologic phenotype characteristic of the disease. Regenerative medicine can be defined as the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. This can be done through a variety of approaches including the replacement of tissue function with synthetic constructs (artificial organs) and using cellular therapies such as stem cells or genetically modified cells to generate new tissues and organs (ESF, 2012).

THE STEM CELL CONTROVERSY

Because the derivation of hES cells involves the destruction of human embryos, the scientific community and others immediately recognized that the use of these cells raises important ethical questions regarding the moral status of the embryo; whether research that involves the destruction of embryos is morally acceptable; and if so, whether such research should be funded by federal or state governments. Given the continuing and sharply different perspectives on these key ethical issues, the controversy regarding the appropriateness of public funding for research that requires creat-

ing and/or using hES cells has remained unresolved. The tension between this unsettled ethical controversy and the perceived potential of this new area of biomedical research is reflected in the fact that Presidents Clinton, George W. Bush, and Obama all found it necessary to clarify their differing views on these matters by issuing a series of policy guidelines governing the provision of federal funds for research that involves creating and/or using hES cells.[9]

It is also important to recall that the controversy over federal funding of research using human embryos or aborted fetuses predates these more recent developments in stem cell research. Embryo research was, for example, the focus of considerable controversy in the mid-1990s, which led to the Dickey-Wicker Amendment of 1995 forbidding the expenditure of federal funds for research that created or harmed human embryos. Indeed, as early as the 1960s, scientists were already experimenting with the use of aborted human fetal tissue in an effort to understand human development (e.g., August et al., 1968; IOM, 1994; NIH, 1994). As a matter of policy, however, no federal funding was available for research using human embryos during the administrations of Presidents Reagan and George H.W. Bush.

This moratorium on federally funded research using human fetal tissue was lifted, with certain restrictions, relatively early in the administration of President Clinton.[10] Very soon thereafter, however, President Clinton further clarified his views to ensure that federal funds would not be used for research involving the destruction of human embryos.[11] After Thomson and colleagues (1998) had demonstrated the possibility of creating and sustaining hES cell lines, the Clinton Administration, through the National Institutes of Health (NIH), issued guidelines in 2000 for grants funding hES cell research. No federal funding was to be allowed for the creation of new hES cell lines, and in fact, no grants for research with hES cells were issued before the end of the Clinton administration.[12]

The administration of George W. Bush took an immediate interest in this controversy, and on August 9, 2001, the president announced that

[9]See *National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells* (65 Fed. Reg. 51976-51981 [2000]) for the Clinton administration's policy; *Address to the Nation on Stem Cell Research from Crawford, Texas* (37 Weekly Comp. Pres. Doc. 1149 [August 9, 2001]) for the Bush administration's policy; and *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells* (74 Fed. Reg. 10667 [2009]), and *National Institutes of Health Guidelines for Human Stem Cell Research Notice* (74 Fed. Reg. 32170 [2009]) for the Obama administration's policy.

[10]*National Institutes of Health Revitalization Act of 1993*, Public Law 103-43, 107 Stat. 122 (1993), 42 U.S.C. § 201.

[11]*Statement on the Federal Funding of Research on Human Embryos*, 30 Weekly Comp. Pres. Doc. 2459 (December 2, 1994).

[12]*National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells* (65 Fed. Reg. 51976-51981 [2000]).

federal funds would be available only for work with hES cell lines that had been developed prior to that date.[13] The impact of this new policy was widely debated in the scholarly and disease advocacy communities.[14] In fact, because NIH was unable to take the lead in this area, the National Academies convened a committee to draft voluntary guidelines for hES cell research (NRC and IOM, 2005).

In March 2009, shortly after taking office, President Obama issued an executive order allowing NIH support for hES cell research to the extent permitted by law. Executive Order 13505—*Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*—states that the Secretary of Health and Human Services, through the director of NIH, "may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell (hESC) research, to the extent permitted by law."[15] Recognizing the controversial ethical issues involved, the new guidelines, issued in July 2009, contain provisions designed to ensure informed consent from donors, address potential conflicts of interest, and limit federal funding to research on hES cell lines derived from embryos originally created for reproductive purposes. Specifically, the guidelines state that, to be eligible for federal funding, hES cell lines must be created from embryos that were produced for reproductive purposes and are no longer needed for that purpose, that the embryos used to produce the lines must be donated by individuals who sought reproductive treatment and who have given voluntary consent for the embryos to be used for research purposes, and that no payments—cash or in kind—must be offered for the donated embryos. NIH also established a stem cell working group to formulate recommendations for the NIH Advisory Committee to present to the director regarding the acceptability of lines that predate the new guidelines. With the new guidelines in place, 178 hES cell lines have been approved by NIH as being eligible for federal funding (as of August 30, 2012).

In August 2009, a suit was filed in U.S. District Court to block the Department of Health and Human Services (HHS) from implementing the new guidelines on the grounds that they were in violation of the Dickey-

[13] *Address to the Nation on Stem Cell Research from Crawford, Texas* (37 Weekly Comp. Pres. Doc. 1149 [August 9, 2001]).

[14] Approximately 1 month after the President's announcement, an NAS report and an unpublished NIH analysis both stated that additional hES cell lines would have to be available to federally funded researchers to fulfill the promise of research announced in 2001 (NRC, 2002). In addition, several studies have examined the geographic distribution of publications in the field (e.g., Levine, 2008; Owen-Smith and McCormick, 2006).

[15] *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells* (74 Fed. Reg. 10667 [2009]).

Wicker Amendment.[16] In August 2010, the court ruled in favor of the plaintiffs and issued a preliminary injunction ordering HHS to cease funding research using hES cells. The Obama administration appealed this decision to the U.S. Court of Appeals for the District of Columbia Circuit, which resulted, in September 2010, in a preliminary stay of the injunction and then, in April 2011, its reversal. Following this decision, in July 2011, the underlying case was decided in District Court in favor of the Obama administration. This ruling has been appealed to the U.S. Court of Appeals for the District of Columbia, and as of this writing, a final decision is being awaited.

Thus the past 15 years have seen continuing uncertainty regarding the federal government's willingness to fund research using hES cells—an ongoing disappointment to those scientists and other citizens who believe the nation is foregoing a highly promising opportunity to relieve human suffering. Given that the federal government has traditionally been the largest source of funding for biomedical research outside of industry and the largest funder of basic research, it appeared to some that the United States was foregoing an important opportunity to be a pioneer in developing the basic research necessary to produce critical new clinical applications. Within industry itself, the uncertainty surrounding both state and federal policies on this research also has produced some hesitancy to enter this research arena. It was in this context that a broad group of California-based scientists, leaders in California higher education, disease advocates, and others mounted the Proposition 71 initiative.

Since the early years of this century, when the campaign for CIRM was energetically under way, a great deal of progress has been made in stem cell research. In particular, the increased ability to reprogram adult cells has made the field of regenerative medicine somewhat less dependent on hES cells, a development that is fully reflected both in CIRM's programs and the field of regenerative medicine worldwide. Indeed, this is one of the key factors that CIRM has considered in updating its strategic plan. These issues are discussed more fully in Chapter 4.

ORGANIZATION OF THIS REPORT

The remainder of this report presents the results of the committee's response to its statement of task (Box 1-1), including its findings, conclusions, and recommendations; Table 1-1 shows where in the report each element of the statement of task is addressed. Chapter 2 provides an overview of the process by which CIRM was created and the committee's assessment of what can be learned from this history, as well as the impact of the Insti-

[16] *Sherely et al. v. Sebelius et al.*, 686 F. Supp. 2d 1 (D.D.C. 2009).

TABLE 1-1 Elements of the Study Charge and Chapters Where They Are Addressed

Element of Charge	Chapter
CIRM's initial processes—What can be learned from the history and process of building consensus in the public and scientific communities to support the inception and work of CIRM?	2
CIRM's programmatic and scientific scope—Does CIRM have the portfolio of projects and grant opportunities necessary to meet its scientific goals? How can CIRM improve upon its existing array of programs? What additional programs and initiatives are recommended to meet its goals? What impacts have been seen from international agreements? Does CIRM's scientific strategic plan address the range of relevant issues in regenerative medicine within CIRM's mandated scope of work?	4
CIRM's organizational and management systems—Are the internal organizational and management systems (in particular the board and working group structures and operations, the peer review system, the conflict of interest guidelines, and the grants management system) effective in working toward the Institute's scientific goals? Are the systems that are in place scientifically and ethically valid and rigorous? Do they achieve the level of transparency and the level of stakeholder and scientific community involvement needed to meet the Institute's public responsibilities and scientific goals?	3
CIRM's funding model—Has the funding model for CIRM had an impact on the work of the Institute? What are the advantages of CIRM's model for covering long-term costs of medical research? Could aspects of this funding model serve as a paradigm for other states or countries? What has been the economic impact of CIRM's research and facilities awards and grants?	2
CIRM's intellectual property policies—What are the strengths and weaknesses of CIRM's policy for sharing revenue generated by intellectual property? How does this model compare to the model governing federally supported research?	5

tute's funding model and whether it might serve as a model for other states or countries. This chapter also provides, for comparative purposes, a review of analogous efforts by other states. Chapter 3 assesses the effectiveness of CIRM's governance structure, including issues of conflict of interest. Chapter 4 evaluates CIRM's scientific and programmatic scope and how the organization can improve its processes and programs to better meet its goals. Finally, Chapter 5 provides an assessment of CIRM's intellectual property policies.

The committee's findings are presented throughout these chapters; each chapter ends with the committee's conclusions and recommendations on the

respective topic. It is important to note that CIRM is in a constant state of transition in various aspects of its work as it adapts to its own experience, to rapid scientific developments in regenerative medicine, to some public concerns, and to its own concerns regarding its longer-term financial condition. This assessment is as current as the committee could make it, but inevitably some further changes in response to these various influences are under way even as the committee completes this report.

REFERENCES

Alberro, J. 2011. *Economic impact of research funded by the California Institute for Regenerative Medicine*. http://www.cirm.ca.gov/files/PDFs/Publications/Economic_Impact_March_2011.pdf (accessed July 2, 2012).

August, C. S., F. S. Rosen, R. M. Filler, C. A. Janeway, B. Markowski, and H. E. Kay. 1968. Implantation of a foetal thymus, restoring immunological competence in a patient with thymic aplasia (Digeorge's syndrome). *Lancet* 2(7580):1210-1211.

Baker, L., and B. Deal. 2004. *Economic impact analysis—Proposition 71 California Stem Cell Research and Cures Initiative*. http://www.analysisgroup.com/uploadedFiles/News_and_Events/News/Proposition_71_report.pdf (accessed July 2, 2012).

Baker, L., and B. Deal. 2008. *CIRM—Interim economic impact review*. http://www.cirm.ca.gov/pub/pdf/EcoEval_091008_rpt.pdf (accessed July 2, 2012).

CIRM (California Institute for Regenerative Medicine). 2012. *CIRM's response to the Little Hoover Commission report on CIRM*. http://www.cirm.ca.gov/files/meetings/pdf/2009/081909_item_7A.pdf (accessed July 13, 2012).

EAP (External Advisory Panel). 2010. *Report of the External Advisory Panel*. http://www.cirm.ca.gov/files/PDFs/Administrative/CIRM-EAP_Report.pdf (accessed July 2, 2012).

ESF (European Science Foundation). 2012. *Regenerative Medicine (REMEDIC)*. http://www.esf.org/nc/activities/research-networking-programmes/medical-sciences-emrc/current-esf-research-networking-programmes/regenerative-medicine-remedic.html (accessed November 14, 2012).

Grskovic, M., A. Javaherian, B. Strulovici, and G. Q. Daley. 2011. Induced pluripotent stem cells—opportunities for disease modeling and drug discovery. *Nature Reviews Drug Discovery* 10(12):915-929.

IOM (Institute of Medicine). 1994. *Fetal research and applications: A conference summary*. Washington, DC: National Academy Press.

IOM. 2005. *Guidelines for human embryonic stem cell research*. Washington, DC: The National Academies Press.

ISSCR (International Society for Stem Cell Research). 2011. *Stem cell facts*. http://www.isscr.org/public/ISSCR08_PubEdBroch.pdf (accessed August 30, 2011).

Levine, A. D. 2008. Identifying under- and over-performing countries in research related to human embryonic stem cells. *Cell Stem Cell* 2(6):521-524.

LHC (Little Hoover Commission). 2009. *Stem cell research: Strengthening governance to further the voters' mandate*. http://www.lhc.ca.gov/studies/198/report198.html (accessed July 2, 2012).

Moss Adams, LLP. 2012. *California Institute for Regenerative Medicine FY 2010-2011 performance audit*. http://cirm.ca.gov/files/meetings/pdf/2012/052412_item_6.pdf (accessed July 13, 2012).

The National Academies. 2009. *Understanding stem cells: An overview of the science and issues from The National Academies*. http://dels.nas.edu/resources/static-assets/materials-based-on-reports/booklets/Understanding_Stem_Cells.pdf (accessed August 30, 2011).

NIH (National Institutes of Health). 1994. *Report of the Human Embryo Research Panel*. Bethesda, MD: NIH.

NIH. 2010. *Resource for stem cell research*: *Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#stemcells (accessed August 30, 2011).

NRC (National Research Council). 2002. *Stem cells and the future of regenerative medicine*. Washington, DC: National Academy Press.

NRC and IOM. 2005. *Guidelines for human embryonic stem cell research*. Washington, DC: The National Academies Press.

Owen-Smith, J., and J. McCormick. 2006. An international gap in human ES research. *Nature Biotechnology* 24(4):391-392.

Robinton, D. A., and G. Q. Daley. 2012. The promise of induced pluripotent stem cells in research and therapy. *Nature* 481(7381):295-305.

Takahashi, K., and S. Yamanaka. 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126(4):663-676.

Takahashi, K., K. Tanabe, M. Ohnuki, M. Narita, T. Ichisaka, K. Tomoda, and S. Yamanaka. 2007. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 131(5):861-872.

Thomson, J. A., J. Itskovitz-Eldor, S. S. Shapiro, M. A. Waknitz, J. J. Swiergiel, V. S. Marshall, and J. M. Jones. 1998. Embryonic stem cell lines derived from human blastocysts. *Science* 282(5391):1145-1147.

Yu, J., and J. A. Thomson. 2010. *Embryonic stem cells*. http://stemcells.nih.gov/info/Regenerative_Medicine/2006chapter1.htm (accessed July 2, 2012).

2

CIRM's Initial Processes and Funding Model

As noted in Chapter 1, CIRM was founded in response to the uncertainty regarding the availability of federal funds for stem cell research, particularly research employing human embryonic stem (hES) cells, and with the aim of both moving stem cell research and its applications forward and establishing California as a leader within the broader field of regenerative medicine. This chapter reviews the origins of CIRM and the committee's assessment of the implications of those origins for the Institute's ongoing work. The chapter then examines the funding model that supports CIRM's work, the impact of this economic investment, and the consequences of CIRM's funding model for the broader scientific enterprise. Next is a comparison of CIRM's funding model with comparable science funding programs in other states. The final section presents the committee's conclusions and recommendation regarding the future of CIRM once the funds originally authorized for the Institute have been expended.

CIRM'S ORIGINS

CIRM is in many ways a bold social innovation. Its existence is the result of the work, initiative, commitment, and imagination of a broad, diverse, and evolving group of dedicated citizens, scientists, university leadership, disease advocacy organizations, and some members of the California Legislature. The various constituencies involved were united by their shared desire to promote additional efforts in an arena of the biomedical frontier that they believed to be especially promising and that was not expected to

receive adequate support from the more traditional sources of funding in biomedicine. In addition, they believed that a state initiative in this arena would not only hasten the development of new disease treatments and/or cures but also strengthen California's position as one of the world's major centers of biotechnology.[1]

Assembling such a broad coalition of citizens and institutions that were united in their enthusiasm for stem cell research but had somewhat different agendas had implications not only for the design of Proposition 71 but also for the ongoing programs and operations of CIRM. The built-in allocation of ICOC board seats to university leadership, patient advocates, and members of the biotechnology industry, for example, ensured that a high percentage of those seats would be permanently occupied by persons with almost unavoidable, conflicts of interest, whether actual or perceived, between their roles as ICOC board members and their other, non-CIRM responsibilities. At the very least perceived conflicts are one factor that have led some observers, perhaps unfairly, to continue to question the integrity and independence of some of CIRM's decisions (Darnovsky, 2012; Hayden, 2008; Jensen, 2012). In addition, while the restrictions on amending the administrative structure of CIRM established in Proposition 71 had the advantage of protecting the Institute's ongoing operations from outside interference in an ethically controversial arena, they also made it difficult to modify the organization's structure in response to experience and/or changing circumstances (LHC, 2009). Moreover, these protections, whatever their benefits, appear to some to shield CIRM from the normal accountability mechanisms in place for state agencies (Darnovsky, 2012). The point the committee wishes to stress here is that the manner in which an organization is created and sustained and the understandable desire to protect its initial structure and objectives from being undermined have long-term consequences that may be difficult to anticipate and address.

In adopting Proposition 71 in the 2004 general election, the voters of California approved an amendment to the state constitution making it a constitutional right for California residents to engage in stem cell research, including research using hES cells, and requiring the state to devote considerable resources to such efforts and to the field of regenerative medicine more generally. Once again, it is important to stress that this was accomplished at a time in the nation's history when, as outlined in Chapter 1, the ethics of research using hES cells was the focus of serious disagreement in Washington, DC, and elsewhere; when future federal funding for research in this arena was highly uncertain; and when additional methods of creating

[1]California Stem Cell Research and Cures Initiative, Proposition 71 (2004) (codified at California Health and Safety Codes § 125291.10-125291.85).

pluripotent stem cells by reprogramming somatic cells (induced pluripotent stem cells) had not yet been demonstrated.

In addition to work to accelerate stem cell science and its translation into effective new disease treatments and/or cures, another stated goal of the establishment of CIRM was to invigorate California's biotechnology sector and produce a set of economic benefits for the state (Baker and Deal, 2004; Klein, 2011; Klein and Trounson, 2011). These potential economic benefits ranged from improving economic productivity, to generating new high-paying jobs in the biotechnology and related sectors, to lowering health care costs and thus improving the state's budget situation. CIRM's central mission, however, is to "support and advance stem cell research and regenerative medicine under the highest medical and ethical standards for the discovery and development of therapies and cures" (CIRM, 2010, p. 2). Those eligible for CIRM funds are California's universities, hospitals, medical schools, and other research institutions, including for-profit organizations doing research and development in this area.

Implications of CIRM's Origins

The structure of the evolving coalition assembled to enact Proposition 71 and then reflected in its articulation ensured broad buy-in to the overall project by a diverse array of stakeholders that were able to convince the voters of California to support the initiative.[2] Not surprisingly, the need to keep such a broad coalition together had direct implications for CIRM's governance structure, for the claims made about the potential benefits of the initiative, and for the evolving nature of CIRM's programs. While all stakeholders were motivated by the strong desire to find cures for certain currently intractable diseases, some members of the coalition and their supporters were especially interested in the prospect of stable long-term support for a significant and promising new area of biomedical research, others were most interested in the implications for access and social justice, and still others in the benefits to the California economy and the state's taxpayers (YESon71, 2004). Needless to say, many supporters were interested in all of these objectives. All stakeholders understood that achieving these objectives would require significant progress on the scientific frontier; nonetheless, as stem cell research developed rapidly in California and elsewhere, these varied interests conflicted at times, creating some friction in the process of deciding about the allocation of CIRM funds among various priorities or particular aspects of the frontier in this aspect of regenerative medicine (Adelson and Weinberg, 2010). In short, the challenges confronted

[2]The energetic campaign for Proposition 71 included polling of the electorate to discern both their aspirations and their concerns.

in dealing successfully with the political processes surrounding attempts to require the government to fund scientific projects of any kind can have consequences for the ongoing nature and integrity of the resulting scientific program. This is true for CIRM, but CIRM is not unique in this regard.

The nature of the vigorous and expensive campaign mounted to promote the passage of Proposition 71 also had implications for the initial development and operations of CIRM. On the one hand, the broad public mandate that resulted from the proposition's passing easily (59 percent to 41 percent) with the support of more than 7 million California voters gave CIRM momentum to start rapidly and persevere through legal challenges that hindered the early implementation of its programs (Hayden, 2008). On the other hand, the competitive nature of the political campaign may have led some proponents of Proposition 71 to overpromise either clinical or economic benefits of its passage. If this was the case, as some critics allege, it may affect how voters evaluate CIRM and, equally important, how the Institute sets its funding priorities in the years immediately ahead (Hiltzik, 2009). As discussed in Chapter 4, although CIRM's early emphasis was largely on funding investigators examining the fundamentals of stem cell biology, the development of special facilities, and a wide variety of training programs, the Institute is currently placing much greater emphasis on the translation of discoveries in the laboratory toward the effective treatment of a wide range of disease areas.

CIRM's Governance

Proposition 71 outlined a detailed governance structure for CIRM. Most important, it provided for a 29-member Independent Citizens Oversight Committee [ICOC] as the Institute's governing authority. The ICOC was to be composed of representatives of specific disease advocacy groups, leaders of California's research universities, and representatives of both California's biotechnology industry and other nonprofit California-based research institutions. While this profile of the ICOC was understandably designed to include representatives of a broad range of stakeholders most concerned and most knowledgeable about the future of regenerative medicine, they were also the constituency expected to benefit most directly and immediately from CIRM's grants. Detail on the Institute's governance structure and the committee's assessment of its effectiveness and challenges is presented in Chapter 3.

As noted above, one consequence of the context surrounding CIRM's origins was the desire to build into Proposition 71 an oversight structure that would be difficult to change and by its design would be characterized by inherent conflicts of interest. Proposition 71 permitted legislative modifications to CIRM for 3 years after its adoption and instituted a supermajor-

ity requirement for legislative changes following this initial period. These restrictions offered CIRM some genuine and useful protections from political interference—a real risk given the ethical controversy surrounding hES cell research—but also created barriers to changes that might have helped the Institute optimize its operations in response to its accumulating experience within a rapidly changing scientific field.

CIRM'S FUNDING AND ECONOMIC IMPACT

CIRM's Funding Model

One way in which CIRM differs from most other scientific research programs is its funding model. Proposition 71 specified a financing scheme to support CIRM's programs whereby the state would issue general obligation bonds,[3] effectively transferring the burden of financing CIRM'S programs from current to future taxpayers. These bonds were estimated to cost the state about $5.5-$6.0 billion in interest and principal (Baker and Deal, 2004) over their 30-year life.[4] Proposition 71 also required the state to capitalize all interest expenses during the first 5 years, thus shielding the state's general fund from any CIRM-related charges during this initial period.[5]

The critical underlying concepts of this funding model were twofold. First, as already noted, it would provide a relatively stable source of funds in an important and exciting arena of biomedical research where ongoing uncertainty regarding the availability of federal funding was especially acute. In this respect, however, it is important to note that CIRM funding is competitive for any particular institution or individual researcher or research group, and none is assured of continued funding throughout the 10-year period. Thus while the availability of funds for the field of regenerative medicine as a whole enjoyed a certain stability in California, there were no such guarantees for individual researchers or research teams. Moreover,

[3]General obligation bonds are a form of long-term borrowing in which the state issues municipal securities and pledges its full faith and credit to their repayment. The bonds are repaid over many years through semiannual debt service payments. The California Constitution requires that general obligation bonds be approved by a majority vote of the public and sets repayment of general obligation debt above all other obligations of the state except those for K-14 education (Department of General Services of State of California, 2010).

[4]This estimate reflects not only interest costs on the general obligation bonds but also a provision calling for all interest costs during the first 5 years to be capitalized.

[5]This provision also allowed for the possibility that by the time any associated charges impacted the general fund, the fiscal benefits of CIRM's activities might already be supplementing general fund revenues. Although not specifically provided for in Proposition 71, from time to time the state may choose to meet its obligations to CIRM by issuing commercial paper pending a large placement of general obligation debt by the state.

in both basic and clinical research, even a decade is not a long time for the full maturation of important research and development initiatives. Nevertheless, the availability of this substantial and relatively stable funding source for the field of regenerative medicine has been important in enabling CIRM to adopt strategic long-term goals; allowing grantees to attract more than $1 billion in matching funds from private sources, primarily for facilities; and helping to make California an attractive destination for both early-stage and established stem cell scientists (Levine, 2006, 2012).

Second, this unique funding model was designed to spread the ultimate financial burden of supporting CIRM's efforts over those future cohorts of patients and taxpayers expected to be the most likely beneficiaries of these efforts, who would also be the ones obligated to repay the bonds. While many studies have estimated very high economic returns on investments in science (e.g., Health Economics Research Group et al., 2008; Mansfield, 1991, 1998; Murphy and Topel, 2003; OTA, 1986), the economic impact of any particular scientific project or work in one small arena of the scientific enterprise is subject to much greater uncertainty. Moreover, scientific progress made in one particular locale, such as California, is dependent on complementary scientific developments elsewhere. Thus in the globalized world of biomedical research, it is always a challenge to isolate the actual dividends that can be attributed to any local efforts from those due to discoveries made elsewhere, or in the present context, even those resulting from efforts in California not funded by CIRM. In any case, if the best efforts in stem cell research in California and elsewhere were not to yield clinical or other benefits to the next generation, that generation would bear a cost burden not offset by any corresponding clinical benefit or any long-term economic benefits to the state.[6]

In many ways, investments in research and development appear to be analogous to more prosaic infrastructure investments in, for example, roads, bridges, and power networks, which often are financed through the issuance of long-term bonds. Perhaps the most significant difference, however, is the uncertainty surrounding investments in the biomedical enterprise and the precise nature and timing of the benefits expected to accrue. This is especially true, as noted above, if the investments are focused in one particular arena of the biomedical frontier. In such cases, it is particularly difficult to decide whether the risks should be borne by current or future generations of taxpayers. It is, of course, attractive to be relieved of annual negotiations over the allocation of current tax revenues, but as a general approach to financing research and development, the CIRM model simply

[6]Studies that estimate the economic returns on investments in science and technology have their critics, who focus on the methodologies used to estimate those returns. A concise summary of such views is provided by Macilwain (2010).

replaces the annual discussion surrounding the allocation of current tax revenues with arguments over the allocation of future tax revenues. If, however, particular initiatives are viewed as a modest complement to the more standard "pay as you go" model of biomedical research funding, these matters are not of great concern.

In summary, there are two principal differences between the CIRM funding model and the more conventional model used, for example by the National Institutes of Health (NIH) and private foundations: the use of long-term bond financing for contemporary research, and the stability of the state's financial commitment to CIRM and the field of regenerative medicine over the 10-year period. It is also important to note that although CIRM's funding as provided through the terms of Proposition 71 is assured for only 10 years, the Institute itself has no such time limit, and if additional funds were to become available or if the bond proceeds were not fully allocated, CIRM's activities could continue for a longer period. On the other hand, it is worth reemphasizing that the timeline for continued funding of particular scientists or scientific projects is much more limited than CIRM's horizons, usually 3 to 4 years (CIRM, 2012a). This situation is in fact analogous to that of NIH, in which funding for the institutes tends not to shift dramatically from year to year, but the funding of particular researchers and research areas may shift relatively rapidly.[7] Of course, continued funding is always much more uncertain in areas where there are serious ethical controversies.

It is quite clear that the overall stability of CIRM funding facilitated a longer-term outlook and thus the prioritizing of crucial long-term investments in both specialized facilities and human capital. These are substantial benefits. Although the relative stability CIRM offered the field of regenerative medicine in California was a notable improvement over the uncertain prospects for federal funding, especially for hES cell research, the roughly 10- to 15-year period for expending the agency's initial bond funding, as noted above, is not a long time in which to realize the full benefits of basic or clinical biomedical research. Thus, the creation of CIRM and the development of its programs almost immediately raised questions about its long-term future and the impact of the expiration of its funding on the full career path of scientists recruited to the field or the state. CIRM has developed an initial transition plan, but as the end of its bond funding draws closer, this uncertainty persists, creating challenges for both the Institute and scientists in the field. In essence, CIRM faced and continues to face the unusual challenge of ramping up a major new program in biomedical research and making the associated long-term investments while knowing

[7]It is useful at this point to note that annual NIH funding for biomedical research in California is roughly 10 times the CIRM annual budget.

that the generous state support enjoyed by the program might be limited to 10 years.

Perhaps the best way to consider the role of CIRM, as well as its distinctive funding model, is both as a creative supplement to the more traditional sources of biomedical research funding in the United States and as an innovative initiative designed to strengthen California's biotechnology efforts. Whenever an exciting portion of the biomedical research enterprise is operating under conditions of uncertainty and/or inadequate commitments by traditional funding sources, this model can provide a strategic opportunity for a state to make an investment aimed at both maximizing the vitality of efforts in that state and giving the state's biomedical enterprise a long-term competitive edge (Klein and Trounson, 2011). The appropriateness of the particular approach selected by California voters in approving Proposition 71 for other states likely varies, depending on the nature of the science to be supported, the health and vitality of the state's other research institutions and their investments in research and development, the state's financial situation, and the willingness of voters and/or legislatures to impose costs on future generations in exchange for potential but uncertain benefits. It is clear, however, that CIRM's perceived success did not go unnoticed by other states, which responded in some cases with initiatives and models of their own in the area of regenerative medicine and/or in the broader biomedical arena, some of which are discussed below.

Economic Impact of the Investment in CIRM

California's substantial investment in CIRM quite naturally raises the question of the actual economic benefits generated by this investment and just how these benefits relate to the costs of the program.[8] Although overall investments in science and technology have transformed society and yielded enormous economic dividends, this does not mean that all investments in science and technology produce substantial economic dividends (Maddison, 2007).

Many potential economic dividends can flow from thoughtful investments in biomedical research. These include enhancing economic productivity, expanding employment opportunities, and possibly providing some relief to government budgets through increased tax revenues and declining health care costs. In estimating the economic impact of investments in biomedical research, two broad tasks must be undertaken. First, the economic benefits of any health gains must be compared against the costs of provid-

[8]The committee realizes that any health benefits generated by CIRM's efforts not only may yield some economic dividends but also have value in their own right regardless of their economic benefit.

ing the new disease treatments and/or cures. At this early stage in CIRM's programs this component cannot be adequately assessed because the final costs of developing any treatment are unknown as are both the benefits to be realized and the time lag between the research investments and the development of new treatments. The second task is to consider the direct and indirect gains in gross state domestic product (GSP) from CIRM's investments in the biomedical enterprise and any further economic activity these investments stimulate. In this regard, although CIRM's expenditure of $300 million a year clearly supports additional employment within California's research community, as would any thoughtful investment of this magnitude, reliable estimates of the overall long-term economic impact on the state's economy must await the accumulation of more information and a better understanding of the dynamics of the state's contemporary economy. In particular and as already noted, the economic rates of return are highly sensitive to the lag between research and development expenditures and the deployment of new clinical modalities. In the case of CIRM's research and development portfolio, the length of this lag is presently unknown. However, it is important to note that the same could be said of any investment in work in a new arena of the scientific frontier.[9]

In short, assessing the long-term economic impact of particular biomedical research activities is a complex task that requires considerable time and experience with any treatments and/or cures that are developed. In addition, one must disentangle the dividends realized from scientific work conducted elsewhere and from the efforts of CIRM-sponsored investigators. Thus, CIRM's long-term impact on such critical aspects of the California economy as employment, state tax revenues, and health care costs beyond the shorter-term and temporary impact of its direct expenditures cannot be reliably estimated at this point in CIRM's history. In this respect, the estimate of Baker and Deal (2008) that the CIRM program alone would support about 3,400 jobs as long as it was allocating about $300 million per year in research and development grants appears quite reasonable to the committee. To put this estimate in context, however, total employment in California is roughly 16 million, and NIH alone provides more than $3.5 billion per year to California research institutions.

In conclusion, measuring the economic impact of biomedical research, especially work in a specific arena such as regenerative medicine, remains a difficult and complex task. At this stage of CIRM's program, one can know only that (1) money has been borrowed and thoughtfully spent on a highly promising arena of the biomedical frontier; (2) CIRM's expenditures are supporting approximately 3,400 jobs; (3) CIRM's resources have

[9]The committee believes the decision to finance CIRM with future rather than current tax revenues has no discernible long-term impact on California's economy.

attracted substantial additional private and institutional resources to this research arena in California; (4) CIRM's training programs have made a direct contribution to the training of stem cell researchers and research technicians; (5) CIRM's funding has led to the publication of more than 1,168 articles, the submission of 92 disclosures and 40 patent applications, and the finalization of three license agreements (as of July 2012); and (6) CIRM has initiated energetic efforts to translate the scientific results of its programs to the bedside. These are substantial achievements, but assessing their longer-term economic impact is simply not possible with the information currently available.

Consequences of CIRM's Funding Model for the Broader Scientific Enterprise

Although Proposition 71 clearly increased significantly the total national and international level of resources devoted to this area of regenerative medicine, any prior constraints on how local resources can be allocated entail at least some modest costs for the global enterprise. In this case, the constraint is that the resources must be spent in California. While California has a large and excellent biomedical research community, CIRM must operate under this constraint, and the intellectual property regulations adopted by the Institute, for example, could impose transaction costs on working with other groups outside of California. This constraint is understandable given the direct burden of funding CIRM on future California's taxpayers, but as already noted, it is also true that CIRM's programs benefit substantially from work carried on elsewhere and financed by others. The committee does not believe this is currently a serious problem for CIRM and the field of regenerative medicine. If many states were to adopt similar programs, however, then it would be important to consider the impact on the vitality of the overall national effort if harmonization of policies and regulations were not achieved. This would be a particularly important consideration as progress on the research frontier induced movement toward commercialization, which is, for the most part, a national and international enterprise. Over time there would be a national benefit in the harmonization of regulations. Because CIRM-financed researchers benefit, often for free, from research being conducted elsewhere and the commercialization of any discoveries, it might be easier to attract business partners if one set of national rules were understood and followed by all.

CIRM IN THE CONTEXT OF OTHER STATE-BASED SCIENCE AND TECHNOLOGY INITIATIVES

Historically, the states took little direct interest in stimulating the vitality of the scientific enterprise within their borders, although their support for state colleges and universities certainly advanced their scientific enterprise indirectly. In the initial post–World War II decades, the states greatly expanded their support for postsecondary education, but for the most part left science policy to initiatives of the federal government. Subsequently, however, the states began to assume a more independent role in science and technology policy as a means of enhancing their economic prospects through improvements to their research and development base, as well as providing new opportunities for their citizens. Indeed, many states began to notice that states with a tradition of support for research within their systems of higher education attracted technology-intense industries, which were growing in importance.

Although CIRM is unique among state programs in many respects, it reflects this pattern of state efforts over the past few decades to support initiatives in science and technology. Although there is substantial heterogeneity among such state programs, reflecting in part the role of states as policy laboratories, several trends have been observed in the development of these programs over time (Plosila, 2004). Often, a key element in this dynamic has been greater recognition by state policy makers of the potential role of particular components of university research programs in state and regional economic development. Over time, the result has been a number of initiatives to support targeted university-based research. These research funding policies represent a shift from earlier state policies that tended to focus on recruiting existing firms or large-scale scientific projects, such as the Microelectronics Computer Consortium and the Superconducting Super Collider (Plosila, 2004). The creation of CIRM by California voters and the agency's focus on advancing stem cell science and the field of regenerative medicine fall squarely within these larger trends.

As states focused their targeted science and technology policy initiatives more on certain university-based efforts in the 1980s and 1990s, a wide variety of programs were developed (Berglund and Coburn, 1995). A recent examination of the development of state science policies has identified three major classes of programs intended to build state scientific capacity: university research grant programs, eminent scholars programs, and centers of excellence programs (Feldman et al., in press). Of these, CIRM most closely parallels university research grant programs, the oldest of which date to the early 1980s, which have been adopted in some form by nearly 30 states. Initially, most of these programs supported a broad range of science, but states have increasingly narrowed their focus so as to develop expertise

and competitive advantage in a specific area (e.g., information technology or biosciences). A focus on life sciences or health-related research has been particularly common over the past decade, as at least 17 states have chosen to contribute at least a portion of their tobacco settlement funds to support such research (NGA, 2001). At the same time, it should be noted that, while specialization and focus can have substantial benefits, they must be balanced by the realization that scientific progress in specific areas usually depends on complementary developments in other arenas of the scientific frontier and in other geographic areas. Other common state programs include those designed to attract highly productive researchers to a state. These programs—often termed eminent scholars programs—date to the 1960s, when Virginia adopted its program, and have gained in popularity in recent decades. CIRM's research leadership grants, which provide funding to recruit leading stem cell scientists to California, fall within the tradition of these programs.

The value and impact of these state programs designed to fund research grants or to recruit scientists should be assessed in the broader context of a state's support for its overall research and development enterprise, including, for example, its research universities. If these programs come at the expense of other key aspects of the state's investments in the vitality of its research and development enterprise, then they may represent at best little more than a reallocation of existing funds and may have little if any net effect on either the enterprise or its economic prospects.

Even as these supportive policies have been adopted, numerous states have taken action to restrict scientific inquiry in morally contentious areas. Many of these state policies have focused on fetal and embryonic research. These policies take several forms, including an outright ban on research using aborted fetal tissue or human embryos created in vitro; a ban on specific techniques, such as somatic cell nuclear transfer; or a restriction on the use of state funding for certain research. Befitting the ethically contentious nature of these fields, some states have adopted essentially opposite policies, indicating that specific types of research are legal in the state. In some cases, including California's, these rules have accompanied or been followed by state funding, while in other cases, they are stand-alone policies. States adopting these sorts of supportive policies have pursued two main strategies: (1) identifying and establishing the legality of specific research techniques or (2) adopting laws indicating that any research legal under federal law is legal under state law.[10]

[10]More information on these state laws can be found in Andrews (2004) and in a National Conference of State Legislatures (NCSL) database updated through 2008 (NCSL, 2008).

Comparison of CIRM and Analogous State Science Funding Programs

While CIRM fits into some of the broader patterns seen in state science and technology policy, it differs from other state-based efforts on several important dimensions. To provide an additional perspective on CIRM and better understand how it is similar to and different from other state science funding programs, the committee reviewed a small number of other state programs that are comparable in some ways to CIRM. It is important to note that the committee is not evaluating these programs, but reviewing some of their key characteristics to provide additional perspective on CIRM.

Given CIRM's focus on stem cell research and regenerative medicine, the committee's comparison concentrated on other state programs specific to these fields. In addition to California, five other states have adopted programs that provide funding specifically for stem cell research, including research on hES cells (Karmali et al., 2010). These state programs vary in scale, but none are as large as CIRM. New York's program, the New York State Stem Cell Science Research Fund (NYSTEM), is closest in size, with a $600 million, 11-year commitment. Connecticut, a much smaller state than either California or New York, also has a long-term program, with a $100 million, 10-year commitment. Other states have chosen to provide funding for stem cell research without a specific long-term commitment. These states include Maryland, which has provided approximately $91 million in funding since 2006, and New Jersey and Illinois, both of which provided stem cell–specific funding in the past decade. These latter two programs were on a smaller scale than those of the other states (approximately $15 million each) and are not awarding new grants, and thus are not considered further here. CIRM's challenge—creating and thoughtfully administering a much larger-scale funding program—distinguishes it in important ways from these smaller state stem cell programs. For this reason, the committee also included the Cancer Prevention Research Institute of Texas (CPRIT) in its comparison. While the focus of this program differs from that of CIRM, the two have numerous similarities, including the use of bond funding, a $3 billion total budget, and an approximately 10-year time frame. These programs are described briefly below and also discussed in Chapters 3 and 5.

NYSTEM: New York's Stem Cell Program

NYSTEM dates to early 2007, when, as part of the state's 2007-2008 budget, the Legislature and Governor Eliot Spitzer committed to providing $600 million in funding for stem cell research over 11 years. With the adoption of this law, New York became the second-largest state funder of stem cell research, behind California. Although the program is scheduled

to continue for 11 years, its funding is subject to the annual appropriations process and, because of budget pressures, has lagged slightly behind the $50 million annual appropriation that was anticipated. At one point, financial concerns led to a delay in issuing new requests for applications (RFAs) and to an approximately year-long gap in funding of new awards, illustrating the benefits of the more secure bond funding model used by CIRM. The program has a broad funding portfolio, supporting various types of research grants and education and training efforts, as well as renovation or improvement of shared laboratories. NYSTEM awards grants both in response to broad investigator-initiated RFAs and for more targeted programs. One recent award focuses on the use of somatic cell nuclear transfer to create hES cell lines. This research takes advantage of NYSTEM's decision to allow the compensation of oocyte donors for biomedical research (Roxland, 2012) and would be unlikely to be undertaken by a CIRM-funded scientist given CIRM's rules against compensating egg donors and the difficulties scientists have experienced in recruiting uncompensated donors (Egli et al., 2011). In late 2011, NYSTEM issued an RFA (*Consortia to Accelerate Therapeutic Applications of Stem Cells*) intended specifically to move stem cell research toward the clinic.

Connecticut's Stem Cell Research Program

Connecticut's stem cell research program was signed into law by then-Governor Jodi Rell on June 5, 2005, making Connecticut the third state (after New Jersey and California) to develop a program focused specifically on funding stem cell research. Through July 2012, the state had awarded approximately $69 million in stem cell grants to Connecticut researchers. The initial act creating the program appropriated $20 million for grants supporting embryonic or adult stem cell research and specified that an additional $10 million should be dispersed from the state's Tobacco Settlement Fund for the following 8 fiscal years (through the fiscal year ending June 30, 2015). Connecticut's stem cell research program typically offers one grant cycle per year. This annual funding cycle includes investigator-initiated grants for established investigators as well as smaller seed grants. Connecticut also funds larger group projects involving collaborations among multiple laboratories. In the two most recent RFAs, the state explicitly indicated that it would give priority to group projects that bring together academic and industry partners to focus on the development of stem cell therapies for specific diseases. This program shares some similarities with CIRM's disease teams and represents Connecticut's most direct effort to move its funding toward translational research. Connecticut also provides funding for core facilities to support stem cell research by multiple investi-

gators, akin in principle to the infrastructure awards made by CIRM early in its existence (see Chapter 4).

The Maryland Stem Cell Research Fund

Maryland's stem cell research program was established through legislative action in 2006, following a contentious multiyear debate. Specifically, then-Governor Bob Ehrlich signed the Maryland Stem Cell Research Act of 2006 on April 6, 2006, creating the Maryland Stem Cell Research Fund (MSCRF), designed to promote state-funded stem cell research through grants and loans to both public and private entities in the state. Funding levels for the MSCRF are determined each year by the General Assembly and have ranged from $10.4 million in 2011 to $23 million in 2008. Through June 2012, Maryland had completed six rounds of funding, awarding more than 250 grants totaling approximately $91 million. Maryland's program typically offers one funding cycle each year. This cycle includes a broad investigator-initiated program designed for faculty with preliminary data, a smaller exploratory grant program, and funding for postdoctoral fellowships. The MSCRF requires that funded grants include human stem cell research but imposes no requirements on the specific type of human stem cells studied. In early 2012, Maryland issued a new RFA focused on preclinical and clinical research, which specifically targets for-profit companies conducting stem cell research in the state.

The Cancer Prevention Research Institute of Texas

CPRIT was established following passage of a constitutional amendment by Texas voters in 2007 that authorized the state to issue $3 billion in bonds to support cancer research and prevention programs. CPRIT's authorizing legislation was modeled, at least in part, on CIRM, but with a focus on a less controversial research field (Ackerman, 2007). CPRIT's tasks include implementing the Texas Cancer Plan, increasing the research capacity of the state's institutions of higher education, and expediting innovation in cancer research. CPRIT funds awards for both basic and translational cancer-related research; commercialization awards, designed to help bring cancer-fighting drugs and appropriate medical devices to market; and cancer prevention awards, designed to support evidence-based screening and prevention projects and, ultimately, increase cancer survival rates. CPRIT research grants must be supported by matching funds from another source equal to one-half of the CPRIT award. These matching funds must be spent in the same general area of cancer research as the CPRIT-funded project and can come from a range of sources, including federal sources such as NIH, state sources, and unencumbered university funds, as well as nongov-

TABLE 2-1 Characteristics of CIRM and Comparable Funding Programs

	California	New York	Connecticut	Maryland	Texas
Origin	Voter initiative	Legislature	Legislature	Legislature	Voter initiative
Financial commitment	$3 billion	$600 million	$100 million	Not specified	$3 billion
Funding mechanism	Bonds	Annual appropriations	Annual appropriations (tobacco settlement funds)	Annual appropriations	Bonds
Awards announced to date	~$1.6 billion	~$221 million	~$69 million	~$91 million	~$760 million
Approximate duration	10 years	11 years	10 years	Open-ended	10 years
First awards	2006	2008	2006	2007	2009

NOTE: Funding totals as of August 2012.
SOURCES: California Program: http://www.cirm.ca.gov; New York Program: http://stemcell.ny.gov; Connecticut Program: http://www.ct.gov/dph/cwp/view.asp?a=3142&q=389702&dphNav_GID=1825; Maryland Program: http://www.mscrf.org; Texas Program: http://www.cprit.state.tx.us.

ernmental funds (e.g., private funds, venture capital investors, foundation grants). Through August 2012, CPRIT had awarded 429 grants totaling approximately $760 million. CPRIT encountered controversy in May 2012 when its chief scientific officer resigned, citing concerns about the Institute's scientific review process (Weber, 2012).

Summary of Comparable State Programs

The above brief review of comparable state programs illustrates that state policy makers have a range of options to consider when attempting to support biomedical research and encourage biotechnology-related economic development. These programs differ substantially in their origins, their scale, their duration, and their financing mechanisms, among other characteristics (as discussed in greater detail in Chapters 3 and 5). As was the case with CIRM, each of these policy designs and implementation choices can affect how the program operates and how well it fulfills its goals and the goals of the taxpayers who provide it with financial support. A high-level summary of CIRM and the comparable programs discussed in this section is shown in Table 2-1.

CONCLUSIONS AND RECOMMENDATION

In many ways, CIRM represents an extraordinary experiment resulting from the dedication, interest, drive, and imagination of its sponsors. Its initial efforts to establish human and physical capital certainly are necessary steps toward the development of a scientific environment for regenerative medicine in California that is conducive to establishing and sustaining leadership in this area of medical research and to eventual clinical success. Moreover, the work of CIRM-sponsored researchers continues to enrich regenerative medicine everywhere, just as CIRM's efforts continue to benefit from and be inspired by many exciting new developments in regenerative medicine taking place both within and outside of California. The CIRM funding model, like all investments on the scientific frontier, represents a wager on the future, but the distinctive aspect of this model is the imposition of current research costs on future generations. If all goes well, the costs and benefits will be experienced by the same cohort of taxpayers. Given the uncertainty of progress in any specific arena of the biomedical frontier, however, the costs could be shouldered by a generation that neither approved nor benefited from this investment.

Regarding the origins of and funding model used by CIRM, the committee reached the following conclusions:

- The creation of CIRM was the result of the efforts of a broad-based coalition of California citizens that was successful in mobilizing a significant state investment in a particular arena of the biomedical frontier. At the time of its establishment CIRM was an imaginative social innovation.
- To support both an initial set of investments in facilities and an initial and ongoing stream of research in this arena, Proposition 71 included a financing mechanism that, although no longer unique in the area of scientific research, was a funding innovation at the time. Instead of being financed by current tax revenues, these investments have been financed by future tax revenues through the issuance of long-term general obligation bonds of the State of California. As a result, the costs of these contemporary investments in the science of regenerative medicine have been transferred to future cohorts of taxpayers, who were presumed to be the principal beneficiaries of CIRM's programs.
- The stability offered by the terms of Proposition 71 to critical aspects of the field of regenerative medicine in California has allowed CIRM to engage in long-term planning; develop a comprehensive long-term funding strategy, including support for training, infrastructure, and research; attract significant private funding to its capital projects; and recruit scientists to the state. At the very least, this should enable California to sustain an enhanced presence in this arena over the longer term.
- The CIRM initiative, although unusual in its size and with many distinctive features, falls into a long-term pattern of initiatives by individual states that promote the vitality of particular aspects of their research and development sectors.
- It is not possible at this stage of CIRM's work to provide any reliable estimate of its long-term economic impact, particularly with respect to initial projections of cost savings to the state's health care budget.

For other states and countries that may look to CIRM's funding paradigm for their own initiatives, the committee offers the following observations:

- The development of a broad coalition of supporters facilitated both the passage and implementation of CIRM. Such coalition building and substantial financial resources are probably a necessary condition for other states or countries developing targeted research funding programs dependent on the support of a broad constituency.

- States vary in their use and availability of a public initiative mechanism that can require state government to undertake particular initiatives independently of the state legislature and/or administration. Where such a mechanism is available, it offers the benefits of wide public engagement, but also entails the danger that regardless of how well intentioned these initiatives are, they may produce an overall portfolio of state research and development efforts that is suboptimal. This is also a danger of any action by state government that pursues particular interests at the expense of a broader set of needs. As with all efforts to promote science, moreover, whether by voter initiative, research proposal, or legislative initiative, it is necessary to guard against the risk of overselling the program's potential benefits in an effort to win the necessary support.
- The appropriateness of the CIRM model for other states depends greatly on various contextual factors. In particular, it depends on the health and vitality of the state's existing research institutions, its financial situation, and its willingness to transfer the risks and costs as well as the potential benefits to the next generation.

CIRM is a dynamic organization that continues to be in a constant state of transition. Given the time frame established by Proposition 71, the committee believes it is important for CIRM to continue to develop its plans for taking fullest advantage of its achievements in order to help support a sustainable future in which its funding circumstances could be quite different. The committee believes that in this process, it will be important for CIRM to give increased attention to industry inputs since the latter are crucial to a fuller understanding of what it will take to attract the much larger sums required to take laboratory findings to the "bedside." As part of its 2012 Strategic Plan, CIRM set forth plans to establish a platform to enable grantees, and industry, among others, to continue their pursuit of CIRM's mission after the Institute's bond funding expires (CIRM, 2012b). The committee agrees with this goal. In addition, CIRM should share with the public any plans to obtain private-sector support for its ongoing activities and how any such arrangements may affect continuing public obligations, including those related to CIRM-funded intellectual property and its access plans (see the discussion in Chapter 5).

CIRM and those it has funded have set in motion a significant scientific enterprise. Whether or not the state of California will choose to continue its support beyond the $3 billion already committed, there is an obligation to both the resulting scientific enterprise and the citizens of California to try to sustain the most promising initiatives. In principle a wide variety of initiatives might at least in part substitute for the initial decade of support from the state. These might include new and novel partnerships with industry, or

other funders of biomedical research and/or the expansion of efforts with CIRM's existing partners both of which could attract new funding sources. If developments emanating from CIRM-supported research projects suggest promising clinical possibilities very large sums will be required to take these developments to the bedside and the closer the partnership with CIRM and California's venture capital and biotechnology industry the more likely that real dividends will ensue. Indeed, such relationships might be a key to realizing the initial expectations of substantial dividends flowing from the entire effort. In support of CIRM's strategic planning goal with respect to enabling grantees and others to carry on CIRM's work, the committee makes the following recommendation.

Recommendation 2-1.[11] ***Develop a Sustainability Platform.*** **CIRM should work with its current and future partners and those who have been substantial recipients of CIRM support to develop and present to the public its plans for sustaining the momentum of its achievements as it moves beyond its first decade of operations. Any such plan should address the following key strategic areas:**

- **How, if at all, CIRM intends to obtain funding after the bond proceeds have been spent, including the continuing role, if any, of additional state support and plans to obtain private-sector funding (e.g., from private foundations, industry, venture capitalists, other institutions), in anticipation of declining state support and/or in recognition of the need for a much larger investment of funds to take research findings through clinical trials. Particularly important is understanding how such developments might affect CIRM's ability to meet its obligations to the public, including (1) how management intends to ensure oversight of the ongoing responsibilities of grantees to the state and (2) how intellectual property, access plans, licensing of intellectual property, and revenue sharing will be managed.**
- **A more detailed description of the nonprofit venture philanthropy fund proposed in CIRM's 2012 Strategic Plan and how this organization would interface with the Institute.**
- **How any new funding models would impact the role and structure of the ICOC.**

The next three chapters contain the committee's principal findings, conclusions, and recommendations on the implementation and operations

[11]In the committee's view, this recommendation can be carried out by CIRM without legislative action.

of CIRM, including its governance structure (Chapter 3); the nature, scope, and accomplishments of its scientific program (Chapter 4); and its intellectual property policies (Chapter 5).

REFERENCES

Ackerman, T. 2007. *Does cancer initiative promise too much: Texans will be asked to OK funding $3 billion over ten years for center?* http://www.chron.com/CDA/archives/archive.mpl?id=2007_4394056 (accessed November 27, 2012).

Adelson, J. W., and J. K. Weinberg. 2010. The California stem cell initiative: Persuasion, politics and public science. *American Journal of Public Health* 100(3):446-451.

Andrews, L. B. 2004. Legislators as lobbyists: Proposed state regulation of embryonic stem cell research, therapeutic cloning and reproductive cloning. In *Monitoring stem cell research: A report of the President's Council on Bioethics*. Washington, DC: Government Printing Office. Pp. 199-224.

Baker, L., and B. Deal. 2004. *Economic impact analysis: Proposition 71 California stem cell research and cures initiative*. http://www.analysisgroup.com/uploadedFiles/News_and_Events/News/Proposition_71_report.pdf (accessed July 2, 2012).

Baker, L., and B. Deal. 2008. *CIRM – Interim economic impact review.* http://www.cirm.ca.gov/pub/pdf/EcoEval_091008_rpt.pdf (accessed October 19, 2012)

Berglund, D., and C. Coburn. 1995. *Partnerships: A compendium of state and federal technology programs*. Columbus, OH: Battelle Press.

CIRM (California Institute for Regenerative Medicine). 2010. *Advancing the effective research oversight: 2010 regional workshops on regulatory compliance*. http://www.cirm.ca.gov/files/PDFs/Standards/Evaluation_Initiative_Report_5_11_10.pdf (accessed July 2, 2012).

CIRM. 2012a. *CIRM funding commitments: Funding for ICOC approved award*. http://www.cirm.ca.gov/GrantsSummary (accessed August 1, 2012).

CIRM. 2012b. *Strategic plan update: Accelerating the opportunity for cures*. http://www.cirm.ca.gov/files/PDFs/Publications/2012CIRMstratplan.pdf (accessed August 16, 2012).

Darnovsky, M. 2012.* *Statement to Institute of Medicine Committee on a Review of the California Institute for Regenerative Medicine*. Presentation at the 3rd IOM meeting of Committee on a Review of the California Institute for Regenerative Medicine (CIRM), April 10, Irvine, CA.

Department of General Services of State of California. 2010. *State administrative manual—Chapter 6800: 6871 General obligation (GO) bonds*. http://sam.dgs.ca.gov/TOC/6000/6871.aspx (accessed November 28, 2012).

Egli, D., A. E. Chen, G. Saphier, D. Powers, M. Alper, K. Katz, B. Berger, R. Goland, R. L. Leibel, D. A. Melton, and K. Eggan. 2011. Impracticality of egg donor recruitment in the absence of compensation. *Cell Stem Cell* 9(4):293-294.

Feldman, M. P., L. Lanahan, and I. Lendel. in press. Experiments in the laboratories of democracy: State scientific capacity building. *Economic Development Quarterly*.

Hayden, E. C. 2008. Stem cells: The 3-billion-dollar question. *Nature* 453(7191):18-21.

Health Economics Research Group, Office of Health Economics, and RAND Europe. 2008. *Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK*. London: UK Evaluation Forum.

Hiltzik, M. 2009. *California stem cell program needs a new treatment*. http://articles.latimes.com/2009/mar/30/business/fi-hiltzik30 (accessed July 13, 2012).

Jensen, D. 2012.* *California stem cell report: Statement to IOM-CIRM review panel*. Presentation at the 3rd IOM meeting of Committee on a Review of the California Institute for Regenerative Medicine (CIRM), April 10, Irvine, CA.

Karmali, R. N., N. M. Jones, and A. D. Levine. 2010. Tracking and assessing the rise of state-funded stem cell research. *Nature Biotechnology* 28(12):1246-1248.

Klein, R. N. 2011.* *Institute of Medicine: Review of the California Institute for Regenerative Medicine*. Presentation at the 1st IOM meeting of Committee on a Review of the California Institute for Regenerative Medicine (CIRM), October 19, Washington, DC.

Klein, R. N., and A. Trounson. 2011. A new political financial paradigm for medical research: The California model? In *The delivery of regenerative medicines and their impact on healthcare*, edited by C. D. Prescott and J. Polak. Boca Raton, FL: CRC Press, Taylor & Francis Group. Pp. 12-31.

Levine, A. D. 2006. Research policy and the mobility of US stem cell scientists. *Nature Biotechnology* 24(7):865-866.

Levine, A. D. 2012. State stem cell policy and the geographic preferences of scientists in a contentious emerging field. *Science and Public Policy* 39(4):530-541.

LHC (Little Hoover Commission). 2009. *Stem cell research: Strengthening governance to further the voters' mandate*. http://www.lhc.ca.gov/studies/198/report198.html (accessed July 2, 2012).

Macilwain, C. 2010. Science economics: What science is really worth. *Nature* 465(7299): 682-684.

Maddison, A. 2007. *Contours of the world economy 1-2030 AD: Essays in macro-economic history*. New York: Oxford University Press.

Mansfield, E. 1991. Academic research and industrial innovation. *Research Policy* 20(1):1-12.

Mansfield, E. 1998. Academic research and industrial innovation: An update of empirical findings. *Research Policy* 26(7-8):773-776.

Murphy, K. M., and R. H. Topel. 2003. *Measuring the gains from medical research: An economic approach*. Chicago, IL: The University of Chicago Press.

NCSL (National Conference of State Legislatures). 2008. *Embryonic and fetal research laws: Stem cell research*. http://www.ncsl.org/issues-research/health/embryonic-and-fetal-research-laws.aspx (accessed July 13, 2012).

NGA (National Governors Association). 2001. *2001 state tobacco settlement spending initiatives (issue brief)*. Washington, DC: NGA Center for Best Practices.

OTA (Office of Technology Assessment). 1986. *Research funding as an investment: Can we measure the returns? A technical memorandum*. OTA-TMSET-36. Washington, DC: U.S. Congress, Office of Technology Assessment.

Plosila, W. H. 2004. State science- and technology-based economic development policy: History, trends and developments and future directions. *Economic Development Quarterly* 18(2):113-126.

Roxland, B. E. 2012. New York State's landmark policies on oversight and compensation for egg donation to stem cell research. *Regenerative Medicine* 7(3):397-408.

Weber, P. J. 2012. *"Political considerations" alleged in cancer funds*. http://www.chron.com/news/article/Political-considerations-alleged-in-cancer-funds-3600523.php (accessed August 3, 2012).

YESon71 (The California stem Cell Research and Cures Initiative). 2004. *Key facts about Prop. 71*. http://web.archive.org/web/20041012023148/http://www.yeson71.com/facts.php (accessed July 15, 2012).

References with an asterisk (*) are public access files. To access those documents, please contact The National Academies' Public Access Records Office at (202)334-3543 or paro@nas.edu.

3

CIRM's Governance Structure

Proposition 71 specified in considerable detail a distinctive governance structure for the California Institute for Regenerative Medicine (CIRM), including organization and management systems. As with other provisions of the proposition, these governance provisions could not be changed until the third year following adoption, and then only with the approval of 70 percent of each house of the legislature and the signature of the governor. Nonetheless, in 2010, Senate Bill (SB) 1064 made several amendments to Proposition 71, some of which pertained to these systems[1] (see Appendix C for details of Proposition 71 and Appendix D for details of SB 1064). Because these systems can be modified either by legislation or by voter initiative, the committee takes a broad view of its charge to review them and offers recommendations for changes, even if these changes would require modifying current law.

This chapter begins with a brief overview of certain distinctive features of CIRM's governance structure as articulated in Proposition 71 and a comparison of this structure with that of similar programs in other states. The chapter then turns to its principal focus—an assessment of the effectiveness of CIRM's organization and management systems and recommendations for changes in those systems that might better serve CIRM's mission going forward.

[1]Senate Bill (SB) 1064 left unchanged the existing membership composition of the Independent Citizens Oversight Committee.

ORGANIZATION OF CIRM'S GOVERNANANCE STRUCTURE

Proposition 71 established the 29-member Independent Citizens Oversight Committee (ICOC) as CIRM's governing board. It set forth detailed provisions specifying qualifications for each seat on the ICOC, allocating power to certain University of California chancellors and particular state constitutional officers to fill seats in a way that ensured representation of specified stakeholders (CIRM, 2012a). The chancellors of the University of California, Davis, Irvine, Los Angeles, San Diego, and San Francisco, were each assigned one seat to fill with an executive officer from the respective campus, with four additional executive officers of the University of California to be selected for ICOC membership by the governor, lieutenant governor, treasurer, and controller, for a total of nine ICOC members from the University of California system. The same four state constitutional officers were each assigned further seats on the ICOC to fill with executive officers of academic and research institutions that are not part of the University of California (four members), California-based life sciences companies (four members), and representatives of specified disease advocacy groups (eight members), while the speaker of the assembly and the president pro tempore of the Senate were each assigned to appoint representatives of additional disease advocacy groups, for a total of 10 disease advocacy representatives on the ICOC (CIRM, 2009a, 2012b). The only seats on the ICOC that were specifically to be filled by individuals without a direct stake in the activities of CIRM were the four seats for executive officers of California-based life sciences companies, who by law could not come from entities that were actively engaged in stem cell research or that had been awarded or applied for CIRM funding at the time of appointment. Members from the University of California campuses and advocacy groups serve 8-year terms, while other members serve 6-year terms (CIRM, 2012b).

Although as a formal matter, the ICOC members are authorized to elect their own chair and vice chair,[2] Proposition 71 specifies stringent criteria for these positions, including that the chair and vice chair must be qualified for one of the appointments set aside for representatives of disease advocacy organizations. The chair and vice chair are both to be CIRM employees and may not concurrently be employed by or on leave from an institution that is a prospective recipient of a CIRM grant or loan, a provision that effectively disqualifies ICOC members from academic and research institutions

[2] "The Governor, the Lieutenant Governor, the Treasurer, and the Controller each nominate a candidate for Chair and a candidate for statutory Vice Chair. (*Id*., § 125290.20(a)(6).) The Board has the authority and responsibility to elect a Chair and a statutory Vice Chair from among the individuals nominated by the Governor, the Lieutenant Governor, the Treasurer, and the Controller" (CIRM, 2012b).

for these positions even if they otherwise meet the specified requirements (CIRM, 2012a).

Proposition 71 also calls for the creation of three working groups—a 19-member Scientific and Medical Accountability Standards Working Group (Standards Working Group), a 23-member Scientific and Medical Research Funding Working Group (Grants Working Group), and an 11-member Scientific and Medical Facilities Working Group—to provide guidance to the ICOC. Membership of each of these advisory bodies is set by law to include the ICOC chair, a specified number of ICOC members from the disease advocacy groups, and nonmembers who provide additional expertise and manpower (CIRM, 2012a).

The recommendations of the working groups to the ICOC have been important and influential, but the groups have no formal decision-making authority beyond offering recommendations. The Scientific and Medical Facilities Working Group, although important in the early stages when CIRM was financing the building of new facilities for stem cell research, is now inactive (CIRM, 2009b). The Standards Working Group continues to play a key role in setting the ethical standards for CIRM-sponsored programs (CIRM, 2009c). The Grants Working Group has played a large role in the review of grant applications (CIRM, 2009d), as discussed more fully in Chapter 4. In addition to the working groups, the bylaws of the ICOC allow for the establishment of subcommittees to facilitate its work.[3]

The generous size of the ICOC and its working groups stands in contrast to a parsimonious approach toward staffing the Institute itself.[4] As originally passed, Proposition 71 set a cap of 50 on the number of CIRM employees, excluding members of the working groups. SB 1064 eliminated that cap, but retained a cap on administrative expenses of 6 percent of bond funding, including not more than 3 percent for research and research facility implementation costs and not more than 3 percent for general administration of the Institute, as well as a provision that allows the ICOC to determine the total number of authorized employees. The wording of SB 1064 reflects the original design set forth in Proposition 71, which relies heavily on the governing board and its working groups to perform tasks that in many research organizations are usually allocated to management-supervised staff.

A similar allocation is apparent in the way Proposition 71 divides responsibility for leadership of operations between the CIRM president, who serves as the Institute's chief executive officer, and the board chair, who has significant management responsibilities for operations in addition

[3]Currently, there are subcommittees on governance, finance, legislative, intellectual property, industry, communications, science, and evaluation (CIRM, 2009a).

[4]See Annex 3-1 for figure depicting organizational structure of CIRM.

to managing the ICOC itself. In some cases, the allocation of responsibility for important management functions splits these responsibilities down the middle. For example, the chief financial officer reports to both the chair and the president, with responsibility for external financing resting with the chair and that for internal financial reporting and analysis with the president (CIRM, 2011a). Communications also are a joint responsibility, with the chair being responsible for public communications and the president for scientific communications (CIRM, 2011b).[5] To some extent, this allocation follows from the original language of Proposition 71: the chair is directed "to manage and optimize the institute's bond financing plans and funding cash flow plan" and "to interface with the California Legislature, the United States Congress, the California health care system, and the California public," while specific directives for the president begin with the provision of staff support for the ICOC and working groups and then list responsibilities for internal management, budgeting, and compliance.[6]

These somewhat unique arrangements reflect, in part, the unique origins of CIRM that relied on sustaining a very broad and effective coalition of patient advocates, scientists, and leaders of important research institutions. Although the committee believes that the structure served the institute well in its first several years, there are reasons to consider some changes going forward.

GOVERNANCE STRUCTURE OF PROGRAMS COMPARABLE TO CIRM

The committee thought it would be helpful to compare CIRM's governance structure with that of the similar state research initiatives discussed in Chapter 2. Connecticut, Maryland, New York, and Texas each have initiated programs to support science and technology with the goal of furthering economic development and the scientific enterprise in the state. Although the governance structure of each of these programs shares some key similarities with that of CIRM, such as the use of a board to provide guidance to staff managing the program on a day-to-day basis, there are differences in the structure and composition of these boards, the manner in which they provide oversight, and the extent to which they have management responsibilities. The programs also are integrated into state government in different ways and thus interact with existing agencies differently. One of the unusual aspects of CIRM is that it was created as a separate state

[5]In these two areas of joint responsibility, the chair and president are expected to collaborate in order "to ensure that CIRM speaks with one voice" (CIRM, 2011b, p. 4).

[6]California Stem Cell Research and Cures Initiative, Proposition 71 (2004) (codified at California Health and Safety Codes § 125291.10-125291.85), p. 4.

agency. Finally, with the exception of the Cancer Prevention and Research Institute of Texas (CPRIT), the governing board of each of the other state programs has members with built-in conflicts of interest because they are from institutions that are current recipients of agency funds. A high-level comparison of the oversight boards of CIRM and the four comparable programs is shown in Table 3-1.

PRIOR ASSESSMENTS OF CIRM'S GOVERNANCE STRUCTURE

CIRM has been the subject of a number of thoughtful evaluations during the past 5 years. Its governance structure, its internal financial controls and compliance record, and its scientific program have been separately assessed by various review bodies, including an External Advisory Panel (EAP), initiated and selected by CIRM itself; the independent Little Hoover Commission, whose review was undertaken at the behest of California legislators; and, most recently, Moss-Adams, LLP, which performed an external audit required by SB 1064. These assessments have praised CIRM's effectiveness in developing and managing its research portfolio and in meeting its most important responsibilities under Proposition 71 and as modified by SB 1064. They have also raised a number of consistent criticisms.

In 2008, Senators Sheila Kuehl and George Runner[7] asked the Little Hoover Commission to evaluate and recommend ways to strengthen CIRM's governance structure, as well as to recommend ways in which CIRM could improve accountability and reduce conflicts of interest. The Commission's 2009 report found that CIRM had been successful in establishing California as a leader in stem cell science and credited the Institute with attracting $900 million in matching funds, as well as drawing scientists to California from elsewhere in the United States and abroad (LHC, 2009). The Commission also recommended a number of changes in CIRM's governance structure to address conflict of interest issues and otherwise improve governance and accountability. CIRM rejected many of these recommendations as inconsistent with the dictates of Proposition 71 (CIRM, 2009e). The committee suggests that CIRM reconsider this position, because the committee believes many of the recommendations are sound and would enhance CIRM's ability to accomplish its goals. As the passage of SB 1064 demonstrates, when CIRM and the California legislature work together in

[7]Senators Kuehl and Runner authored the proposed and subsequently vetoed California bill SB 1565, which would have enacted intellectual property policy provisions covering research funded by CIRM and would have asked the Little Hoover Commission to review CIRM's governance. When the bill was vetoed, the senators wrote a letter directly to the Commission to request the study.

TABLE 3-1 Overview of Oversight Boards

	California	New York	Connecticut	Maryland	Texas
Board Name	Independent Citizens Oversight Committee (ICOC)	Empire State Stem Cell Board[a]	Stem Cell Research Advisory Committee	Maryland Stem Cell Research Commission	Cancer Prevention and Research Institute of Texas (CPRIT) Oversight Committee
Size	29	13	17	15	11
Term Length	6 or 8 years (maximum of two terms)	3 years (maximum of two terms)	4 years (maximum of two terms)	2 years (maximum of three terms consecutive)	6 years
Chair	Elected by the ICOC following nominations by California constitutional officers	Commissioner of Health	Commissioner of the Department of Public Health	Elected from membership by board members	Elected from membership by board members

Appointed by (no. of members)	• Chancellors of University of California (UC) schools (5) • Governor (5) • Lt. governor (5) • Treasurer (5) • Controller (5) • Speaker of the Assembly (1) • President pro tempore of the Senate (1)	• Governor (12) • Temporary president of the Senate (4) • Speaker of the Assembly (4) • Senate minority leader (2) • Assembly minority leader (2)	• Governor (4) • President pro tempore of the Senate (2) • Speaker of the House (2) • Senate majority leader (2) • House majority leader (2) • Senate minority leader (2) • House minority leader (2)	• Governor (4) • President of the Senate (2) • Speaker of the House (2) • University of Maryland (3) • Johns Hopkins University (3)	• Governor (3) • Lt. governor (3) • Speaker of the House (3)
Ratio of Members at Recipient Institutions to Total Board Members[b]	14/28	4/9	3/12	7/15	0/11

[a]The Empire State Stem Cell Board consists of two committees: the funding committee and the ethics committee. Information is provided here for the entire board, except for the ratio of members at recipient institutions to board members, which includes only funding committee members for comparability with the other state programs.

[b]The ratio of board members at recipient institutions to total board members is current as of August 2012. The total number of board members is less than the board size for some programs because of vacancies.

SOURCES: California Program: http://www.cirm.ca.gov; New York Program: http://stemcell.ny.gov; Connecticut Program: http://www.ct.gov/dph/cwp/view.asp?a=3142&q=389702&dphNav_GID=1825; Maryland Program: http://www.mscrf.org; Texas Program: http://www.cprit.state.tx.us.

the interests of the state's citizens and the field of regenerative medicine, they can enact useful modifications to Proposition 71.

In 2010, CIRM commissioned the EAP review to provide external and objective advice on its scientific strategy (discussed further in Chapter 4) and its associated policies and procedures. The report of this group of experts in stem cell research, ethics, and business states that "in a remarkably short period of time, CIRM has initiated an ambitious and comprehensive program." The report congratulates the ICOC and CIRM staff for the "extraordinary and rapid start up of [CIRM] programs" (EAP, 2010, p. 3).

The 2012 audit by Moss-Adams examined CIRM's functions, operations, management systems, policies, and procedures. The audit was required under SB 1064, which called for a performance audit every 3 years beginning with the 2010-2011 fiscal year. Overall, the report finds that CIRM is in full compliance with its stated policies. It characterizes CIRM staff as mission-driven, talented, dedicated professionals who are "committed to transparency and good stewardship of public funding" (Moss-Adams, LLP, 2012, p. 2).

CONCLUSIONS AND RECOMMENDATIONS

The committee agrees with the largely positive findings of the previous evaluations summarized above concerning the achievements of CIRM. The committee recognizes that the Institute's current governance structure, as designed by Proposition 71, may have been appropriate at the start of the endeavor and contributed to its early success. Proposition 71 was passed at a time when stem cell research faced considerable political opposition at the federal level, making it important to protect the Institute from potentially hostile political oversight. Moreover, when CIRM was starting up, it may have been expedient to meld operations and oversight. The initial structure, delegating expansive management roles to a large board of stakeholders and centralizing a great deal of authority in the chair position, provided the energy and expertise needed to get the organization up and running and to fund important foundational work as quickly as possible.

The committee also agrees with the observations of previous evaluations—especially the report of the Little Hoover Commission—concerning the need for improvements in CIRM's governance structure as it moves beyond the startup phase. Now that CIRM is a more mature organization, it and the citizens of California would be better served by a modified governance structure. The Little Hoover Commission made a series of recommendations, some of which were echoed in the 2012 performance review by Moss-Adams, regarding more efficient and effective governance and administration.

This section provides the committee's assessment of various elements of

CIRM's current organization and management systems and makes a series of recommendations intended to strengthen CIRM.

Separate Operations from Oversight

In the current governance structure, oversight and operations are pervasively intertwined. Proposition 71 established a large board, relying on working groups that report directly to the board to perform operations that in many research organizations are the job of staff reporting to the president. Additionally, the strict composition requirements of the board as detailed in Proposition 71 create inherent conflicts of interest for most board members. With respect to conflicts of interest, the committee did not uncover or search for evidence of any inappropriate behavior by any board members. The point is that the board suffers from a wide range of perceived conflicts generated directly by the particular and unique governance requirements of Proposition 71.

The committee believes CIRM would benefit from a clear and appropriate separation of duties, with the board having primary responsibility for oversight and strategy and the staff for implementation through day-to-day operations. While management has made significant strides to more carefully define duties of senior staff (Trounson, 2012), by themselves, these new position descriptions do not deal with the challenge of allowing the ICOC to provide independent oversight of management. Without such separation of duties, CIRM and the California taxpayers, who will repay the public funds that CIRM is expending, are deprived of the benefits of objective oversight that an independent board can provide. The current structure of the ICOC impedes independent oversight because it relies on the ICOC to function as both overseer and executer. The current structure makes sense as a way of protecting one kind of independence—the independence of CIRM from political pressures and the shifts in public opinion. But it fails to protect another kind of independence—independent oversight over the actions of CIRM itself that the people of California are entitled to expect from the board of a public institution.

Interface Between the ICOC and Management

The board currently makes decisions that would more typically be handled by management and staff. For example, a key management responsibility such as grants selection is performed by the board's Grants Working Group and subsequently modified by the board. The committee believes these allocations of roles and responsibilities should be revised—that the board should transfer management responsibilities to management so it

can provide truly independent oversight and evaluation of management, strategic planning, and broad direction for resource allocation.

While organizations such as the National Association of Corporate Directors provide guidance regarding the functions and benefits of an independent board, the committee is not aware of similar guidance for not for profit boards. However, the committee believes that the independence of the board is all the more important for a state agency supported by tax payers.

In the corporate governance setting, a typical concern is that excessive management control of the board may threaten the board's independence (Investopedia, 2008), while in the case of CIRM, the greater concern may be that the board itself is performing management functions. Either way, however, the board is compromised in its ability to serve as an independent check on the actions of management.

Prior groups evaluating CIRM have also suggested that CIRM should separate the roles and responsibilities of the ICOC from those of staff, delegating some of its current functions to management as is consistent with good governance practice. The EAP report suggests that the role of the ICOC should be limited to strategy setting and oversight. It states

> The CIRM Governing Board has had a very hands-on approach to CIRM in its first six years. This approach is appropriate for start-ups, especially one that is publicly funded and accountable such as CIRM. As CIRM transitions to Stage II, we believe this is an appropriate time for the Governing Board to examine its role and composition, mindful of the legal reporting, fiduciary and accountability requirements of the state of California. (EAP, 2010, p. 11)

Results of the 2011 survey of the board commissioned by the ICOC itself suggest that some board members agree with the above external assessments of the board's performance and the appropriateness of its current management role. Fully 90 percent of the board members stated that the board was too involved in operations and administrative/management details (Remcho, Johansen & Purcell, LLP, 2011). The attorneys who were commissioned to carry out the survey provided their own recommendation for addressing this concern within the strictures of Proposition 71: they suggested that the board could use its discretion with regard to its statutory duties to shift functions to the staff. They offered two models: a partnership model in which the chair and vice chairs would carry out their duties in partnership with the president, or a delegation model in which the board could request that the chair and vice chairs delegate duties to staff to the extent permitted by law, with the board playing an oversight rather than an operational role. Yet while these suggestions may offer a short-term solution to the legal constraints that CIRM believes currently prevent it from

separating management and oversight functions, more effective adaptations need to be identified and implemented for the longer term.

Limiting the involvement of the board and its chair in day-to-day management might also make it easier for CIRM to attract and retain good senior management. There has been a high degree of turnover in the Institute's senior management positions. Since 2006, CIRM has had five acting, interim, or official presidents, four chief scientific officers, four general counsels, and four financial/administrative officers (CIRM, 2011d). This high turnover rate, together with the creation and then elimination of the role of vice president of operations, may reflect unresolved management issues and a lack of clarity about roles and responsibilities both within management ranks and between the board and management (Hayden, 2009; Miller, 2010). At her departure after just 14 months in 2009, chief scientific officer Marie Csete said she hoped her leaving would mark "a new start" for the agency. "I had tried everything I could to change what I think needed to change from the inside, and that was not going to happen," she said. "I felt I would have more impact by stepping away and advising the leadership of the board on my way out about ways to revise the structure and management of the agency to make it more optimal" (Hayden, 2009, p. 17).

Interface Between the Chair and President

A related issue to the interface between the ICOC and management is the division of responsibilities between the chair and the president. As noted above, Proposition 71 assigns considerable responsibility for CIRM operations to the chair:

> The chairperson's primary responsibilities are to manage the ICOC agenda and work flow including all evaluations and approvals of scientific and medical working group grants, loans, facilities, and standards evaluations, and to supervise all annual reports and public accountability requirements; to manage and optimize the institute's bond financing plans and funding cash flow plan; to interface with the California Legislature, the United States Congress, the California health care system, and the California public; to optimize all financial leverage opportunities for the institute; and to lead negotiations for intellectual property agreements, policies, and contract terms.[8]

By contrast, Proposition 71 charges the president with overseeing staff support for the ICOC and its working groups, in addition to serving as chief executive of the Institute and overseeing its staff:

[8]Proposition 71, 125290.45. ICOC Operations, 4.b.1.A.

> The president's primary responsibilities are to serve as the chief executive of the institute; to recruit the highest scientific and medical talent in the United States to serve the institute on its working groups; to serve the institute on its working groups; to direct ICOC staff and participate in the process of supporting all working group requirements to develop recommendations on grants, loans, facilities, and standards as well as to direct and support the ICOC process of evaluating and acting on those recommendations, the implementation of all decisions on these and general matters of the ICOC; to hire, direct, and manage the staff of the institute; to develop the budgets and cost control programs of the institute; to manage compliance with all rules and regulations on the ICOC, including the performance of all grant recipients; and to manage and execute all intellectual property agreements and any other contracts pertaining to the institute or research it funds.[9]

At present, the ICOC Internal Governance Policy, instead of delegating management tasks to the president, is moving in the opposite direction and adding management tasks to the chair's responsibilities, including supervising the preparation of the annual financial plan. This tendency to add managerial roles to the ICOC also is reflected in the addition of another vice chair. CIRM's willingness to embrace this innovation in the structure of the ICOC stands in notable contrast to its reliance on the strict terms of Proposition 71 in rejecting other proposed innovations. It also shows an inclination to enlarge rather than contract the role of the ICOC in day-to-day operations. In the committee's judgment, the critical tasks performed by the vice chairs should be reassigned to management. In particular, the important tasks of government relations and corporate relations both should be carried out by staff reporting to the president rather than by the vice chairs of the board.

CIRM's Internal Governance Policy also calls for the president and chair to jointly recommend an organization chart to the Governance Subcommittee, and assigns to the chair employment and compensation authority for staff in the Office of the Chair. In addition, the policy delegates responsibility for public communication to the chair and responsibility for scientific communication to the president, with a director of public communications reporting to the chair (CIRM, 2011a,b,c). This organizational structure adds further day-to-day operational responsibilities to the Office of the Chair, which the committee believes is inconsistent with good governance practices. Evidence suggests that the trend toward blurring oversight and operations is continuing with the newly created position of chief financial officer reporting jointly to the chair and the president (CIRM, 2012c). Certain roles and functions that the committee feels should be the

[9]Proposition 71, 125290.45. ICOC Operations, 4.b.1.B.

responsibility of the president currently are handled, in whole or in part, by the chair and the ICOC. One-quarter or 12 of 53 of the staff report to the chair, while Proposition 71 states that one of the president's responsibilities is to "direct ICOC staff" and "to hire, direct, and manage the staff of the institute."[10] The committee believes good governance requires that the board delegate more authority and responsibility for day-to-day affairs to the president and senior management.

As noted earlier, the committee's concerns with respect to the CIRM governance structure have been voiced previously by others. The Little Hoover Commission called for CIRM and the Legislature to eliminate overlapping authority between the chair and president and to improve the clarity and accountability of each. The Commission stated that "the board chair position, as structured, conflates day-to-day management with the independent oversight that the board is supposed to provide, straddling the roles of accountability and operations" (LHC, 2009, p. iii). It stated further that

> To strengthen lines of communication and provide clear direction for the agency, the co-CEO management approach at CIRM should end, with the agency president placed in charge of all operations and the chair fulfilling only oversight duties, external affairs and board administration. The administrative limits set in Proposition 71 require a careful allocation of staffing and resources: the current overlapping roles of the president and the board chair complicate this effort, creating multiple reporting channels and functional redundancy. (LHC, 2009, p. iv)

This recommendation was echoed by the EAP, which called for clarity in roles and responsibilities between these two positions, particularly with regard to strategic direction, policies, international partnerships, funding decisions, public communications, and oversight. EAP member Alan Bernstein reported to the committee that:

> In most organizations, the role of the Board is to deal with governance issues, including approving the vision, mission and strategic plan, oversee broad directions, policies, integrity, etc and to recruit the president/CEO. It is typically the president's/CEO's role to oversee the management of the organization, guide the board's strategic discussions, etc. These roles can frequently become somewhat blurred during the start-up phase of an organization. As an organization starts to mature, it is important for the Board to step back, allowing the CEO and his/her executive to assume the roles and functions normally associated with management. Although we had not been asked to comment directly on this issue, our sense was that CIRM was evolving from its initial start-up phase into phase 2 and hence it would be important and timely for the Board and senior management

[10]California Stem Cell Research and Cures Initiative, Proposition 71 (2004) (codified at California Health and Safety Codes § 125291.10-125291.85).

> to clarify roles and responsibilities between the Board and board chair and the president and senior management. (Bernstein, 2012)

While CIRM has clarified and defined roles, it has not, in the committee's judgment, allocated responsibilities in the most effective manner. The key issue from the committee's perspective is not only clarification of roles, but also allocation of responsibilities between the board and CIRM management in a way that best serves the interests of the Institute, California, and the field of regenerative medicine, consistent with sound governance practices regarding separation of duties and oversight.

The committee recommends that the ICOC diminish its involvement in day-to-day governance by delegating to the president and staff the operational tasks that Proposition 71 assigns to the chair. The committee believes problems with the current allocation of responsibilities between the chair and the president are not limited to a lack of clarity. The committee agrees with the Little Hoover Commission and the EAP that the current governance structure gives the board and chair too much involvement in day-to-day operations to the detriment of their ability to provide independent oversight.

> ***Recommendation 3-1.***[11] ***Separate Operations from Oversight.*** **The board should focus on strategic planning, oversee financial performance and legal compliance, assess the performance of the president and the board, and develop a plan for transitioning CIRM to sustainability. The board should oversee senior management but should not be involved in day-to-day management. The chair and the board should delegate day-to-day management responsibilities to the president. Each of the three working groups should report to management rather than to the ICOC.**

Change the Composition and Structure of the Board and Working Groups

Board Composition

The committee believes the predominance of direct stakeholders—defined as individuals with a direct stake in the processes and outcomes of CIRM's activities that arises outside of their service to the Institute—in the composition of the ICOC compromises its independence in another manner beyond the entanglement of oversight and operations. Board members with personal and professional interests in the activities of CIRM that go beyond the interests of the general public undoubtedly bring considerable energy

[11]CIRM may need to work with the state legislature in order to fully implement this recommendation.

and commitment to the tasks before them, but they may also introduce bias into the board's decisions that compromises its stewardship over CIRM as a public institution. In its report, the Little Hoover Commission recommended that the California Legislature amend the Health and Safety Code to reduce the board size, shorten terms of board members, and restructure membership to add independent voices in order to increase efficiency and transparency.

In the committee's opinion the board's composition should be modified to include a majority of members who are "independent" in the sense of having no direct personal or professional interest that might compete or conflict with the interests of CIRM and the people of California in ways that bias their decisions. The size of the board should be maintained or decreased in this process. The committee did not find empirical data indicating the optimal size for an organization's board. However, in the committee's opinion the size of the board should not be enlarged in the process of increasing the number of independent members. The board should include representatives of the diverse constituencies with interests in stem cell research, but no institution or organization should be guaranteed a seat on the board.

To bring fresh perspectives from diverse representatives while maintaining continuity, the ICOC should phase in a plan to stagger members' terms. Doing so would allow broader representation over time from a wider variety of stakeholders while providing both continuity and new perspectives.

Working Groups

As noted previously, CIRM has relied heavily on the three working groups specifically outlined and charged in Proposition 71 to perform a series of critical tasks. These working groups have provided critical advice to the ICOC in such areas as facilities; ethics and standards; and, perhaps most important, assistance to CIRM in building its scientific programs. They have unquestionably played an important role in the Institute's evolution. The high-quality input they provide will continue to be critical in the coming years. At present, these working groups report directly to the chair. However, the committee believes they would more properly report to CIRM's senior management, thus reserving the ICOC to exercise its high-level and independent strategic oversight responsibilities. As discussed further in Chapter 4, some decisions made by the Grants Working Group are overturned by the ICOC. There has been an increase in the number of extraordinary petitions (applicants' written petitions to the ICOC regarding the application after review by the Grants Working Group). As of October 2012, 32 percent of petitions were successful. This increase in successful

appeals undermines the credibility and independent work of the Grants Working Group.

Therefore, it is important that the chair and other ICOC members not serve on the working groups. As board members are replaced, the working groups should not lose the fundamental and critical perspective of disease advocates. Instead, the disease advocate board members should be replaced on the working groups with an equal number of disease advocates who are not board members. In this way, an even broader group of patient advocates would have a role in the activities of the Institute and the ICOC will make strategic decisions. Working groups should report to the same management team, not to members of senior management, so that continuity and coherence are not lost.

Recommendation 3-2.[12] ***Change the Composition and Structure of the Board and Working Groups.*** **CIRM should put systems in place to restructure the board to have a majority of independent members, without increasing the size of the board. It should include representatives of the diverse constituencies with interests in stem cell research, but no institution or organization should be guaranteed a seat on the board. Consideration should be given to adding members from the business community. The terms of board members should be staggered to balance fresh perspectives with continuity.**

The chair and other ICOC members should be prohibited from serving on the working groups. During the reconstitution of the working groups, the current level of representation of disease advocates should be maintained, such board members being replaced with other disease advocates who are not board members.

Revise Conflict of Interest Definitions and Processes

The ICOC is overwhelmingly composed of representatives of (1) organizations that receive substantial CIRM funding and (2) disease advocacy communities. This composition raises questions about whether decisions delegated to the board—particularly decisions about the allocation of funds—will be made in the best interests of the public or will be unduly influenced by the special interests of board members and the institutions they represent. Such conflicts, real or perceived, are inevitable given the provisions of Proposition 71 and were not addressed by SB 1064. Proposition 71 attempts to set aside the concern about conflict of interest through

[12]CIRM may need to work with the state legislature in order to fully implement this recommendation.

statements that no such conflict exists. For example, Proposition 71 states that service on the ICOC "shall not, by itself, be deemed to be inconsistent, incompatible, in conflict with, or inimical to the duties of the ICOC member as a member of the faculty or administration of any system of the University of California" and that service on the ICOC "by a representative or employee of a disease advocacy organization, a nonprofit academic and research institution, or a life science commercial entity shall not be deemed to be inconsistent, incompatible, in conflict with, or inimical to the duties of the ICOC member as a representative or employee of that organization, institution, or entity."[13] Although this language may be adequate to protect ICOC members from legal liability, it has not prevented persistent accusations regarding conflicts of interest (LHC, 2009). According to the Little Hoover Commission report, "Even though a board with interested parties can operate within legal bounds, the Commission is concerned that the lack of disinterested members on the ICOC weakens the board's ability to make sound decision [sic], and limits the likelihood that there will be substantial debate and dissent among board members about key funding and policy decisions. Such a dynamic also erodes confidence that the board is capable of making broader strategic decisions that go beyond awarding research dollars" (LHC, 2009, p. 16).

The committee received divergent responses to questions about conflict of interest in its questionnaire to ICOC members.[14] Although a majority of respondents stated that personal interests did not play a role in their work on the ICOC, some responses were more equivocal. One respondent replied that it was "hard to tell" given that "so many decisions take place off camera in secret meetings," while another acknowledged that "ICOC members are human, and of course their decisions are influenced by personal beliefs and interests. . . . Board members also have a sincere dedication to represent their constituents, for example patients who suffer from diseases or disorders that might benefit from stem cell therapies." One member suggested that the different biases of stakeholders on the board "can be seen as positive" and that "although self-interest cannot be completely eliminated, the separate range of interests of the different board members provides a good measure of protection from runaway, and risky, decisions" (IOM, 2012). At a minimum, these divergent responses suggest that the ICOC members do not have a shared understanding of conflict of interest and its role in their deliberations, indicating a need to address the issue through regulations and training.

Properly understood, conflict of interest is not misconduct, but bias

[13]California Stem Cell Research and Cures Initiative, Proposition 71 (2004) (codified at California Health and Safety Codes § 125291.10-125291.85).

[14]See Appendix B for a summary of questionnaire responses.

that skews the judgment of a board member in favor of interests that may be different from or narrower than the broader interests of the institution. Inherent conflicts arise from the interests of board members as employees of grantees and as representatives of disease advocacy organizations. Board members who are especially concerned with the interests of particular institutions or disease areas may not recognize when those interests depart from the best interests of the people of California. Whatever the behavior of the board, conflicts of interest, real or perceived, threaten to distort and to undermine respect for its decisions.

Although the committee did not uncover or search for any evidence that conflicts of interest have overtly influenced decision making by ICOC members, studies from psychology and behavioral economics show that conflict of interest leads to unconscious and unintentional "self-serving bias" and to a "bias blind spot" that prevents recognition of one's own bias (IOM, 2009, pp. 358-374). Bias distorts the evaluation of evidence and the assessment of what is fair (IOM, 2009, pp. 258, 364). There recently has been an increased focus on the importance of minimizing bias and conflict of interest in science fields (Broccolo and Geetter, 2009; Ehringhaus et al., 2008; IOM, 2009; Vogeli et al., 2009). A 2009 report from the Institute of Medicine concludes that "the goals of conflict of interest policies in medicine are primarily to protect the integrity of professional judgment and to preserve public trust rather than to try to remediate bias or mistrust after they occur" (IOM, 2009, p. 5).

CIRM should acknowledge and manage the full range of conflicts that are inherent in the current composition of the ICOC. California law focuses primarily on financial conflicts of interest, but the committee believes that personal conflicts of interest arising from one's own or a family member's affliction with a particular disease or advocacy on behalf of a disease area also can create bias for board members. In this regard, almost all members of the ICOC are interested parties with a personal or financial stake in the allocation of CIRM funding that goes beyond their interests as representatives of the people of California. These members include representatives of institutions that seek CIRM funding and representatives of disease advocacy groups with missions that might be affected by the allocation of CIRM funding. Although this conflicted board composition is specified and sanctioned by the terms of Proposition 71, it raises questions about bias that could distort the decisions made by ICOC members in their role as stewards of the interests of the taxpayers who will have to repay the borrowed funds that CIRM is spending. Over the years, reports from stakeholders and consumer advocates have criticized CIRM's lack of transparency, particularly as it relates to the process of awarding of research grants (LHC,

2009; Simpson, 2012). The committee believes that by addressing conflict of interest, issues of transparency will be alleviated.

The primary mechanism in CIRM's policies for managing conflict of interest is recusal from participating in deliberations and voting on matters that affect the financial interests of a conflicted individual (CIRM, 2006). Voting records from ICOC meetings show many members recusing themselves from participation in particular decisions. CIRM has no policies to manage nonfinancial conflicts, such as those arising from affiliation with a disease advocacy group or an individual's interest in a specific disease. Nonfinancial conflicts may call for more sensitive and flexible tools than CIRM currently uses to manage financial conflicts of interest. Although they may be powerful sources of bias, nonfinancial conflicts may have important privacy implications, especially when they touch on matters of personal health. Moreover, the same interests that give rise to such conflicts may give conflicted individuals valuable insights that could be lost from deliberations if those individuals were excluded from participation. These considerations complicate the task of managing nonfinancial conflicts of interest, but they do not justifying ignoring these conflicts. The committee urges CIRM to consider these competing considerations fully in revisiting its conflict of interest policies. Even for purely financial conflicts, recusal becomes a less satisfactory tool as the number of conflicts increases.

The presence of conflicts for individual board members would be less cause for concern if the board had more nonconflicted members. CIRM should address real and apparent conflicts of interest, including and beyond financial interests, built into its governance structure regardless of whether these conflicts have in theory been waived by the voters or excused under California law. EAP member Alan Bernstein stated in an interview with the committee: "Regarding the composition of CIRM's governing board, the panel thought there should be a better balance between individuals representing recipient institutions and individuals who represent the broader California public" (Bernstein, 2012). The Little Hoover Commission in its report indicated that "the board lacks truly independent voices to balance out those of interested board members. The founding board members' terms are too long and are not conducive to adding fresh perspectives about the agency's future given the rapid advancement of stem cell science" (LHC, 2009, p. iv). Other state programs (described above) have addressed conflicts of interest among board members by adding out-of-state members (Connecticut) or removing university leadership from the primary oversight board and creating a university advisory committee (Texas).

Recommendation 3-3.[15] ***Revise Conflict of Interest Definitions and Policies.*** **CIRM should revise its definitions of conflict of interest to recognize conflicts arising from nonfinancial interests, such as the potential for conflict arising from an individual's interest in a specific disease, and should reassess its policies for managing conflict of interest in light of this broader definition.**

Conclusion

In conclusion, the governance structure for CIRM is unusual in important respects that the committee believes could diminish its effectiveness going forward. The legislatively mandated composition of the ICOC was structured to tackle a challenging mission at a challenging time. However, in the committee's judgment both CIRM and the citizens of California would be better served going forward with a modified governance and administrative structure as outlined above. The ICOC has had more extensive operational responsibilities than is typical for a governing board, and the chair and vice chairs have duties that are more typically performed by a CEO. The working groups that report to the ICOC and that include ICOC members perform functions (such as peer review of grant proposals) that other institutions more commonly delegate to independent advisors reporting to scientific staff. The size of the ICOC, augmented by the non-ICOC members of the working groups, is large compared with the size of the CIRM staff.

The membership of the ICOC is skewed toward representatives of institutions that have a direct stake in how CIRM allocates its funding. Although this profile of the ICOC was understandably designed to include representatives from a broad range of those most concerned and most knowledgeable regarding the future of regenerative medicine, they also were the constituencies expected to benefit most directly and immediately from CIRM's grants. These features make a certain amount of sense as a reflection of CIRM's origins and the challenges it faced in its early years. But each feature has drawn criticism, raising questions about whether at this stage the original governance structure best serves the interests of CIRM and of the California taxpayers who will repay the funds that CIRM is spending. The current structure has created challenges for CIRM which distract from the Institute achieving its core mission. For example, high staff turnover, increasing number of extraordinary petitions (discussed further in Chapter 4), and persistent criticisms and perceptions that conflicts of interest and lack of independence of board members influence grant funding.

Many of these problematic features of CIRM's structure are prescribed

[15]CIRM may need to work with the state legislature in order to fully implement this recommendation.

by California law and can be changed only by the California Legislature or by another voter initiative. In assessing CIRM's current governance structure and proposals for reform, the committee did not limit considerations and recommendations to the boundaries imposed by Proposition 71. Instead, the committee worked to develop recommendations that would best serve CIRM and the California taxpayers from this point forward.

The committee believes that CIRM and the California taxpayers would be better served by a governance structure in which the role of the ICOC would remain focused on broad oversight and strategic planning rather than involvement in day-to-day management issues. The level of ICOC involvement in peer review and grant funding is particularly inappropriate given the stakeholder composition of the board. The ICOC should include more independent members who have no financial or other interests, either as individuals, as employees or officers of grantee institutions, or as representatives of disease advocacy organizations, in the work of CIRM that are distinct from the broader interests of the taxpayers and that might influence their judgment.

An important theme of the committee's governance recommendations is for CIRM to transition from the governance structure initially outlined in Proposition 71 to one the committee believes would better serve the interests of the citizens of California and the field of regenerative medicine. The committee fully appreciates that even in the best of circumstances, such a transition, if done thoughtfully, can take place only over time and that there may be challenges and resistance to any proposed changes. Moreover, the committee is aware that its recommendations regarding governance come at a time when CIRM may well be faced with even more pressing challenges resulting from the expiration of Proposition 71 funding and/or dynamic changes in the field of regenerative medicine. Nevertheless, issues of governance are critical for sustaining trust and should be given careful consideration.

REFERENCES

Bernstein, A. 2012.* *Summary of conversation with member of the External Advisory Panel*. Committee on a Review of the California Institute for Regenerative Medicine (CIRM) Phone Interview with Alan Bernstein, December 20, 2011, Washington, DC.

Broccolo, B. M., and J. S. Geetter. 2008. Today's conflict of interest compliance challenge: How do we balance the commitment to integrity with the demand for innovation? *Journal of Health and Life Sciences Law* 1(4):1, 3-65.

CIRM (California Institute for Regenerative Medicine). 2006. *Adopted CIRM stem cell grant regulations: Chapter 1. Conflicts of interest*. http://www.cirm.ca.gov/Regulations#conflicts (accessed August 30, 2012).

CIRM. 2009a. *CIRM Governing Board: Independent Citizens Oversight Committee (ICOC)*. http://www.cirm.ca.gov/GoverningBoard (accessed August 29, 2012).

CIRM. 2009b. *About the Facilities Working Group*. http://www.cirm.ca.gov/WorkingGroup_Facilities (accessed August 27, 2012).

CIRM. 2009c. *About the Standards Working Group*. http://www.cirm.ca.gov/WorkingGroup_Standards (accessed August 27, 2012).

CIRM. 2009d. *About the Grants Working Group*. http://www.cirm.ca.gov/WorkingGroup_GrantsReview (accessed August 27, 2012).

CIRM. 2009e. *CIRM's response to Little Hoover Commission report on CIRM*. http://www.cirm.ca.gov/files/meetings/pdf/2009/081909_item_7A.pdf (accessed August 16, 2012).

CIRM. 2011a.* *President position description*. CIRM's response to IOM's data request: Documentation of roles and responsibilities for senior leadership positions, both ICOC and CIRM (dated December 13, 2011).

CIRM. 2011b. *Internal governance policy: Exhibit C (approved by the board on May 4, 2011): Reorganization proposal introduction*. http://www.cirm.ca.gov/files/PDFs/Administrative/Internal_governance.pdf (accessed August 15, 2012).

CIRM. 2011c.* *Duties of the chairperson of governing board of the California Institute for Regenerative Medicine*. CIRM's response to IOM's data request: Documentation of roles and responsibilities for senior leadership positions, both ICOC and CIRM (dated December 13, 2011).

CIRM. 2011d.* *Governance & management leadership tenure turnover statistics*. CIRM's response to IOM's data requests: Turnover statistics for key leadership positions (dated December 8, 2011).

CIRM. 2012a. *ICOC bylaws*. http://www.cirm.ca.gov/files/PDFs/ICOC/ICOC_Bylaws_05-24-12.PDF (accessed August 22, 2012).

CIRM. 2012b.* *ICOC nomination selection process*. CIRM's response to IOM's data request: Description of the selection and nomination process for ICOC membership (dated January 9, 2012).

CIRM. 2012c.* *California Institute for Regenerative Medicine duty statement: Chief financial officer*. CIRM's response to IOM's data request: Documentation of roles and responsibilities for senior leadership positions, both ICOC and CIRM (dated March 27, 2012).

EAP (External Advisory Panel). 2010. *Report of the External Advisory Panel*. http://www.cirm.ca.gov/files/PDFs/Administrative/CIRM-EAP_Report.pdf (accessed July 2, 2012).

Ehringhaus, S. H., J. S. Weissman, J. L. Sears, S. D. Goold, S. Feibelmann, and E. G. Campbell. 2008. Responses of medical schools to institutional conflicts of interest. *JAMA* 299(6): 665-671.

Hayden, E. C. 2009. *Chief scientist quits California stem-cell agency*. http://www.nature.com/news/2009/090630/pdf/460017a.pdf (accessed August 16, 2012).

Investopedia. 2008. *Evaluating the board of directors*. http://www.investopedia.com/articles/analyst/03/111903.asp/#axzz23j1fnhAI (accessed August 16, 2012).

IOM (Institute of Medicine). 2009. *Conflict of interest in medical research, education, and practice*. Washington, DC: The National Academies Press.

IOM. 2012.* *Summary: Questionnaire for Members of the ICOC*. Institute of Medicine Committee on a Review of the California Institute for Regenerative Medicine online questionnaire launched on February 6, 2012.

LHC (Little Hoover Commission). 2009. *Stem cell research: Strengthening governance to further the voters' mandate*. http://www.lhc.ca.gov/studies/198/report198.html (accessed July 2, 2012).

Miller, G. 2010. CIRM: The good, the bad, and the ugly. *Science* 330(6012):1742-1743.

Moss-Adams, LLP. 2012. *California Institute for Regenerative Medicine FY 2010-2011 performance audit*. http://cirm.ca.gov/files/meetings/pdf/2012/052412_item_6.pdf (accessed July 13, 2012).

Remcho, Johansen & Purcell, LLP. 2011.* *Governance & management memo re ICOC board survey exhibits*. CIRM's response to IOM's data response: Information that can be shared about the 2011 ICOC conducted survey of board members to assess their current view of the role of the chairman and the overall performance of the board as a whole (dated January 28, 2012).

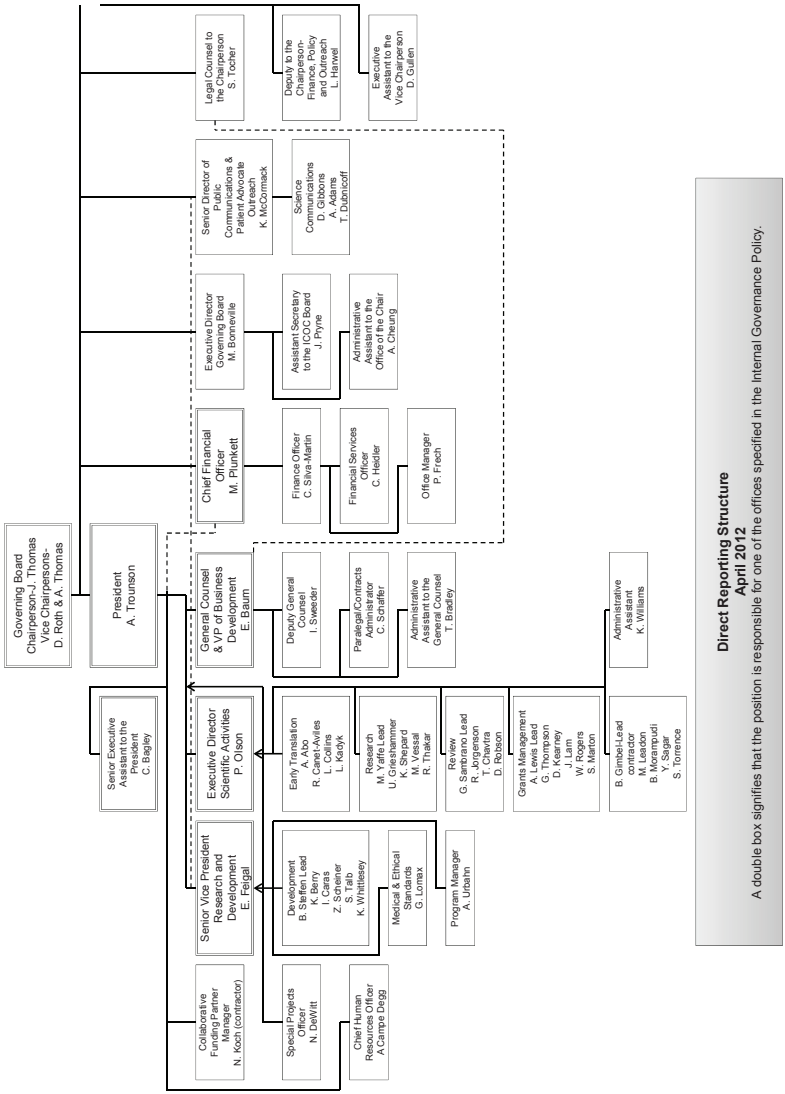
Simpson, J. M. 2012.* Presentation at the 3rd IOM meeting of Committee on a Review of the California Institute for Regenerative Medicine (CIRM). April 10, Irvine, CA.

Trounson, A. 2012.* *CIRM's new strategic direction in basic and translational science*. Presentation at the 2nd IOM meeting of Committee on a Review of the California Institute for Regenerative Medicine (CIRM), January 24, San Francisco, CA.

Vogeli, C., G. Koski, and E. G. Campbell (2009). Policies and management of conflicts of interest within medical research institutional review boards: Results of a national study. *Academic Medicine* 84(4):488-494.

References with an asterisk (*) are public access files. To access those documents, please contact The National Academies' Public Access Records Office at (202)334-3543 or paro@nas.edu.

ANNEX 3-1



4

Nature, Scope, and Accomplishments of the CIRM Scientific Program

The stated mission of the California Institute for Regenerative Medicine (CIRM) is "to support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury" (CIRM, 2012a, p. 5, 2012b). The California Stem Cell Research and Cures Act establishes CIRM as an institute that will be responsible for disbursing the proceeds from the general obligation bonds issued by the state for the purpose of supporting stem cell research in California, emphasizing pluripotent stem cell and progenitor cell research and other vital medical technologies, for the development of life-saving regenerative medical treatments and cures.

The passage of Proposition 71 focused worldwide attention on regenerative medicine, and CIRM's subsequent activities catapulted California into a position as an international hub of research and development in stem cell biology. This chapter first addresses CIRM's strategic planning as it has evolved since the Institute's inception. It then presents an analysis of the Institute's grant management system, as well as the bioethics- and industry-related challenges that lie ahead for clinical applications of stem cell research. As discussed in Chapter 1, it was outside of the scope of the committee's work to rigorously evaluate the details of CIRM's scientific contributions, specific grant awards, or impact on the field of regenerative medicine. Rather, the committee examined CIRM's overall scientific priorities and the quality of the processes instituted to guide its funding priorities and decisions. The final section provides the committee's conclusions and

recommendations on the nature, scope, and accomplishments of CIRM's scientific program.

STRATEGIC PLANNING

This section begins by examining the impact of work resulting from CIRM's research funding as guided by its initial (CIRM, 2006a) strategic goals. It then reviews the goals and funding model articulated in the 2012 strategic plan (CIRM, 2012a), considers the potential impact on the development of cures and therapies for chronic disease and injury, and presents the committee's view of the potential benefit to CIRM of establishing independent guidance for the establishment of its evolving priorities.

The 2006 Strategic Plan

To fulfill CIRM's mission, the Institute's governing board, the Independent Citizens Oversight Committee (ICOC), adopted the first scientific strategic plan in December 2006. This plan served as the blueprint that guided the first 5 years of CIRM's programs. The goals during this initial phase were to develop appropriate laboratory facilities for stem cell research, to fund basic research in stem cell biology, to invest in programs directly focused on research on a broad range of diseases, and to establish a long-term foundation for California leadership in stem cell research and development (CIRM, 2006a).

Because all of CIRM's awards are made on a competitive basis in response to requests for applications (RFAs) issued by the Institute, a grant review process was instituted to evaluate proposals and make funding recommendations to the ICOC, which was responsible for final decisions (CIRM, 2012c). Operationally, CIRM developed RFAs, which were issued to the community after being approved by the ICOC. The initial RFAs were tied to objectives outlined in the 2006 strategic plan; those objectives were informed by a series of workshops convened by CIRM's scientific staff and other interactions with the broader scientific community. Eventually, CIRM's scientific staff, working under the direction of the chief scientific officer,[1] prepared drafts of RFAs, which were then presented to the ICOC. The ICOC considered each RFA in terms of its overall priority and determined the maximum amount of funding that would be available for each of the approved initiatives. All ICOC-approved RFAs were then announced widely and posted on the CIRM website, and applicants were invited to submit proposals with a defined deadline (CIRM, 2012c).

[1]The title of chief scientific officer was later replaced by senior vice president for research and development.

During its early phase, CIRM issued a variety of RFAs. One of these was for the construction of research facilities to house investigators and promote their interaction in close proximity (CIRM, 2007a). Given the political climate at the time of CIRM's authorization, there was concern that federal legislation would continue to preclude stem cell research in facilities constructed with federal dollars. Hence CIRM was authorized to spend up to 10 percent of its research budget on new facilities that could then operate independently of federal stem cell legislation. CIRM also focused heavily on developing the manpower necessary to sustain a long-term capacity in stem cell research and development in California. This objective was operationalized through a series of RFAs to support faculty recruitment, which resulted in both junior investigators and senior faculty being retained in and recruited to California (CIRM, 2007b). In addition, training grants were awarded that included programs for graduate and postgraduate trainees, as well as more innovative programs. An example of the latter is the Bridges Program, designed to encourage students at community colleges to enter the field of stem cell research and its clinical applications (CIRM, 2005, 2008a,b).

This early phase of CIRM also saw RFAs focused largely on the basic science of stem cells, as it was perceived that the fundamental understanding of these cells and their potential functions was still in its infancy (CIRM, 2006b, 2008c, 2009a, 2010a). Such basic research was viewed as a foundation for subsequent translational investigation. These RFAs were followed by RFAs focused on topical areas designed to address perceived roadblocks to the potential use of stem cells for therapy (e.g., an RFA on studying how to overcome the immune response to stem cells) (CIRM, 2009b), and to stimulate the development of new technologies (e.g., tools and technology grants) (CIRM, 2010b) or reagents (e.g., development of new cell lines) that were thought to be critical for the field's further development (CIRM, 2007c).

Overall, the RFAs that were issued in the first few years of CIRM's operations were concordant with the goals outlined in the original 2006 strategic plan. In this first crucial period of operations, CIRM funded—in a remarkably expeditious and thoughtful manner—more than $1.3 billion in awards to 59 institutions.[2] The focus of these awards was fully consistent with CIRM's stated mission and was important for building the infrastructure for stem cell investigation in California. CIRM allocated these funds in an open and competitive manner that was well informed by scientific expertise from outside California. Moreover, CIRM-supported programs have been responsive to scientific advances occurring outside of California.

One example of CIRM's efforts to connect with research outside of

[2]See http://www.cirm.ca.gov/InstitutionList.

California is its collaborations with other centers of excellence in stem cell research located both within the United States and around the world. Collaborations with funding partners and stem cell researchers in Australia, Canada, Germany, Japan, Spain, the United Kingdom, the United States, and several other countries have attracted tens of millions of dollars in matching funds for initiatives in regenerative medicine elsewhere, which enhanced the work of CIRM investigators, and raised the Institute's profile as a global leader in regenerative medicine (CIRM, 2011a). Similar collaborations with the National Institutes of Health (NIH), other stem cell organizations (e.g., in Maryland and New York; see Chapter 2), and foundations (e.g., the Juvenile Diabetes Foundation) have resulted in new levels of cooperation and funding in the field (CIRM, 2011b). Another potential benefit is access to external intellectual property that could be commercialized by California companies.

The committee understands that it is challenging to measure outcomes of these partnerships at this early stage and that it remains to be determined whether the benefits outweigh the cost of initiating, negotiating and managing them because of complex intellectual property (IP) and other policies. The committee is encouraged by CIRM's recent launch of the External Innovation Initiative (created in response to a recommendation of the 2010 External Advisory Panel [EAP, 2010]), which enhances this collaborative program (CIRM, 2011c). However, through interviews with several external partners (including those in the United States and abroad), the committee learned that at least some of CIRM's partners believe they have had insufficient input into the development of the Institute's RFAs (IOM, 2012a,b,c). The committee appreciates this concern, because CIRM would be well served to take the fullest advantage of the special skills and opportunities these collaborators can provide to its joint ventures.[3]

Given the state of science in regenerative medicine, the 2006 5-year strategic plan, and CIRM's 10-year funding horizon, the committee believes it made good sense to begin with investments in basic research; in physical infrastructure (especially given the matching funds that were required and mobilized by each institution awarded a major facilities grant and the requirement that construction be completed with a rapid timeline); in human capital (from young technicians to established researchers); and in collaborations with research partners from other centers of excellence worldwide. It is clear that in this initial period, CIRM substantially enhanced the position of California as one of the key international hubs of activity in regenerative medicine.

[3]Each of CIRM's collaborators outside of California must mobilize the resources necessary to support its own work.

Stimulation of Translational Research

In 2008, CIRM undertook a broadening of its portfolio of grants to stimulate progress toward its translational goals by issuing a call for planning awards to lay the foundation for a subsequent call for disease team research awards. The initial awards were designed to stimulate the planning of projects focused on the use of stem cells in the development of therapies (CIRM, 2007d). The Disease Team Research RFA followed in 2009 (CIRM, 2009c). The goal was to fund multidisciplinary teams that would engage in milestone-driven translational research for the development of stem cell–based therapies. The funded teams were to conduct research and plan for the regulatory activities necessary to support Investigational New Drug (IND) applications to the Food and Drug Administration (FDA), with the goal of eventually enabling or at least moving toward Phase 1/2 clinical trials. The Disease Team Research Awards have now emerged as fundamental to CIRM's core ongoing mission. The following 14 disease team awards (totaling approximately $230 million) were made (CIRM, 2009d,e):

1. Cedars-Sinai Medical Center: Autologous Cardiac-Derived Cells for Advanced Ischemic Cardiomyopathy
2. Stanford University: Development of Therapeutic Antibodies Targeting Human Acute Myeloid Leukemia Stem Cells
3. Stanford University: Embryonic-Derived Neural Stem Cells for Treatment of Motor Sequelae Following sub-Cortical Stroke
4. Stanford University: iPS Cell-Based Treatment of Dystrophic Epidermolysis Bullosa
5. The City of Hope: Stem Cell–Mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials
6. The City of Hope: Zinc Finger Nuclease-Based Stem Cell Therapy for AIDS
7. UCLA: HPSC–Based Therapy for HIV Disease Using RNAi to CCR5
8. UCLA: Stem Cell Gene Therapy for Sickle Cell Disease
9. UCLA: Therapeutic Opportunities to Target Tumor Initiating Cells in Solid Tumors
10. UCSD: Development of Highly Active Anti-Leukemia Stem Cell Therapy
11. UCSD: Stem Cell–Derived Astrocyte Precursor Transplants in Amyotrophic Lateral Sclerosis
12. UCSF: Stem Cell–Mediated Oncocidal Gene Therapy of Glioblastoma
13. USC: Stem Cell–Based Treatment Strategy for Age-Related Macular Degeneration
14. ViaCyte Inc.: Cell Therapy for Diabetes

In 2011, approximately 18 months after disease team funding began, CIRM convened clinical development advisory panels to meet with each team to evaluate progress on the regulatory and scientific pathway toward clinically important products and/or services. Based both on the advisory panels' input and internal deliberations under the guidance of CIRM's president, the Institute decided to continue 12 projects with no change in goals. One project was recommended for continuation but with revisions to its original goals (Cedars-Sinai Medical Center Autologous Cardiac-Derived Cells for Advanced Ischemic Cardiomyopathy), and another project was terminated because it did not achieve appropriate milestones (UCSF Stem Cell–Mediated Oncocidal Gene Therapy of Glioblastoma) (CIRM, 2012d).

Deciding to tackle translation on a broad front was a critical strategic decision. Such an approach has advantages in an arena in which there is a great deal of uncertainty as to where the next important breakthrough might occur. It is not possible to say at this point whether the net cast by CIRM's disease teams is too wide or too narrow. What is clear is that the resources ultimately required to bring any one of these initiatives to the bedside far exceed the resources available from CIRM. Therefore, the committee believes CIRM could make a significant contribution by expanding efforts dealing with regulatory and other challenges of cell-based therapies that are common across diseases. These efforts would diminish the remaining risk for private entities that would need to make the investments necessary to take a promising approach through clinical trials.

Also, as discussed later, CIRM has made other strategic decisions during this initial phase that have resulted in omitting certain important areas from its scientific program. Examples include the lack of RFAs addressing the study of ethical aspects of the clinical applications of potential stem cell therapies and incentives for academic institutions in California to collaborate with the private biotechnology and large pharmaceutical sectors early on in the process. These are important opportunities that fall squarely within the CIRM mandate but have not been pursued.

The 2012 Strategic Plan

In 2012, CIRM developed a new strategic plan outlining 10 goals that build on and extend those of the 2006 plan. The 2012 5-year plan increases the priority of projects clearly focused on moving toward clinical trials to produce evidence of therapeutic benefit and articulates the importance of developing partnerships with both industry and other centers for research in regenerative medicine (CIRM, 2012a). The key goals that, in part, reflect CIRM's response to the EAP review of 2010 can be summarized as follows (EAP, 2010):

- **Scientific**—Accelerate stem cell science and its applications to human diseases and injuries to achieve transformative research discoveries.
- **Clinical**—Advance stem cell science to clinical trials for proof-of-concept stem cell therapies.
- **Sustainability**—Establish a platform that would enable other funding mechanisms to pursue CIRM's mission upon expiration of Proposition 71 bond funding.

To guide its ongoing implementation of the 2012 plan, CIRM proposes forming a Clinical Advisory Panel that would include individuals with appropriate skill sets related to preclinical and clinical research, process development and manufacturing, regulatory standards, stem cell/disease-specific biology, disease-specific clinical expertise, and commercial relevance. In addition, CIRM is proposing to create an Industry Advisory Board with 8-10 internationally recognized expert members representing biotechnology, pharmaceutical, venture capital, and disease organizations (CIRM, 2012a). The goal is to advise CIRM on how to make its programs attractive to industry, identify research areas most appropriate for industry, identify CIRM-funded inventions that should be patented, create opportunities for follow-on funding for CIRM-funded research approaching clinical trials, assist CIRM in fostering industry-academic partnering opportunities, and identify and advance business models for regenerative medicine (CIRM, 2012a).

CIRM has $1.48 billion in funds yet to be awarded, of which $695 million is for programs already concept approved and $856 million for future, currently undefined programs (CIRM, 2012e). CIRM's 2012 strategic plan reflects an intent to shift the relative allocation of funds among its five core target areas to favor translation and development as opposed to facilities, training, and basic research. Two possible scenarios have been outlined for allocating the uncommitted funds (see Table 4-1). In either scenario, funding for training and basic research is reduced relative to translational and development research, thereby impacting what has been an impressive record in providing manpower for stem cell research and developing basic concepts of stem cell biology.

As noted above, the 2012 goals and funding plan significantly shift CIRM's focus toward projects believed to have the potential to move therapies toward and into the clinic. This shift is illustrated further by the July 26, 2012, announcement of an additional eight disease team awards totaling approximately $151 million (CIRM, 2012f). These teams are expected either to have filed a request to begin clinical trials or to have completed a Phase 1/2 clinical trial within 4 years:

1. Cedars-Sinai Medical Center: Progenitor Cells Secreting GDNF for the Treatment of ALS
2. Stanford University: A Monoclonal Antibody That Depletes Blood Stem Cells and Enables Chemotherapy Free Transplants
3. Stanford University: Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure
4. Stem Cells Inc.: Neural Stem Cell Transplantation for Chronic Cervical Spinal Cord Injury
5. UC Davis: MSC engineered to produce BDNF for the treatment of Wheelock-Huntington's disease
6. UC Davis: Phase I Study of IM Injection of VEGF-Producing MSC for the Treatment of Critical Limb Ischemia
7. UC Davis: Treatment of Osteoporosis with Endogenous Mesenchymal Stem Cells
8. UCLA: Genetic Re-Programming of Stem Cells to Fight Cancer

This latest round of disease team awards brings the total funding for this program to roughly $360 million, and CIRM-supported late-stage research projects now address 37 different disease areas (CIRM, 2009d, 2012f). Exactly how CIRM will prioritize its distribution of remaining resources is a question of great importance.

TABLE 4-1 Scenarios for Allocating Uncommitted Funds

Target Area	Funded, 2006-2012 (Millions of $)	Concept Approved $695 million (Millions of $)	Future Scenario 1 $856 million (Millions of $)	Future Scenario 2 $857 million (Millions of $)
Facilities/Core Resources	332.2	30.0	0	25.0
Training/Career Dev.	295.6	122.5	0	60.0
Basic Research	252.6	80.0	135.0	105.0
Translational Research	173.6	100.0	195.0	160.0
Development Research	226.6	317.0	506.0	486.0

SOURCE: Research Funding Strategy: ICOC Board Meeting (March 21, 2012), agenda item #9 (CIRM, 2012e).

GRANT REVIEW AND FUNDING PROCESS

An important aspect of CIRM's organization is how program staff manages pre- and post-award mechanisms. The committee recognizes the magnitude of CIRM's successful effort to develop a grant management infrastructure within a remarkably short period of time following passage of the legislation authorizing its creation. CIRM developed a structure for conceptualizing RFAs, soliciting applications, evaluating proposals, and then managing grant awards. Given the complexity of this endeavor and the legislated limitation on staff size (initially no greater than 50 full-time equivalents), the overall success of the grant management infrastructure is impressive.

CIRM staff are available to potential applicants to discuss ideas and to answer questions about published RFAs and the conformity of a particular proposal to the goals of announced programs. From responses to a questionnaire submitted to the committee by the California stem cell scientific community,[4] it appears that views on discussions of this type vary, with some individuals being highly appreciative of these preliminary discussions and others finding the CIRM staff less accessible (IOM, 2012d). The committee agrees that having a system for communicating with potential applicants early in the process is important, in particular to ensure that neither applicants nor CIRM staff are spending large amounts of time writing or assessing proposals that are not in keeping with the goals of any particular RFA. The committee also suggests that CIRM continue making its scientific staff available to potential applicants and working with this constituency to maximize the effectiveness of this aspect of the grant submission process.

CIRM staff recognized that the number of applications that would potentially be received for a given RFA could overwhelm the Institute's ability to review each rigorously for scientific merit. Accordingly, during its early years, CIRM restricted the number of applications that would be accepted from any one institution in response to a particular RFA. The reasoning was that doing so would limit the overall number of applications, making the review process manageable while guaranteeing that applications would represent the scientific communities at a wide range of California institutions. This was especially important given that CIRM's enabling legislation limited administrative expenditures, requiring that the process for grant-making decisions be streamlined. However, there was considerable pushback from potential grantees, because it was thought that some individuals, in particular junior investigators or those new to stem cell biology, were at a disadvantage in competing with colleagues at their home

[4]See Appendix B for a summary of the questionnaire responses.

institutions for the right to submit a proposal and hence had limited access to possible CIRM support.

To address this concern while keeping the number of proposals sent for full review manageable, CIRM established a pre-application procedure and eliminated the restriction on the number of applications that could be submitted from any single institution (CIRM, 2011d). The preapplication procedure is similar to a process used by a number of private foundations that provide support for biomedical research. Applicants are asked to provide a shortened version of their proposal through the CIRM website. CIRM staff evaluate these shortened proposals to ensure that they are in keeping with the RFA. Those deemed responsive to the RFA are then sent to three outside reviewers, who are also provided the RFA. Each reviewer is asked to evaluate the pre-application, indicating whether it should definitely, possibly, or definitely not be invited as a full proposal. Additionally, each reviewer is asked to identify proposals that are among the two to three best in the group being evaluated by that reviewer (each reviewer typically is given 10-25 pre-applications to consider). No written critique is requested of the evaluators. Using these initial external evaluations, CIRM staff determine which applicants will be invited to submit full proposals. Once invited, proposals must be based on the pre-application proposal that was submitted. There is no appeal process for pre-applications that are not invited for a full proposal submission (CIRM, 2011e).

After the pre-application process was piloted, applicants, reviewers, CIRM staff, and the ICOC board members were surveyed regarding its acceptability (CIRM, 2011e). As might be expected, applicants often expressed frustration that there was no feedback on why their pre-application was not selected to move forward. Additionally, in responses to the committee's questionnaire,[5] some principal investigators raised concern about whether a short proposal contains sufficient detail for an informed review (IOM, 2012d). On balance, however, there appeared to be overwhelming support for the pre-application process, especially in comparison with the previous model whereby there was a limit on the number of applications that could be submitted from any single institution (CIRM, 2011e). The committee agrees that, despite its limitations, the current pre-application procedure opens up the opportunity for CIRM funding to a broader cohort of investigators and is, in principle, an appropriate process. The committee recognizes the tension between providing applicants as much information as possible and not overburdening reviewers, and it suggests that CIRM consider ways of offering applicants more information on the shortcomings perceived in pre-applications that were not selected for further consideration.

[5]See Appendix B for a summary of the questionnaire responses.

The Scientific and Medical Research Funding Working Group, designated in most CIRM materials as the Grants Working Group (GWG), is the entity charged with reviewing scientific proposals and making recommendations to the ICOC with respect to those that should be funded. The GWG is appointed by the ICOC and consists of 23 members, including the chair of the ICOC, 7 of the 10 ICOC patient advocates, and 15 non-California scientists known for their expertise in stem cell biology (CIRM, 2009f, 2012g). The 15 scientists are selected based on the particulars of the individual RFAs and are drawn from a pool of more than 150 individuals chosen by CIRM as highly qualified to review proposals. Participation of these experts, none of whom, as non-Californians, is eligible for CIRM funding and stand to gain directly from CIRM, is instrumental in providing the rigorous scientific review required for making funding decisions. The success that CIRM has had in commissioning outstanding review committees for each of its RFAs is a testament both to the Institute's stature in the eyes of the stem cell community and the willingness of stem cell scientists outside of California to contribute their time and effort to facilitate the work of their California colleagues

Full proposals received by CIRM by the RFA deadline are entered into the CIRM database, and all GWG members assigned to this review cycle declare any conflicts of interest with any of the applications (CIRM, 2009g). Any GWG member in conflict for a particular application is recused during discussions, scoring, and final voting. The GWG members are then assigned applications for which no conflict exists based on their unique expertise. Typically, three external scientists review each application. The GWG can call on additional specialist reviewers as needed if its own expertise is insufficient to evaluate the science in any individual application adequately. Prior to the GWG's face-to-face meeting, each reviewer and ad hoc specialist submits a scientific score (1-100, with 100 being best) and a written critique for each assigned application. A meeting of the GWG is then announced on the CIRM website. This meeting starts with a session open to the public, during which GWG business is conducted. The GWG then meets in closed session for a two-stage review of the applications (CIRM, 2011g).

The first stage of the review is scientific in nature, led by the chair of the GWG (an external scientist member appointed to this role by the ICOC). The assigned reviewers declare their scores for the application being discussed and briefly summarize the basis for their recommendations. This is followed by full discussion of the application by GWG members, ending with the assigned reviewers suggesting revised scores based on the discussion. Each scientific member of the GWG not in conflict with that application then submits a final scientific score. Although ad hoc specialist reviewers can suggest scores in their written evaluations and, if present, during the discussion, only GWG members can submit a final score.

The final scientific score is the arithmetic mean of the reviewers' scores. If there is a wide divergence in scores with a sizable proportion (greater than 35 percent) of the GWG being in disagreement with the majority view, a minority report is forwarded to the ICOC along with the final score (CIRM, 2011g).

The next stage is the programmatic review, chaired by one of the patient advocate members of the GWG appointed to this position by the ICOC (CIRM, 2011g). The purpose of this review is to evaluate all of the applications taking into account not only their scientific scores but also the overall purpose of the RFA, with the goal of segregating the applications into three tiers—recommended, provisionally recommended, or not recommended for funding. This process has two steps. First, a histogram of the scores of all of the applications is generated. Of note, at this stage the applications are deidentified, and only the scores are revealed. The GWG examines this histogram and identifies natural breaks to divide the applications into the three tiers based on their scores. Next, the applications are identified so that the scientific score (and tier) of each is made known. GWG members (except those with conflicts, who leave the room) begin a discussion to determine whether any of the applications should be moved from one tier to another in an effort to achieve a balanced portfolio representing a spectrum of priority disease areas, scientific approaches, innovation, and so forth. For an application to be moved from one tier to another, a majority vote of the GWG is required; all members of the GWG not in conflict (scientists and patient advocates) participate in this vote. Once the GWG is satisfied with the final ranking of proposals, a final vote is taken, and the rank order is proposed to the ICOC for approval. For each application, in addition to its final ranking, the scientific score voted by the scientists on the GWG is provided to the ICOC (CIRM, 2011g; IOM, 2012e).

The ICOC makes funding decisions at a meeting scheduled and publicized in advance. As with other ICOC agenda items, deliberations on the funding of applications begin in a session that is open to the public. ICOC board members in conflict with any particular application are recused from both this public discussion and any subsequent private deliberations. Prior to the ICOC meeting, summary information about each application is available on the CIRM website, including how that particular application ranked relative to the others and its tier designation. Applications are redacted, however, to remove information that would identify applicants or institutions. Individual applicants are aware of how their proposal scored and how likely it is to be funded, and they have the opportunity to make an "extraordinary petition" to the ICOC. Any ICOC board member may request that the petition be heard. In such cases, petitioners are invited to the ICOC meeting to explain why they believe the assigned score and priority ranking are not appropriate. The ICOC takes this information into

consideration as it deliberates about the final ranking of applications. If it is necessary to discuss proprietary information, then the ICOC may meet in closed session before a final vote is taken on which applications will be funded. As a result of its private and public deliberations, the ICOC may move applications from one tier to another before taking a final vote, after which applicants are notified about funding decisions. Examination of ICOC records indicates that the shifting of applications from one tier to another does occur. For example, as of October 22, 2012, 62 extraordinary petitions were heard by the ICOC, of which 20 (32 percent) were successfully funded (CIRM, 2012h). Although most of this shifting is between adjacent tiers, there have been cases in which applications have been moved from tier 3 to tier 1 (CIRM, 2011g; IOM, 2012e); this has occurred with applications for major programs with large budgets. As discussed in greater detail below, the committee is troubled by the extraordinary petition mechanism and suggests that this practice be eliminated. The committee recognizes that CIRM has recently initiated a self-study regarding all aspects of extraordinary petitions.

BIOETHICS

Bioethics is part of the portfolio of issues that range across the entire spectrum of projects moving toward the clinic. As stated above, CIRM describes its mission in the 2012 strategic plan as supporting and advancing stem cell research and regenerative medicine under the highest ethical and medical standards. To achieve this mission, CIRM has proposed as one of its main goals advancing stem cell research to clinical trials to establish evidence of therapeutic benefit to patients. The most important milestone toward this goal is achieving clinical proof of concept for new therapies within the next 5 years (CIRM, 2012a). This is an ambitious goal, and CIRM acknowledges the importance of fostering a new regulatory path for stem cell therapies.

Current NIH standards for informed consent and human subjects research do not address specific challenges related to clinical trials involving complex stem cell–based biologic products. Unlike drugs and many medical devices, transplanted progenitor cells have the potential to integrate and proliferate within their human recipient and as a result may be difficult to remove if necessary. Transplanted cells can last for the lifetime of the recipient and cause deleterious effects that are difficult to ameliorate. In light of the complexity and novelty of new stem cell–based biologics—many of which may not be directly analogous to local, well-characterized donor tissue transplants or drug therapies—all stem cell–based clinical trials research raises crucial ethical concerns. Given the nature of stem cell–based therapies, safety and clinical proof-of-principle studies are likely to involve

patient research subjects. Thus, there is an immediate need for researchers and regulators to define reasonable risks, appropriate study endpoints, appropriate experimental comparators, standards for long-term follow-up of research subjects, and other aspects of ethical clinical trial design, in addition to formulating practical ways to minimize the threat of therapeutic misconception in patient research volunteers.

CIRM projected in its 2006 strategic plan that $25.5 million should be spent over the 10-year span of CIRM funding on Stem Cell Research and Society: Implications and Impact. These funds were meant to span three aspects of CIRM's mission: (1) laying the foundation, (2) preparing for the clinic, and (3) clinical research (CIRM 2006 Strategic Plan) (CIRM, 2006a). To date, however, very little CIRM funding has been spent in the area of Stem Cell Research and Society. Most of CIRM's ethics and public policy spending has focused on intramural funding for public outreach and education and the internal development of technical, instrumental, and procedural policy frameworks for basic stem cell research, including, for example, CIRM policies on oocyte donation for stem cell derivation. To its credit, CIRM has spent much time developing its own regulations for basic CIRM-funded stem cell research, regulations that are harmonious with the current NIH policies for stem cell line registration and eligibility for federal funding. These CIRM regulations were not imposed on California stem cell researchers and institutions, but were developed organically through consultations with these groups. The result of this interactive process was that scientists and institutions were encouraged to help establish and comply with oversight of stem cell research.

Furthermore, the Scientific and Medical Accountability Standards Working Group (Standards Working Group) recently drafted CIRM-specific guidelines for the reporting of incidental findings by secondary researchers using induced pluripotent stem (iPS) cell lines derived from living donors. The Standards Working Group also recently provided model-informed consent documents for iPS cell research in conjunction with CIRM's new RFA for iPS cell derivation and banking (CIRM, 2012i). These efforts were the culmination of several Standards Working Group meetings and workshops involving bioethics experts and researchers outside of CIRM. Although the committee applauds CIRM and the Standards Working Group for taking the initiative to address these important emerging issues in the ethical conduct of human stem cell research, the drafting of sample consent forms for iPS cell research and banking could have been aided greatly by empirical studies examining the most effective ways to bolster patient-informed consent during the consent interview process—studies the Standards Working Group did not sponsor or utilize. Such efforts at policy development should continue in other areas of stem cell science supported through CIRM funding.

INDUSTRY ENGAGEMENT

Proposition 71 clearly states as one of its key objectives: "Benefit the California economy by creating projects, jobs, and therapies that will generate millions of dollars in new tax revenues in our state … [and] advance the biotech industry in California to world leadership, as an economic engine for California's future."[6] Chapter 2 includes a discussion of the challenges entailed at present in assessing the long-term economic benefits of CIRM's investment in stem cell research. One aspect of this issue is CIRM's engagement with the biotechnology and pharmaceutical industry in California.

California is already home to a vibrant biotechnology community with more than 2,240 companies, estimated revenues of $114 billion, and approximately $2.6 billion in venture capital investment in 2010 (CHI, 2011). In that same year, an estimated 50 percent of all venture capital investment in the United States went to companies in California, with life sciences being the sector receiving the largest tranche of funds. Although venture capital investment in California returned to 2003 levels in 2010 (approximately $8 billion), its overall level has been relatively stable during CIRM's lifetime ($8-$15 billion) (CHI, 2011).

Regenerative medicine is still an emerging industry, so leading companies in the field are at a relatively early stage, representing a small fraction of the total number of biotechnology companies in California. Indeed, given how much research and development remains to be done before the risks attendant to the successful commercialization of a cell-based product can be adequately characterized, investments in the field of regenerative medicine will likely remain modest in scale in the short term. Nevertheless, the well-developed entrepreneurial ecosystem in California represents a unique potential asset in moving discoveries in regenerative medicine to the bedside.

Through the halfway point in its existence, CIRM has engaged industry in a number of ways. Four representatives of commercial life science entities sit on the ICOC, and individuals with industry experience serve on the GWG. CIRM also supports the Alliance for Regenerative Medicine (ARM), a multistakeholder advocacy organization that promotes legislative, regulatory, and reimbursement initiatives in regenerative medicine; CIRM and ARM co-organize an annual meeting in La Jolla, California (Stem Cell Meeting on the Mesa) touted as the industry's premier investor and partnering forum and recognized nationally as bridging academia, industry, and investors. With input from industry, CIRM has adopted detailed intellectual property, profit sharing, and access plan policies (see Chapter 5) governing

[6]California Stem Cell Research and Cures Initiative, Proposition 71 (2004) (codified at California Health and Safety Codes § 125291.10-125291.85).

the commercialization of discoveries supported by CIRM funding. Most important, for-profit entities can receive direct support from CIRM to advance their product pipelines in the form of either grants or loans. The loan vehicle was adopted specifically to "supplement [CIRM's] grant funding by offering research loans to for-profit organizations" (CIRM, 2011f, p. 1). These loans are awarded in two forms—product-backed (forgiveness) or company-backed—both subject to various terms and conditions (including warrant coverage) and payable within up to 10 years (CIRM, 2011f). Approximately 15 for-profit entities have received CIRM grants and loans, totaling around $80 million, covering a broad spectrum of research and development topics: basic research, translation, tools and technologies, disease teams, and clinical trials. CIRM also supports the supply side of the regenerative medicine industry by requiring that 70 percent of supplies used for CIRM-funded research be procured from California companies on a good faith effort basis.

CIRM's 2012 strategic plan emphasizes the need to attract both risk capital and support from the biotechnology and pharmaceutical industries to take CIRM-funded Phase 2 candidates through clinical validation. This emphasis was endorsed by the 2010 External Advisory Panel, which recommended that CIRM strengthen its engagement of industry and proposed a number of initiatives to that end. CIRM's president has acknowledged this need by stating that "industry will and should have a role in providing stem cell therapies … they provide the focus, manufacturing, quality control programs, pharmacokinetic data, and substantive capacity in preclinical investigational new drug (IND)—enabling research" (Trounson et al., 2012, p. 1). However, CIRM's relatively small investment in industry projects (roughly 6 percent of its total budget) and the notable absence of industry on most disease teams was cited by participants in the committee's industry forum and in interviews with external medical and industry experts as examples of the failure of CIRM's translational/development RFAs to place appropriate emphasis on what is needed to enable regulatory approval for stem cell–based therapies (CIRM, 2008d, 2010c,d,e, 2011h; IOM, 2012f).

CONCLUSIONS AND RECOMMENDATIONS

This section presents the committee's conclusions and recommendations with respect to the nature, scope, and accomplishments of CIRM's scientific program in the areas of strategic planning, grant management, bioethics, and industry engagement.

Strategic Planning

Regarding CIRM's 2012 Strategic Plan, although the committee supports the Institute's intent to establish advisory boards, it recommends that one Scientific Advisory Board (SAB) be established, comprising individuals with expertise in the scientific, clinical, ethical, industry, and regulatory aspects of stem cell biology. The members should be appointed by and report to the CIRM president. A single SAB, as opposed to multiple advisory boards as currently proposed, would serve as a mechanism for providing cohesive, integrated, and longitudinal advice to the president regarding strategic priorities, which is lacking in the current CIRM organizational structure. The committee believes such an external board would be invaluable in vetting ideas for new RFAs, suggesting RFAs that would not otherwise have been considered, and helping CIRM maintain an appropriate balance in its research portfolio. The SAB could form subcommittees, provided the necessary expertise was available on the SAB. The SAB could supplement its subcommittees on an ad hoc basis whenever additional external expertise is determined to be useful. Input from such an external board is essential to help CIRM make fundamental decisions on efforts to deal with challenges that cut across particular diseases, on which discoveries should progress toward the clinic, and on how best to engage industry partners in developing new therapies. The SAB's reports and the president's response to these reports should be delivered to the ICOC and discussed in sessions open to the public.

The committee affirms the need for translational studies, as laboratory experiments or preclinical models cannot accurately predict the consequences and complications of a therapeutic intervention in humans. The 2012 strategic plan calls for proof-of-principle animal models for more than 10 diseases (Goal IV) and for 10 therapies in Phase 1 or 2 clinical trials in at least five different therapeutic areas based on stem cell research (Goal VIII) (CIRM, 2012a). As noted earlier, these ambitious goals reflect a shift in the emphasis of CIRM's funding from basic and preclinical research to the generation of new treatments for patients. Depending on one's perspective, this change may reflect a thoughtful progression from basic to more applied research or a rush to translation. Striking the proper balance in research across the portfolio of basic, translational, and clinical studies will require CIRM to solicit broad input in executing its strategic plan. The committee believes the proposed SAB could serve an invaluable role in this process.

Recommendation 4-1.[7] ***Establish a Scientific Advisory Board.*** **CIRM should establish a single Scientific Advisory Board comprising individuals with expertise in the scientific, clinical, ethical, industry, and regulatory aspects of stem cell biology and cell-based therapies. A single Scientific Advisory Board, as opposed to multiple advisory boards as proposed in the 2012 strategic plan, would provide cohesive, longitudinal, and integrated advice to the president regarding strategic priorities, which is lacking in the current CIRM organizational structure. The majority of the members of the Scientific Advisory Board should be external to California, appointed by and reporting to the CIRM president. Such an external board would be invaluable in vetting ideas for new RFAs, suggesting RFAs that otherwise would not have been considered, and helping CIRM maintain an appropriate balance in its research portfolio. Input from this board would help CIRM make fundamental decisions about dealing with challenges that cut across particular diseases, decide which discoveries should progress toward the clinic, and determine how best to engage industry partners in developing new therapies. The board's reports and the president's response to those reports should be delivered to the ICOC and discussed in sessions open to the public.**

The 22 funded disease teams represent translational efforts in diverse disease areas. The committee and solicited experts note that the approaches of several of the disease teams do not fit neatly into what is generally considered stem cell research; rather, they are extensions of more conventional therapeutic strategies not tied to CIRM's basic stem cell research portfolio. This observation is not meant as a criticism of the validity of these efforts or the quality of these disease teams or as denial of the importance of developing these technologies to counter these illnesses. Rather, the focus of these disease teams likely reflects the immaturity of the stem cell field with respect to the development of novel translational opportunities. Particular diseases or injuries will vary greatly in the point at which they are poised for translation. Given pressure for CIRM to show progress in disease applications within its limited time frame, the rapid transition to the disease teams and the stated goals of the 2012 strategic plan are understandable. Based on the consensus of both academic and industrial stem cell experts who provided comments, however, the committee believes the translational goals enumerated in the 2012 strategic plan are unrealistic in light of both the lengthy time frame generally required for the development of new therapies and the high failure rate of clinical trials at Phase 1 or 2. Instead of focusing

[7]In the committee's view, this recommendation can be carried out by CIRM without legislative action.

on purely quantitative measures, such as numbers of trials and diseases, the committee suggests that CIRM also devote considerable attention to fundamental biological mechanisms that ultimately determine the success or failure of a specific disease intervention and the careful design of translational studies to make them maximally informative even in the absence of any demonstrable clinical benefit. Furthermore, a concerted effort focused on working with the Food and Drug Administration (FDA) to overcome regulatory hurdles and facilitate approval pathways for cell-based therapies agnostic to any particular disease would benefit the entire field, and its broad portfolio of programs places CIRM in an excellent position to undertake such an effort.

Historical precedents provide a perspective on the pace of clinical translation. Initial efforts in bone marrow transplantation, the most widely used and validated stem cell therapy, began in the late 1950s and were uniformly unsuccessful except in the setting of transplants between monozygotic twins. Subsequently, it took more than 20 years of studies in patients before the efficacy of allogeneic stem cell transplantation in various disease contexts was established. The high failure rate in early transplant experiments in patients would challenge contemporary regulatory and approval pathways for new therapies. Experience has been similar in the field of gene therapy, in which it has taken more than 20 years for clinical success; the field suffered significant setbacks from adverse events in early clinical trials.

CIRM's 2012 strategic plan also outlines the proposed creation of new alpha stem cell clinics. This effort is in part a response to "stem cell tourism," whereby people suffering from diverse conditions travel to clinics with unproven and potentially harmful therapies. The goal of the creation of alpha stem cell clinics is to establish a stem cell therapy clinical infrastructure with the requisite scientific, technical, and medical expertise, combined with operational efficiencies, to foster clinical trials, to evaluate and establish safe and effective therapies, and to develop and maintain the delivery of therapies approved by the FDA or other regulatory agencies (CIRM, 2012a; Trounson et al., 2012). Patients accessing these clinics would range from those with no therapeutic options seeking counseling or experimental treatment to those seeking standard-of-care treatment that would be paid for by their insurance.

The development of alpha stem cell clinics is anticipated to occur in a staged manner. Initially, the clinics would provide counseling to patients on therapeutic options, as well as information regarding emerging trials and technology. A goal is to provide clinical trial capacity for those studies moving toward IND registration, establishing proven therapies with benefits exceeding those of the alternative treatments presently available, and therefore allowing patients the possibility of a broader range of treatments. The alpha stem cell clinics are envisioned to provide a venue for

participation of industry, along with experts from academic medical centers (Trounson et al., 2012).

The committee agrees that the alpha stem cell clinic concept is important and holds great potential for bringing new therapies to the people of California in a setting where these therapies can be evaluated rigorously for safety and efficacy. However, the committee believes this step requires more careful planning. These facilities, providing a site for clinical trials of stem cell therapies, would house multidisciplinary activities, cell production capabilities, and trained personnel in a setting attractive to industry involvement. When fully developed, these clinics might resemble Clinical Translational Research Centers (CTRCs), NIH-supported facilities located at academic medical centers throughout California and the United States. CTRCs, coupled with NIH's Clinical and Translational Science Awards (CTSAs), provide an infrastructure for the training of personnel as well as resources for state-of-the-art patient-oriented research. The alpha stem cell clinics could be integrated into the existing clinical investigation infrastructure at academic medical centers so as to avoid duplication of facilities and personnel at a time of strained resources. The more CIRM utilizes and partners with facilities in academic medical centers, the more wisely it can deploy its remaining, precious resources.

The plans developed by CIRM also should ensure that these clinics adhere to strict ethical and professional standards. The committee appreciates that CIRM itself has identified some of the potential concerns. In a recent article (Trounson et al., 2012), CIRM's president cites some of the ethical challenges facing this proposal (including, for example, the need for qualified medical and clinical expertise, long-term patient monitoring, and regulatory and institutional oversight). It is also imperative that a management plan for addressing the possibility of therapeutic misconception be formulated and operationalized for all CIRM-funded alpha stem cell clinics, especially because patient populations would be served across a spectrum of clinical services ranging from the clinically accepted to the highly experimental. For example, the use of patient advisors who were independent of the clinical research or treatment team might help facilitate the voluntary and informed consent of patients contemplating either treatment or research participation at an alpha stem cell clinic.

Grant Review

CIRM's credibility requires that the grant review process be expert, transparent, and fair. The committee focused its assessment on the process of awarding grants, not post-award management. The committee appreciates that creation of a mechanism for soliciting and evaluating applications over a broad portfolio was a difficult task. It is particularly notable that

CIRM has engaged a cadre of outstanding stem cell scientists from outside of California to serve as peer reviewers, both as ad hoc reviewers and as GWG members. The committee also acknowledges the importance of having patient advocates participate in the grant-making process; as discussed below, however, the committee believes the process adopted by CIRM may not be the most appropriate. CIRM's efforts to engage investigators as they prepare applications are laudable, but it appears that the scientific community has differing perceptions of the success of these efforts. Formalizing this process and making clearer to the community what role CIRM staff can play during the preparation of applications would be beneficial. The committee agrees that the pre-application process is a practical solution to avoid overwhelming the GWG; however, CIRM should consider ways to provide more information to applicants who are not invited to submit full proposals.

As discussed in detail in Chapter 3, the committee has considerable concern regarding the management versus oversight roles of the ICOC, a particularly cogent issue with respect to the grant-making process. Under the current structure, ICOC members (both as participants in the GWG and through deliberations of the ICOC itself) have considerable influence at all levels with respect to which grants are funded. Given the ICOC composition, which includes individuals with vested interests in what disease areas are supported by grants and others who represent institutions that stand to gain greatly from grant-making decisions, it is not surprising that, even if no actions have been based on these interests, many in the community believe that irreconcilable conflicts exist. The committee believes these inherent and perceived conflicts diminish the credibility of the ICOC and thus decrease the potential for CIRM to be effective as a transparent, impartial body. Recent controversy surrounding the Cancer Prevention and Research Institute of Texas grants process illustrates the importance of rigorous scientific review free from inherent or perceived conflict and the consequences when these boundaries appear to be breached.[8] The committee therefore strongly recommends that CIRM restructure the application review and grant-funding processes to separate oversight and strategic planning from day-to-day operations. The ICOC should remain responsible for performing oversight and articulating an overall strategic plan and for approving and determining the allocation of funds for each RFA before it is announced. Going forward, however, all aspects of application review, funding recommendations, and grant administration should be the sole responsibility of the CIRM scientific staff, reporting to the president. While the ICOC should remain responsible for ultimate approval of grants, it should not be empowered to act on individual applications. The committee

[8]See *Nature* 486:169-171 (June 14, 2012).

believes these structural changes would eliminate many concerns related to conflicts while also placing the review and funding processes in the hands of those individuals, both scientists and patient advocates, best equipped to make these decisions.

The committee deliberated on the best way to operationalize these structural changes and decided that RFAs should continue to be developed through the CIRM scientific staff (and, as noted above, with input from an SAB appointed by the president) and that the ICOC should provide final approval and funding amounts for each grant. At the same time, the GWG should be reconstituted to exclude any members of the ICOC. The group should continue to include scientists outside of California with expertise in stem cell science and regenerative medicine, with ad hoc scientific reviewers continuing to participate as needed, still as nonvoting members. The committee also believes it is important for patient advocates to continue to be involved in the application review process, in addition to their participation in the ICOC and its decisions about which RFAs to announce and the level of funding for each. However, the committee believes patient advocates participating in the GWG should not be ICOC board members; instead, the ICOC should appoint up to seven patient advocates to participate in any GWG meeting, drawing on a panel of appropriate individuals from inside and outside of California. The committee believes further that the patient advocates should be encouraged to continue to participate in the discussions of proposals and to lead the programmatic phase of the review. Neither the system for assigning scientific scores nor the tiering of applications following the discussion of programmatic fit need be altered. This step would actually increase the role of patient advocates with those sitting on the ICOC being involved in deciding which RFAs should be issued as well as the overall level of funding for each major initiative, and another independent group of patient advocates involved in programmatic ranking of proposals that have been scientifically reviewed. Finally, CIRM scientific staff should be present at all GWG meetings, not to serve as voting members but to provide information about CIRM processes and procedures and to clarify aspects of the RFA as necessary. The committee agrees that GWG meetings must remain closed whenever specific applications are discussed.

The committee recommends that after the GWG has completed its work, the CIRM scientific staff, under the direction of the senior vice president for research and development, should examine the rank order of applications that emerged from the GWG meeting to determine whether, for programmatic reasons, reordering of the applications is necessary. If this is the case, the senior vice president for research and development should meet with the CIRM scientific staff to adjust the rank order of applications, with an explanation being provided for any that have been moved relative

to the score voted by the GWG. Once this proposed final slate has been determined, applicants should be notified of their scores, given copies of the critiques, and informed about the likelihood that they will be funded. Applicants should then have a 10-day period within which to inform the CIRM scientific staff if they believe there are conflicts or factual errors in the reviews that may have impacted their score and they wish to appeal the decision. In this case, the CIRM scientific staff, in consultation with members of the GWG, should review the appeal and recommend to the senior vice president for research and development whether the rank order of that particular application should change. The senior vice president for research and development and the president should then decide on a final slate of proposals, taking into consideration any appeals made by applicants. This slate should then be provided to the ICOC for a vote "yes" or "no" on the entire slate. Should the ICOC vote down the slate of proposals, this would be communicated immediately to the CIRM scientific staff along with a justification for the vote. The CIRM scientific staff would consider this justification and propose a revised slate of grants for approval at the next ICOC meeting. Under no circumstances, however, would the ICOC be empowered to evaluate individual applications or move applications from one tier to another. Additionally, although applicants could, at the discretion of the ICOC, present their views on funding decisions at open ICOC meetings, there should be no mechanism for the ICOC to change funding decisions based on such petitions.

Recommendation 4-2.[9] ***Restructure the Grant Review and Funding Process.*** **CIRM should restructure the grant review and funding process to separate oversight and strategic planning from day-to-day operations. The ICOC should remain responsible for oversight and articulation of an overall strategic plan. However, grant management, funding recommendations, and grant administration should be the responsibility of the CIRM scientific staff, reporting to the president. This restructuring would help mitigate concerns related to conflicts of interest and would also put the review and funding process in the hands of those best equipped to make those decisions. The committee recommends the following specific structural changes:**

- **Development and approval of RFAs—CIRM scientific staff, with input from the Scientific Advisory Board, should develop RFAs. The ICOC should provide final approval and funding amounts for each RFA.**

[9]CIRM may need to work with the state legislature in order to fully implement this recommendation.

- **Composition of the Grants Working Group—To ensure separation of oversight and operations, the ICOC board chair should not be a member of the Grants Working Group. Similarly, patient advocates participating in the Grants Working Group should not be ICOC board members.**
- **Reordering of rankings by CIRM staff—After the Grants Working Group has completed its rankings, the CIRM scientific staff, under the direction of the senior vice president for research and development, should examine those rankings and determine whether, for programmatic reasons, proposals need to be reordered. If so, the senior vice president for research and development should meet with the CIRM executive leadership to adjust the rank order of applications; any reordering should be accompanied by an explanation. The CIRM president should then create a final slate of applications recommended for funding.**
- **Notification of applicants—Once the proposed final slate has been determined, applicants should be notified of their scores, given copies of the critiques, and notified of the likelihood that they will be funded. Applicants should then have a 10-day period during which they can inform the CIRM scientific staff if they believe factual errors in the reviews may have impacted their score and wish to appeal the decision.**
- **Final decisions—The senior vice president for research and development and the president should then decide on a final slate of proposals to submit to the ICOC for a "yes" or "no" vote on the entire slate. The ICOC should not be empowered to evaluate individual applications or move applications from one tier to another. This process would also eliminate the use of extraordinary petitions.**

Bioethics

Given the speedy timeline and the scientific and regulatory complexities entailed in the goal of bringing stem cell research to clinical trials within the next 5 years, the committee recommends that CIRM sponsor projects and offer new grant opportunities aimed specifically at identifying and addressing ethical and regulatory issues surrounding stem cell–based clinical trials research. CIRM should use the information resulting from these initiatives to strengthen its ethical standards for human subjects research. Expanding CIRM's portfolio of projects and grant opportunities in this manner is consistent with (indeed, even mandated by) Proposition 71. According to Proposition 71, the ICOC was to begin CIRM funding for stem cell

research by initially adopting ethical standards based on the NIH standards for informed consent and human subjects research that were in place as of January 1, 2003. After initially adopting these NIH standards for ethical research, the ICOC was to add further requirements so as to adopt the highest standards for informed consent and human subjects research.[10]

Given CIRM's stated goal in the 2012 strategic plan of initiating clinical trials research, the ICOC needs to adopt additional ethical standards and expectations specific to stem cell research for all its funded human trials. Doing so would help ensure that CIRM remains true to its mission of advancing stem cell research and regenerative medicine under the highest ethical and medical standards. To this end, CIRM should offer additional programs and initiatives within its research portfolio. In the short term, the Standards Working Group should convene with federal regulators, research ethics experts, and clinicians outside CIRM to identify and discuss the ethical and regulatory challenges entailed in stem cell–based clinical trials. One of the key outcomes of this initial discussion should be the identification of strategically important areas for RFAs in ethics for which California research ethicists and social scientists could apply.

While the Standards Working Group created and operationalized many rigorous ethical standards for basic stem cell research during CIRM's early years, it has not been equally productive of late in formulating CIRM policies for the ethical conduct of human clinical trials research. The Standards Working Group should be encouraged and empowered to focus on this unmet need. According to Proposition 71, the Standards Working Group shall "recommend to the ICOC standards for all medical, socioeconomic, and financial aspects of clinical trials and therapy delivered to patients, including, among others, standards for . . . clinical efforts for the appropriate treatment of human subjects in medical research." Furthermore, the Standards Working Group is to advise the ICOC and other working groups on relevant ethical and regulatory issues on an ongoing basis.[11] CIRM could make a major contribution to regenerative medicine and advance stem cell research by issuing a series of RFAs aimed at advancing understanding of what constitutes an ethical human subjects research policy in the area of stem cell research. The ultimate purpose of these RFAs should be to enhance the Standards Working Group's ability to draft recommendations to the ICOC.[12] The ethical issues facing stem cell–based clinical trials must be addressed not only through careful deliberations during

[10]Proposition 71, 125290.35, b1 and b2.

[11]Proposition 71, 125290.55, b2 and b5.

[12]The committee's recommendations regarding governance (Chapter 3) suggest that the Standards Working Group would report directly to the senior vice president for research and development.

CIRM-sponsored workshops but also through the collection and analysis of important empirical information using rigorous social scientific methodologies. Ethics and policy studies would help support CIRM's commitment to advancing stem cell research under the highest ethical standards. By providing extramural funding for ethics and policy work conducted by researchers outside the organization, CIRM could fulfill an important aspect of its mission in an independent manner, drawing on the expertise of others working in the ethics of human subjects research.

Furthermore, CIRM should commit financial resources to support training programs for stem cell bioethicists and research regulators. These bioethics training programs should be similar to CIRM's training programs for basic scientists but would focus on bioethics capacity building at CIRM-supported research institutions and stem cell alpha clinics throughout the state. CIRM-sponsored bioethics training programs would help address emerging ethical challenges associated with moving stem cell therapies to the clinic.

In summary, the committee strongly recommends that CIRM fund primary research projects on the ethical, social, and legal dimensions of stem cell research and enable bioethics training programs at institutions that have invested heavily in such research. It is difficult for researchers to find appropriate funding for stem cell–specific ethics and policy work, and filling this funding gap is well within CIRM's budget. Other ethical aspects of stem cell research need attention besides ethical issues in stem cell–based clinical trials. These areas include (but are not limited to) the legal and ethical rights of somatic cell donors in iPS cell research, the appropriate use of stored tissues for stem cell research, and the use of pediatric and other somatic cell donors with diminished decision-making capacity.

Recommendation 4-3.[13] ***Fund Research and Training on Ethical and Regulatory Issues.*** **CIRM should sponsor training programs and workshops and offer new grant opportunities aimed specifically at identifying and addressing ethical and regulatory issues surrounding stem cell–based clinical trials research. CIRM should use the information resulting from these initiatives, together with current knowledge, to strengthen its ethical standards for CIRM-funded human subjects research based on sound empirical and theoretical grounds.**

[13]In the committee's view, this recommendation can be carried out by CIRM without legislative action.

Industry Engagement

Because large industry investments will be required to carry CIRM's most promising new therapies through clinical trials and to the bedside, enhanced industry representation in the Institute's work is needed in a number of ways. The committee recommends additional industry representation on the ICOC, the SAB, the Standards Working Group, and the GWG to leverage industry's expertise and resources. Investors in and representatives of biotechnology and pharmaceutical companies should play an explicit role in formulating RFAs, adjudicating awards, and setting strategic directions. This role will be particularly important as CIRM focuses on product development, manufacturing, regulatory approval, and clinical translation. Industry expertise on these issues and the rigor demonstrated by venture capitalists in reviewing commercial opportunities must carry the same weight as the input and oversight already afforded to academicians and patient advocates.

The committee encourages CIRM to create industry-specific RFAs and examine how to integrate industry participation as a highly weighted success criterion for its translational/developmental RFAs. In addition, the committee suggests that investors, entrepreneurs, and companies be solicited for proposals on how to deliver therapies anticipated from the work of the disease teams to the clinic for trials and, ultimately, to their target patient populations. Some of these therapies will require new tools and devices, others large-scale manufacturing, and still others unique business models. The committee believes the best source for these solutions is industry.

The committee notes that CIRM has created a technology transfer fund to support the patenting of CIRM-generated intellectual property. CIRM should be proactive in exploring ways to enhance company creation and outlicensing of its portfolio of patents. It should investigate the creation of financing vehicle(s) to stimulate investment in emerging and existing regenerative medicine companies by engaging the investment community in California, one of the most sophisticated venture capital communities in the world.

CIRM has created an exemplary training program and seeded a pipeline of intellectual property and translational projects that are primed for industry involvement, outside funding, and unique therapy delivery mechanisms. The proposed alpha stem cell clinics offer an intriguing solution to the delivery of therapies, but CIRM must also engage industry to

find equally innovative mechanisms for addressing product development, regulatory, manufacturing, and distribution gaps in its pipeline.

Recommendation 4-4.[14] ***Enhance Industry Representation in Key Aspects of CIRM Organization.*** **Industry representation on the ICOC, the Scientific Advisory Board, the Standards Working Group, and the Grants Working Group should be enhanced to leverage industry's expertise and resources in product development, manufacturing, and regulatory approval in support of the ultimate goal of bringing therapies to patients.**

REFERENCES

CHI (California Healthcare Institute). 2011. *California biomedical industry: 2011 report*. http://www.chi.org/uploadedFiles/2011%20CA%20Biomed%20Industry%20Report_FINAL.pdf (accessed August 16, 2012).

CIRM (California Institute for Regenerative Medicine). 2005. *CIRM training grant*. http://www.cirm.ca.gov/RFA_05-01 (accessed August 27, 2012).

CIRM. 2006a. *Scientific strategic plan*. http://www.cirm.ca.gov/meetings/pdf/2006/12/120706_item_7.pdf (accessed August 16, 2012).

CIRM. 2006b. *RFA 06-02: CIRM comprehensive research grant*. http://www.cirm.ca.gov/RFA_06-02 (accessed September 4, 2012).

CIRM. 2007a. *RFA 07-03: CIRM major facilities grant program*. http://www.cirm.ca.gov/RFA_07-03 (accessed August 27, 2012).

CIRM. 2007b. *RFA 07-02: CIRM new faculty awards*. http://www.cirm.ca.gov/RFA_07-02 (accessed August 27, 2012).

CIRM. 2007c. *RFA 07-05: CIRM new cell lines awards*. http://www.cirm.ca.gov/RFA_07-05 (accessed August 27, 2012).

CIRM. 2007d. *RFA 07-04: CIRM disease team planning awards*. http://www.cirm.ca.gov/RFA_07-04 (accessed August 28, 2012).

CIRM. 2008a. *RFA 08-03: CIRM research training program II*. http://www.cirm.ca.gov/RFA_08-03 (accessed August 27, 2012).

CIRM. 2008b. *RFA 08-04: CIRM bridges to stem cell research awards*. http://www.cirm.ca.gov/RFA_08-04 (accessed August 27, 2012).

CIRM. 2008c. *RFA 08-07: Basic biology awards I*. http://www.cirm.ca.gov/RFA_08-07 (accessed August 27, 2012).

CIRM. 2008d. *RFA 08-05: CIRM early translational research awards*. http://www.cirm.ca.gov/RFA_08-05 (accessed August 29, 2012).

CIRM. 2009a. *RFA 09-02: Basic biology awards II*. http://www.cirm.ca.gov/RFA_09-02 (accessed August 27, 2012).

CIRM. 2009b. *RFA 09-03: CIRM stem cell transplantation immunology awards*. http://www.cirm.ca.gov/RFA_09-03 (accessed August 27, 2012).

CIRM. 2009c. *RFA 09-01: CIRM disease team research awards*. http://www.cirm.ca.gov/RFA_09-01 (accessed August 28, 2012).

[14]CIRM may need to work with the state legislature in order to fully implement this recommendation.

CIRM. 2009d. *CIRM, The UK and Canada award more than $250 million to accelerate the pace of bringing stem cell therapies to the clinic: Novel funding mechanism speeds the path of research*. http://www.cirm.ca.gov/PressRelease_102809 (accessed August 28, 2012).

CIRM. 2009e. *Review summaries for RFA 09-01: Disease team research awards*. http://www.cirm.ca.gov/Summaries_RFA_09-01 (accessed September 5, 2012).

CIRM. 2009f. *Bylaws of the Scientific and Medical Research Funding Working Group*. http://www.cirm.ca.gov/files/PDFs/GWG/GWG_bylaws.pdf (accessed August 28, 2012).

CIRM. 2009g. *Conflict of interest policy: Non-ICOC members of the Scientific and Medical Research Funding Working Group*. http://www.cirm.ca.gov/reg/pdf/Reg100003_Conflict_of_Interest.pdf (accessed August 28, 2012).

CIRM. 2010a. *RFA 10-04: CIRM basic biology awards III*. http://www.cirm.ca.gov/RFA_10-04 (accessed August 27, 2012).

CIRM. 2010b. *RFA 10-02: CIRM tools and technology awards II*. http://www.cirm.ca.gov/RFA_10-02 (accessed August 27, 2012).

CIRM. 2010c. *RFA 10-01: CIRM early translational II research awards*. http://www.cirm.ca.gov/RFA_10-01 (accessed August 29, 2012).

CIRM. 2010d. *RFA 10-03: CIRM targeted clinical development awards*. http://www.cirm.ca.gov/RFA_10-03 (accessed August 29, 2012).

CIRM. 2010e. *RFA 10-05: CIRM disease team therapy development awards*. http://www.cirm.ca.gov/rfa_10-05 (accessed August 29, 2012).

CIRM. 2011a.* *Collaborations_CIRM CFPs as of Nov 2011*. CIRM's response to IOM's data request: list of international organizations/companies that work with CIRM (dated December 2, 2011).

CIRM. 2011b.* *Collaborations info re. CFPs productivity evaluation*. CIRM's response to IOM's data request: provide data about all collaborations from 2006 to the present including origination of the collaboration, nature of the collaboration, how the collaboration was funded and monies spent, how the collaboration was managed (dated December 2, 2011).

CIRM. 2011c. *CIRM approves $27 million for initiatives to accelerate promising stem cell research projects*. http://www.cirm.ca.gov/PressRelease_2011-12-08 (accessed August 27, 2012).

CIRM. 2011d.* *GWG review process for CIRM pre-applications*. CIRM's response to IOM's data request: Documentation describing the peer review process (dated December 19, 2011).

CIRM. 2011e.* *Report on CIRM's trial pre-application process*. CIRM's response to IOM's data request: Documentation describing the peer review process (dated December 19, 2011).

CIRM. 2011f. *CIRM loan administration policy.* http://www.cirm.ca.gov/files/Regulations/LAP.OAL_.REVIEWED.FINAL_.pdf (accessed August 16, 2012).

CIRM. 2011g.* *CIRM review process*. CIRM's responses to IOM's data request: Documentation describing the peer review process (dated December 19, 2011).

CIRM. 2011h. *RFA 11-02: CIRM early translational III research awards*. http://www.cirm.ca.gov/RFA/rfa-11-02-cirm-early-translational-awards-iii?q=rfa/rfa-11-02-cirm-early-translational-awards-iii (accessed August 29, 2012).

CIRM. 2012a. *Strategic plan update: Accelerating the opportunity for cures*. http://www.cirm.ca.gov/files/PDFs/Publications/2012CIRMstratplan.pdf (accessed August 16, 2012).

CIRM. 2012b. *About CIRM*. http://www.cirm.ca.gov/about-cirm/ (accessed November 20, 2012).

CIRM. 2012c.* *Grant making process*. CIRM's response to IOM's data request: Document(s) that outline the grants review process (from concept to award approval) (dated April 30, 2012).

CIRM. 2012d.* *Disease teams awards update—March 2012*. CIRM's response to IOM's data request: Information about the interim reviews of the disease teams (dated March 14, 2012).

CIRM. 2012e. *Research Funding Strategy: ICOC Board Meeting (March 21, 2012), agenda item #9*. http://www.cirm.ca.gov/files/meetings/pdf/2012/032112_item_9_funding_strategy.pdf (accessed November 28, 2012).

CIRM. 2012f. *Stem cell agency commits $150 million to develop new therapies*. http://www.cirm.ca.gov/PressRelease_2012-07-26 (accessed August 28, 2012).

CIRM. 2012g.* *The response from the Grants Working Group (GWG) represents the scientific GWG members only.* CIRM's response to IOM's data request: Questions for working groups (dated May 29, 2012) (accessed October 19, 2012).

CIRM. 2012h.* Update of details of extraordinary petitions. CIRM's response to IOM's data request: Details of extraordinary petitions. How many were there, how many were successful, in what tier were they before the petition was made, who are the investigators. (dated October 22, 2012).

CIRM. 2012i. *RFA 12-03: CIRM hiPSC derivation award*. http://www.cirm.ca.gov/RFA/rfa-12-03-cirm-hipsc-derivation-award (accessed August 28, 2012).

EAP (External Advisory Panel). 2010. *Report of the External Advisory Panel*. http://www.cirm.ca.gov/files/PDFs/Administrative/CIRM-EAP_Report.pdf (accessed September 4, 2012).

IOM (Institute of Medicine). 2012a.* *Conversation with former director of Cancer Stem Cell Consortium in Canada*. Institute of Medicine Committee on a Review of the California Institute for Regenerative Medicine open call on June 7, 2012.

IOM. 2012b.* *Conversation with Director of the NIH Intramural Center for Regenerative Medicine*. Institute of Medicine Committee on a Review of the California Institute for Regenerative Medicine open call on June 8, 2012.

IOM. 2012c.* *Conversation with CIRM's international partners in Germany.* IInstitute of Medicine Committee on a Review of the California Institute for Regenerative Medicine open call on July 5, 2012.

IOM. 2012d.* *Questionnaire for CIRM principal investigators*. Institute of Medicine Committee on a Review of the California Institute for Regenerative Medicine Online Questionnaire launched on February 8, 2012.

IOM. 2012e.* *Conversation with CIRM's ICOC member regarding the review process*. Institute of Medicine Committee on a Review of the California Institute for Regenerative Medicine open call on June 28, 2012.

IOM. 2012f.* *Roundtable discussion of CIRM's scientific impact*. IOM Committee on a Review of the California Institute for Regenerative Medicine Subcommittee Meeting with Boston Stem Cell Scientists on June 26, 2012, Boston, MA.

Trounson, A., N. D. Natalie, and G. F. Ellen. 2012. The Alpha Stem Cell Clinic: A model for evaluating and delivering stem cell-based therapies. *Stem Cells Translational Medicine* 1:9-14.

References with an asterisk (*) are public access files. To access those documents, please contact The National Academies' Public Access Records Office at (202)334-3543 or paro@nas.edu.

5

CIRM's Intellectual Property Policies

The California Institute for Regenerative Medicine (CIRM) has devoted considerable effort to the development of its intellectual property policies, repeatedly drafting and revising the policies in response to wide-ranging feedback from different stakeholders.

Intellectual property is a policy tool for motivating investments in innovation. Patents and trade secrecy are two forms of legal protection for intellectual property. A *patent* provides a legal right to exclude competitors from the market for a new invention, thereby allowing an innovator to capture higher profits during the patent term before the invention enters the public domain (and competitors become free to use it). Without such a head-start advantage, innovators who anticipate prompt competition from free-riders in the market for a successful product might be reluctant to take on the costs and risks of new product development. *Trade secrecy* provides legally enforceable rights to confidential treatment of information that is not generally known to competitors, another way of protecting head-start advantage for innovators. Patents require public disclosure, which may make them less valuable than trade secrecy in some fields. In other fields, when secrecy is not possible or practical, innovators and policy makers may prefer patents. Empirical evidence suggests that patents are especially important in motivating biopharmaceutical research and development (R&D) (Cohen et al., 2000).

The argument for intellectual property rights is a bit different in the case of inventions developed with public funds. When the public bears the cost and risk of the R&D that yields an invention, it is arguable whether the public should not have to pay again for the same invention through

higher prices as a result of the exclusionary rights conferred by patents. Often, however, substantial further private investment is necessary to pick up where government funding leaves off, especially when the recipient of government funding is a research institution that is not itself in the business of translating new scientific discoveries into commercial products. Private firms might hesitate to make the very substantial further investment necessary to translate a new scientific finding into a commercial product without some protection from competition. That has been the working assumption for federally sponsored R&D at least since 1980, when Congress passed the first of a series of legislative acts allowing patenting and retention of ownership by grant recipients of inventions developed in the course of research funded by the United States.[1]

The Bayh-Dole Act of 1980 has been particularly influential in setting the ground rules for patenting of inventions by universities. In that framework, universities retain ownership of patents and license those patents to private firms for commercial development, while the government retains a license to use the invention for government purposes, as well as a "march-in" right to grant additional licenses if necessary to achieve practical utilization of the invention.[2] The influence of these rules is not simply a function of familiarity. The pervasive reach of federal funding for academic biomedical research means that even when other funds are used for a particular research project, federal funding has often played a role as well. The difficulty of disentangling federal funding from other funding sources makes it prudent for institutions that receive federal research funding to comply with the terms of the Bayh-Dole Act whenever there is any question about the source of funding for a particular invention so as to avoid potential liability to the federal government.

DESCRIPTION OF CIRM'S INTELLECTUAL PROPERTY POLICIES

CIRM's intellectual property policies follow the broad contours of the Bayh-Dole regime by allowing grantees to retain ownership of inventions and by giving them considerable discretion in deciding when to pursue,

[1]The Bayh-Dole Act of 1980 allows grantees to retain ownership of patents on government-sponsored inventions in certain circumstances, while the Stevenson-Wydler Act of 1980 promotes patenting by government agencies of inventions arising in intramural research. In both cases, the goal is to facilitate technology transfer to the private sector for commercial development. Prior to 1980, some federal agencies required assignment to the government of any patents arising from government-sponsored research, but typically the government did not grant exclusive licenses or otherwise use its patent rights to promote commercial development. For a fuller account, see Eisenberg (1996).

[2]NIH has repeatedly declined to exercise its march-in rights. These decisions are available at http://www.ott.nih.gov/policy/Reports.html.

retain, transfer, and license their rights. CIRM also follows the Bayh-Dole approach in obligating grantees to make reasonable efforts to achieve practical application of their inventions through either commercialization or licensing, and in fortifying this obligation by retaining march-in rights that allow CIRM to grant licenses if necessary. However, CIRM's intellectual property policies also depart from the familiar Bayh-Dole framework in certain notable respects. These departures are sanctioned and required by the text of Proposition 71 and subsequent legislation[3] and set forth in regulations that have the force of law.

First, California law calls for CIRM to use intellectual property not only to motivate firms to pursue commercial development of CIRM-funded technology but also to generate revenue to the state of California's budget. This goal is stated in Section 3 of Proposition 71, which announces an intent to: "Protect and benefit the California budget . . . by funding scientific and medical research that will significantly reduce state health care costs in the future; and by providing an opportunity for the state to benefit from royalties, patents, and licensing fees that result from the research."

Federal law has no comparable provision for revenue sharing or recoupment of federal grant funding; such proposals have repeatedly been rejected as conflicting with the primary goal of promoting further investment in commercial development by licensees. Although federal agencies collect royalties on patents they own on the inventions of their employees, they generally do not attempt to share in the revenues earned by grantees on their patents.[4]

Second, CIRM's approach to intellectual property departs from the federal model in its requirements for (1) access plans to make drugs emerging from CIRM funding affordable for Californians who would not otherwise have access to these products, and (2) the provision of such drugs to eligible Californians and to those purchasing the drugs in California with public funds at prices established in the California Discount Prescription Drug Program.[5] These requirements originated in CIRM regulations rather than in the text of Proposition 71 as approved by the voters, but a requirement

[3]California Legislature (Sen. Bill No. 1064), approved by Governor September 30, 2010. Filed with Secretary of State on September 30, 2010.

[4]The committee is aware of at least one exception to this generalization. The National Medical Test Bed at Loma Linda University Medical Center (NMTB), funded by congressional appropriation pursuant to a cooperative agreement with the Department of Defense, funded a series of research projects between 1992 and 2006 to develop new medical technologies. The cooperative agreement required NMTB to capture royalties from the commercialization of any and all research sponsored under the cooperative agreement, and to use such proceeds to endow a revolving fund to be administered by NMTB in conducting further research (LLUMC, 2012).

[5]CIRM's intellectual property policy makes no mention of stem cell–based therapies.

for access plans was subsequently codified by the California Legislature, subject to certain qualifications.[6]

Third, CIRM's intellectual property policies call for sharing of biomedical research materials within California after publication.[7] Although sharing of such materials is consistent with aspirational norms of the scientific community that NIH attempts to facilitate through guidance documents, it is not required by federal law (NIH, 2003).

Finally, to monitor and enforce compliance with its intellectual property policies, CIRM has established reporting requirements that allow it to keep track of CIRM-funded inventions and related patents, patent applications, licenses, commercialization efforts, and revenues.[8] As noted, CIRM also has march-in rights that allow it to grant licenses to use CIRM-funded inventions in certain circumstances, including if a grantee, collaborator, or exclusive licensee has not made reasonable efforts to achieve practical application of an invention or has failed to provide or comply with an access plan.[9] To the extent that these march-in rights allow CIRM to enforce obligations with no counterpart in federal law (such as the access plan requirement), they go beyond the scope of march-in rights under the Bayh-Dole Act.

Each of these features of CIRM's intellectual property policies has been a source of controversy, as reflected in public comments submitted to the Institute on drafts of those policies. These comments reveal the complex landscape of competing concerns that CIRM has had to reconcile in establishing its intellectual property policies. Constituencies that made their views known include the California legislature, universities, scientists, and the business community. Their comments, submitted at an early stage before any actual intellectual property was on the table, were necessarily conjectures about the future impact of proposed policies that had not yet taken effect for activities that had scarcely begun.

Although CIRM's intellectual property policies are now in effect, there is still little track record with which to evaluate their actual performance. CIRM reports a total of 90 invention disclosures, 69 patents, and 2 license agreements as of January 2012. At this stage, concerns about the impact of CIRM's intellectual property policies remain largely confined to the realm of speculation. But it is in the realm of speculation that patents do their work, motivating new investments by offering an expectation of future monopoly profits on products that do not yet exist. If concerns at this

[6]California Health and Safety Code § 125290.80.
[7]17 California Code of Regulations § 100604.
[8]17 California Code of Regulations § 100602.
[9]17 California Code of Regulations § 100610.

stage are negatively influencing investment decisions, they could become self-fulfilling prophecies.

The discussion that follows begins with a review of the legal sources of CIRM's intellectual property policies. The subsequent sections review the main criticisms of those policies that have emerged in public comments and in the committee's investigation, with a focus on the distinctive features noted above. The final section offers the committee's conclusions and recommendations with respect to CIRM's intellectual property policies.

THE LEGAL FRAMEWORK AND REACH OF CIRM'S INTELLECTUAL PROPERTY POLICIES

Consistent with the approach of the Bayh-Dole Act,[10] Proposition 71 appears to assign a significant role to contracts as a mechanism for implementing CIRM's intellectual property policies by binding grantees to its terms.[11] In practice, however, CIRM has instead used regulations to govern intellectual property for CIRM-funded research results. By their terms, these regulations bind not only CIRM grantees and loan recipients but also their collaborators and licensees, and even third parties who subsequently acquire rights from them.[12] Some flexibility is built into the regulations, but this very flexibility also creates uncertainty as to how the regulations will be applied in the future.

CIRM initially drafted separate intellectual property regulations for nonprofit organizations (17 California Code of Regulations §§ 100300-100306) and for-profit organizations (17 California Code of Regulations §§ 100400-100410). These two sets of regulations were subsequently replaced with a single set of rules applicable to both nonprofit and for-profit organizations for grants executed on or after December 17, 2009.[13] These regulations, with certain exceptions (including an exemption from revenue-sharing obligations), were extended to loan recipients in 2011.[14] CIRM recently revised its intellectual property guidelines to comply with

[10] 35 U.S.C. § 202(c).

[11] Proposition 71 divides responsibility for CIRM's intellectual property policies among the Independent Citizens Oversight Committee (ICOC), which is assigned to "establish policies regarding intellectual property rights arising from research funded by the institute"; the chair, whose responsibilities include "to lead negotiations for intellectual property agreements, policies, and contract terms"; and the president, whose responsibilities include "to manage and execute all intellectual property agreements and any other contracts pertaining to the institute or research it funds." Codified at California Health and Safety Code § 125290.40.

[12] California Health and Safety Code § 125290.40(j); interview with Scott Tocher and Elona Baum, January 24, 2012.

[13] 17 California Code of Regulations § 100600-100610.

[14] 17 California Code of Regulations § 100801.

legislative changes[15] that, among other matters, codified requirements for revenue sharing with the state[16] and for submission of access plans by grantees and exclusive licensees to make commercial products emerging from CIRM funding affordable for low-income Californians.[17] Further proposed modifications currently pending before the Independent Citizens Oversight Committee ICOC would require grantees to provide CIRM with copies of license agreements and would fortify the revenue-sharing obligations of third-party licensees (Tocher, 2012).

CIRM's intellectual property policies apply to a broader range of research outcomes than the Bayh-Dole Act. For example, the revenue-sharing provisions apply to "CIRM-funded inventions," "CIRM-funded technology," and "results of CIRM-funded research." These terms are broadly defined to capture any intellectual property that arises directly or indirectly from CIRM funding. For example, the term "CIRM-funded invention" includes any invention, whether patentable or not, that is either "(1) reduced to practice by a Grantee, Grantee Personnel and/or its Collaborator(s) during a CIRM-Funded Project or Activity; or (2) conceived during a CIRM-Funded Project or Activity and reduced to practice by a Grantee, Grantee Personnel and/or its Collaborator(s) during a CIRM-Funded Project or Activity or within 12 months of the close of the Grant." By contrast, the Bayh-Dole Act defines "invention" more narrowly as "any invention or discovery which is or may be patentable or otherwise protectable under [the Patent Act]" and defines "subject invention" as "any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement."[18] The definition of "CIRM-funded technology," which has no counterpart in the Bayh-Dole Act, is even broader, covering "data, materials, research results or know-how whether patentable or not, that is (1) generated or conceived in the Project Period of a Grant, and is paid for in whole or in part with CIRM-funds." "CIRM-funded project or activity" and "CIRM-funded research" are also defined to include activities that are funded only partially by CIRM. The relatively broad scope of these definitions presents a risk that the rights of the State of California may come as a surprise to innovators if and when they are asserted, perhaps leading to late-stage conflict and litigation that delays product development. This risk is aggravated by the use of binding regulations to establish the rights of the state in intellectual

[15]SB 1064 (2010), available at http://ca.opengovernment.org/documents/1016634-20090sb-106493chp, codified at California Health and Safety Codes § 125290.20-125290.80.

[16]California Health and Safety Code § 125290.30(j). The legislation also codifies an exclusion in the guidelines from the revenue-sharing obligation for loan recipients and facilities grant recipients. California Health and Safety Code § 125290.30(j)(2).

[17]California Health and Safety Code § 125290.80.

[18]35 U.S.C. § 201(d), (e).

property as a matter of law, binding on parties that may never have known about them, in contrast to the approach of the Bayh-Dole Act, which sets forth federal rights in contracts that bind only those institutions that agree to them.

Each of CIRM's current intellectual property provisions has antecedents in proposed CIRM regulations that provoked considerable public comment. Those comments provide a window on the distinct interests and values of the various commentators, as well as their perceptions of the practical impact of the proposed regulations.

REVENUE SHARING

CIRM's intellectual property regulations call for revenue sharing with provisions that distinguish between inventions that are licensed by a grantee and those that are "self-commercialized." In this manner, they effectively distinguish in many cases between the intellectual property of academic institutions (which ordinarily do not commercialize inventions and must license them to firms to earn revenue from them) and that of commercial firms that more typically commercialize inventions (although in some cases a commercial firm may license an invention).

For licensed inventions, grantees (and their collaborators) must remit to the state general fund 25 percent of licensing revenue in excess of $500,000, adjusted annually to account for inflation.[19] If other funding sources contributed to the development of the CIRM-funded invention, the amount due is reduced proportionately.[20]

In the case of a product that is self-commercialized by grantees and collaborators rather than licensed, the amount due is calculated as a 3 percent royalty on "net commercial revenue" from sales of the product up to a total of three times the amount of CIRM grants that led to the product.[21] Additional payments of three times the amount of grant funding are due for blockbuster products when annual sales exceed $250 million[22] and $500 million.[23] In addition, if CIRM funding exceeded $5 million, a royalty of 1

[19]California Health and Safety Code § 125290.30(j)(2)(A)(i); 17 California Code of Regulations 100608(a)(1).

[20]California Health and Safety Code § 125290.30(j)(2)(A)(ii); 17 California Code of Regulations 100608(a)(2).

[21]California Health and Safety Code § 125290.30(j)(2)(B)(i); 17 California Code of Regulations 100608(b)(1).

[22]California Health and Safety Code § 125290.30(j)(2)(B)(ii); 17 California Code of Regulations 100608(b)(2).

[23]California Health and Safety Code § 125290.30(j)(2)(B)(iii); 17 California Code of Regulations 100608(b)(2).

percent of commercial revenue in excess of $500 million is due for the life of any patent covering the CIRM-funded invention.[24]

These provisions stand in contrast to federal law, which has repeatedly rejected proposals that would require licensees to share revenues with federal research sponsors in the face of opposition from industry (Schacht, 2011a). The Bayh-Dole Act does not call for universities to share licensing revenues with the government, although it does require that they share royalties with inventors and that the balance of funds be used to support scientific research or education.[25] The CIRM regulations avoid conflict with the utilization constraints of the Bayh-Dole Act in cases of combined CIRM and federal funding by specifying that the share of revenues paid to the state is "to be used by the State of California in a manner consistent with Title 35 United States Code, Section 202, subdivision (c)(7)."[26]

CIRM is not the only state science funding program that seeks to return financial benefits to the state. The Connecticut stem cell program requires grantees to pay to the state annually 5 percent of revenues derived from licensing or commercializing inventions that result from its grants. In contrast to the CIRM provisions, these revenue-sharing requirements do not phase in at a particular threshold. Moreover, Connecticut's revenue-sharing requirement applies to any inventions resulting at least in part from Connecticut funding, with no reduction for inventions that result from work funded by multiple agencies. The Cancer Prevention Research Institute of Texas (CPRIT) also makes its grants subject to revenue-sharing requirements. Specifically, Texas law makes all CPRIT grants subject to an intellectual property agreement that allows the state to collect royalties, income, and other benefits realized as a result of CPRIT-funded projects. Typical terms for research projects at academic institutions include a requirement that 10 percent of the revenue received by the recipient institution be returned to the state, with the possibility for adjustments when research is funded by multiple entities. CPRIT's investments in early-stage companies can take the form of royalties, milestone payments, equity shares, or other benefits.

On the other hand, the state stem cell programs in New York and Maryland do not impose revenue-sharing obligations on their grantees. Instead, grant recipients in these programs are free to pursue and com-

[24]California Health and Safety Code § 125290.30(j)(2)(B)(iv); 17 California Code of Regulations 100608(b)(3). As originally drafted in the CIRM regulations, the 1 percent royalty obligation extended to CIRM-funded technology regardless of whether it was patented. The California legislature limited this obligation to patented inventions, requiring conforming amendments to the language of the regulation.

[25]35 U.S.C. § 202(c)(7)(B), (C).

[26]17 California Code of Regulations § 100608(a)(1). In other words, the state will use the funds for the support of scientific research or education.

mercialize intellectual property associated with their state-funded research in accordance with pre-existing institutional policies. This choice avoids dampening incentives for commercialization while reducing the administrative burden associated with grants and has been perceived as a benefit by scientists and university administrators.

Industry criticisms of CIRM's revenue-sharing provisions have been muted (ARI, 2007; CHI, 2006a, 2007a,b; Invitrogen, 2007),[27] as has criticism from universities (UCOTT, 2006).[28] Comments in support of revenue sharing have been far more numerous, sometimes calling for larger payments to the state (Consolidated non-profit public comments on CIRM's IP policy, 2012; The Foundation for Taxpayer and Consumer Rights, 2006; Kuehl et al., 2007; Sholes, 2006).[29] Perhaps more important, the revenue-sharing provisions enjoyed the support of California legislators (Kuehl et al., 2007), who subsequently mustered the supermajority necessary to codify these provisions in the California Health and Safety Code, where they can no longer be modified by CIRM through changes in the regulations.

Perhaps the lack of significant controversy over the revenue-sharing provisions reflects recognition that Proposition 71 explicitly requires revenue sharing, or perhaps the revenue-sharing obligations seemed remote and speculative at the time these public comments were submitted. (Indeed, any payment obligations that may arise from these provisions must await successful commercialization of CIRM-funded technology, which may not occur for years.) But the same could be said of the provisions for access plans (see below), which drew far more opposition from both commercial firms and academic institutions. Academic institutions also spoke out more forcefully in opposition to provisions in the intellectual property regulations

[27]See, e.g., letters dated June 15, 2006, October 5, 2007, and November 21, 2007, from the California Healthcare Institute expressing concern that the calculation of "net commercial revenues" may underestimate the expenses of drug development and noting that "direct revenue sharing and royalty provisions may actually reduce the public benefit of Prop 71 funded research" and "could create unnecessary obstacles for commercial enterprises working with the government"; a letter dated April 30, 2007, from the Alliance for Research Innovation (on behalf of a group of life sciences companies) noting concern that regulations should guard against the potential for royalty stacking in the case of a compound product involving multiple proprietary inputs; and a letter dated December 11, 2007, from Invitrogen noting "a few minor, but critical changes that should be made."

[28]See, e.g., a letter dated June 16, 2006, from the University of California Office of Technology Transfer noting concern that "the revenue sharing and other requirements will have the effect of making CIRM funding less attractive to researchers than other funds, and may perhaps even put California at a disadvantage as compared to other states and other countries."

[29]See, e.g., a letter dated June 6, 2006, from the Foundation for Taxpayer and Consumer Rights urging that the threshold for triggering a recoupment obligation on licensing revenue be lowered from $500,000 to $100,000. Approximately 30 individuals submitted comments to the same effect by e-mail in the same time period. See also an e-mail dated June 15, 2006, from Elizabeth Sholes on behalf of the California Church IMPACT to the same effect.

that define "CIRM-funded inventions" broadly to include inventions conceived prior to the grant period or reduced to practice in the year following the grant period (BIMR, 2009; Goldstein, 2009; SRI, 2009; Stanford University Office of Technology Licensing, 2009; UCOTT, 2009a,b) and to cover unpatented and unpatentable inventions (UCOTT, 2009c).[30]

Although it may be premature to assess whether the revenue-sharing provisions will ultimately dampen incentives for commercialization of CIRM-funded inventions, at this point they do not appear to rank high among the concerns of potential grantees and licensees.

ACCESS PLANS

Perhaps the most controversial aspect of CIRM's intellectual property provisions is the requirement that grantees and their exclusive licensees submit to CIRM access plans that will afford access to any drug resulting from CIRM-funded research to "Californians who have no other means to purchase the drug."[31] The term "drug" is broadly defined to include "blood, blood products, and cells," but does not include medical services.[32] Proposition 71 does not explicitly call for access plans, but CIRM introduced the requirement in its intellectual property regulations,[33] and

[30]See, e.g., a letter dated July 31, 2009, from the University of California Office of Technology Transfer. The California Legislature ultimately limited the 1 percent royalty on net commercial revenue in excess of $500 million annually to apply only when CIRM funding exceeded $5 million and generated patented inventions that contributed to the creation of the product, and only during the life of the patent. California Health and Safety Code § 125290.30(j)(2)(B)(iii).

[31]California Health and Safety Code § 125290.80; 17 California Code of Regulations § 100607.

[32]17 California Code of Regulations § 100600(i).

[33]17 California Code of Regulations § 100306(d) (Regulations applicable to nonprofit organizations governing grants prior to December 17, 2009, permit grantee organizations to grant exclusive licenses "only to persons that agree to have a plan in place at the time of commercialization to provide access to resultant therapies and diagnostics for uninsured California patients. In addition, such licensees will agree to provide drugs at prices negotiated pursuant to the California Discount Prescription Drug Program . . . to eligible Californians under that program."); § 100407 (Regulations applicable to for-profit organizations for grants prior to December 17, 2009, require that a grantee or its exclusive licensee "must submit a plan to afford uninsured Californians access to a Drug . . . the development of which was in whole or in part the result of CIRM-funded Research . . . no fewer than 90 days prior to the time the Drug is commercialized . . . the access plan must be consistent with industry standards at the time of commercialization, accounting for the size of the market for the Drug and the resources of the Grantee or its exclusive licensee. . . . A Grantee (or its exclusive licensee) must provide a Drug, the development of which was in whole or in part the result of CIRM-funded Research, at a price as provided in the California Discount Prescription Drug Program . . . to eligible Californians under this program."); and 17 California Code of Regulations § 100607 (similar). Pending amendments to § 100607 make changes to conform to Senate Bill 1064,

the California legislature has now codified it in the California Health and Safety Code.[34] The access plan, which must be submitted within 10-30 days of Food and Drug Administration (FDA) approval of a drug, "must be consistent with industry standards at the time of commercialization in California, accounting for the size of the market for the drug, and the resources of the grantee or exclusive licensee." The plan is subject to ICOC approval following a public hearing. The ICOC may also waive the requirement following a public hearing if it determines "that in the absence of the waiver, development and broad delivery of the drug will be unreasonably hindered or that the waiver will provide significant benefits that equal or exceed the benefits that would otherwise flow to the state."[35] CIRM regulations further require that the grantee, collaborator, or exclusive licensee provide the drug to eligible Californians and to those purchasing the drug in California with public funds at a price provided in the California Discount Prescription Drug Program.[36]

Federal law and other state-funded stem cell programs have no comparable provisions. The closest parallel in recent memory is the policy of the National Institutes of Health (NIH) in the 1990s, ultimately abandoned in the face of persistent industry opposition, to commit industry partners to a "reasonable pricing clause" in the terms of cooperative research and development agreements (Gavaghan, 1995).[37]

CIRM's access plan provisions are much less far-reaching than the abandoned NIH reasonable pricing clause. For one thing, the CIRM provisions apply only to sales in California. Even within California, they do not lower prices to all customers, but only to those who otherwise could not afford to pay the higher price or who are purchasing the drug in California with public funds. Drug companies often have their own programs for providing low-cost access to expensive drugs for uninsured patients who

---

including changing the phrase "uninsured Californians" to "Californians who have no other means of purchasing the drug"; changing the time period for submission of access plans from "no fewer than 90 days prior to the time the Drug is commercialized in California, unless CIRM agrees to a shortened time" to "within 10 business days following final approval of the drug by the Food and Drug Administration unless, within that time period, the Grantee, Collaborator, or Exclusive Licensee seeks an extension from CIRM"; and authorizing the Independent Citizens Oversight Committee (ICOC) to waive access plan requirements if certain requirements are met.

[34]SB 1064, codified at California Health and Safety Code § 12590.80.

[35]California Health and Safety Code § 12590.80(c).

[36]17 California Code of Regulations § 100607(f) in pending version (December 29, 2011).

[37]The story is recounted in Schacht, 2011b.

would otherwise be unable to pay for the drugs—hence the reference in the statute and regulations to "industry standards."[38]

Public comments on the access plan requirement include opposition from industry (BIOCOM, 2007a; CHI, 2007a; StemCells, 2007a,b)[39] and academic institutions,[40] as well as support from consumer advocates (CNA, 2007; Consumer Watchdog, 2009a,b).[41] Industry representatives have argued that the requirement will make industry and investors less interested in licensing CIRM-funded inventions (CHI, 2006b,c),[42] while legislators have argued that the access provisions are "too weak and vague" to ensure "meaningful access for the uninsured" (Kuehl et al., 2007).

Uncertainty about how the system will work could make industry cautious about licensing and investing in CIRM-funded inventions, especially if they have the option of turning to other sponsors that do not impose

[38]On the other hand, firms that are willing to provide a drug at a reduced price as a matter of private charity might oppose regulations that would bind them to that price as a matter of law. Moreover, reduced prices that are formalized in state regulations could become benchmarks in negotiating with other payers, just as private insurers look to Medicare prices as a benchmark in negotiating with providers.

[39]See letters dated October 5, 2007, and November 21, 2007, from StemCells (criticizing the requirement as "overly burdensome, unclear, unworkable and risky as well as beyond the statutory mandate of Proposition 71"); a letter dated November 21, 2007, from BIOCOM (noting that pricing under the California Discount Prescription Drug Program enjoys statutory protection under California law as confidential and corporate proprietary information and would not be made available to CIRM to use as a benchmark); and a letter dated October 5, 2007, from the California Healthcare Institute (noting that without clarification of these provisions, "it would be difficult to attract private investment to develop CIRM-funded technology," that "there is no evidence that an industry standard exists" for access plans, and that the references to prices under the California Discount Prescription Drug Program are forms of price control that "will create a substantial disincentive to commercial interest in licensing CIRM-funded inventions from for-profit grantees").

[40]See, e.g., a letter dated August 18, 2009, from the Stanford University Office of Technology Licensing (suggesting that the access plan requirement may be why Stanford has been unable to find licensees for any of its 13 CIRM-funded patents and asking for a mechanism to allow case-by-case exceptions).

[41]See, e.g., letters dated August 18, 2009, and September 11, 2009, from Consumer Watchdog (first criticizing CIRM for watering down access provisions through definitions that exclude sublicensees from access requirements, then applauding a change in definitions that restored broader application of the requirements); and a letter dated November 20, 2007, from the California Nurses Association (arguing for use of the Medicaid fee schedule rather than the California Discount Prescription Drug Program as a benchmark because the former is more predictable and measurable).

[42]See, e.g., letters dated August 22, 2006, and October 4, 2006, from the California Healthcare Institute noting that access plan provisions "would discourage commercial collaboration, technology transfer and licensing by (a) increasing the administrative complexity of licensing agreements involving CIRM-funded technologies in comparison to the mainstream of academic-industry transactions, which derive from federally-funded research, and (b) increasing investors' financial risk by imposing state price regulation on downstream products."

similar requirements. Perhaps this uncertainty is undermining commercial interest in licensing CIRM-funded inventions, or perhaps the limited licensing activity to date reflects nothing more than continuing uncertainty about the technological viability and commercial value of stem cell therapies.

The principal means of mitigating the effects of the access plan requirement is the provision for the ICOC to waive the requirement. But this provision is unlikely to reassure firms about the impact of the requirement on the future profitability of products that may not come to market for many years. Even if firms had confidence that the ICOC itself would forbear from enforcing the access plan requirement so as not to undermine the profitability of future products, they might worry that the ICOC will no longer exist at the point of successful commercialization, and that the rights of the state will instead be exercised by another agency that is more concerned with containing health care costs than with promoting the development of new products. With little experience to guide future implementation, the access plan provisions introduce considerable risk and uncertainty for product-developing firms.

MARCH-IN RIGHTS

CIRM holds march-in rights that allow it to enter into license agreements on behalf of a grantee or its exclusive licensee with respect to a CIRM-funded invention under three circumstances: (1) the grantee, collaborator, or exclusive licensee is failing to exercise reasonable efforts to achieve practical application of the invention; (2) the grantee, collaborator, or exclusive licensee has failed to submit or comply with an access plan; or (3) the grantee, collaborator, or exclusive licensee has unreasonably failed to use a CIRM-funded invention to alleviate a public health emergency declared by the governor.[43] The first and third of these circumstances correspond to march-in rights retained by federal research sponsors under the Bayh-Dole Act,[44] but the second—failure to submit or comply with an access plan—has no counterpart in the federal system, leading to some uncertainty about how CIRM will exercise its march-in rights (CHI, 2007a,b).[45]

Many comments in opposition to the CIRM march-in provisions stressed the uncertainty that march-in rights create for potential licensees

[43] 17 California Code of Regulations § 100610(b).

[44] 35 U.S.C. § 203(a)(1) and (2).

[45] See, e.g., letters dated October 5, 2007, and November 21, 2007, from the California Healthcare Initiative (stating that inclusion of failure to adhere to pricing and access plans as triggering events for march-in rights distinguishes CIRM provisions from those of the Bayh-Dole Act, increases the risk of litigation, and adds another layer of risk and uncertainty to commercial transactions).

(BIOCOM, 2007a,b; Geron, 2007; StemCells 2007a,b),[46] which could make it difficult for universities to license their inventions.[47] Similar arguments have been made in opposition to the statutory march-in rights retained by the federal government under the Bayh-Dole Act, although the federal government can now point to a track record of declining to exercise these rights. The University of California's Office of Technology Transfer observed that CIRM does not have the same track record of decades of forbearing from the exercise of march-in rights and concluded, "We believe there is a legitimate concern that CIRM will be much more likely to exercise its march-in rights than the federal government has been" (O'Connor, 2006; UCOTT, 2006).[48]

Other comments from public interest groups favored strong march-in rights. Comments from the Center for Genetics and Society, echoed by individual e-mails, urged CIRM to empower the California attorney general to enforce march-in rights (Consumer Watchdog, 2008; Reynolds, 2006),[49] while comments from the Berkeley Center for Law & Technology commended CIRM for improving on the Bayh-Dole Act by making march-in rights less cumbersome to exercise (Samuelson et al., 2006).

Concerns about march-in rights reflect a combination of unhappiness with the underlying rights they enforce (such as access plans) and uncertainty about how CIRM will exercise its discretion. Perhaps over time, CIRM can reassure licensees that it will use its march-in rights as sparingly as NIH has done, but CIRM may run out of time before commercialization begins. It is also possible that in the future, CIRM (or another enforcer of

[46]See, e.g., letters dated April 30, 2007, and November 21, 2007, from BIOCOM (noting that the march-in provisions are "so overly broad and all-encompassing that [they] would present an unacceptable level of risk to most companies" and would be better left to the federal government to avoid conflict between state and federal requirements); letters dated October 5, 2007, and November 21, 2007, from StemCells (arguing that the march-in rights, "especially those tied to public access and public health, are overly burdensome, unclear, unworkable, and risky as well as beyond the statutory mandate of Proposition 71"); and a letter dated April 30, 2007, from Geron (noting differences between CIRM and Bayh-Dole march-in provisions that create uncertainty for firms contemplating commercialization).

[47]See a letter dated August 1, 2009, from Burnham Institute for Medical Research (stating that march-in provisions "will have a chilling effect on the ability to license results" because they "invite legal challenges to every licensee's efforts to commercialize licensed technology").

[48]See a letter dated June 16, 2006, from the University of California Office of Technology Transfer. See also a letter dated June 19, 2006, from Sean O'Conner, Center for Advanced Study and Research on Intellectual Property, noting the potential for conflict if the federal government and CIRM chose to exercise march-in rights on the same invention in inconsistent ways.

[49]See an e-mail dated June 19, 2006, from Jesse Reynolds on behalf of the Center for Genetics and Society. See also a letter dated June 25, 2008, from Consumer Watchdog (urging a provision giving the attorney general the right to intervene in cases of unreasonable pricing of CIRM-funded projects).

march-in rights) will face considerable political pressure to exercise those rights more aggressively in order, for example, to address rising health care costs. Like the requirement for access plans, the march-in rights provisions thus raise considerable uncertainty about the future implementation of rights that may outlive CIRM itself.

DISSEMINATION OF BIOMEDICAL MATERIALS WITHIN CALIFORNIA

Another distinctive feature of CIRM's intellectual property policies is the requirement for distribution of publication-related biomedical materials,[50] a term that is broadly defined to include "tangible research material of biomedical relevance first produced in the course of CIRM-Funded Research including but not limited to unique research resources (such as synthetic compounds, organisms, cell lines, viruses, cell products, cloned DNA, as well as DNA sequences, mapping information, crystallographic coordinates, and spectroscopic data), as described in a published scientific paper."[51] Grantees must share publication-related biomedical materials "for bona fide purposes of research in California" for free or at cost within 60 days of receiving a request unless CIRM determines that doing so is unduly burdensome[52] or approves an alternative method of dissemination (such as making the materials broadly commercially available).[53] A grantee may also comply by providing requesters with the information necessary to reconstruct or obtain identical material.[54] Transfers of materials may be made subject to a "university standard or industry standard Materials Transfer Agreement."[55] Compliance with this requirement is fortified by the further requirement that grantees submit abstracts of publications to CIRM for disclosure to the general public, and that such abstracts include "the URL of a website where a Materials Transfer Agreement (or similar document) can be accessed to facilitate requests for Publication-related Biomedical Materials."[56]

The Bayh-Dole Act does not address the dissemination of unpatented materials. However, NIH requires grant applicants to address plans for dissemination of research results in grant applications seeking more than

[50] 17 California Code of Regulations § 100604. Proposed versions of the regulations had included a broader "research use exemption" that would have allowed researchers in California to use patented inventions covered by the regulations without liability, but CIRM retreated from this proposal in the face of objections from commercial firms.

[51] 17 California Code of Regulations § 100602dd.

[52] 17 California Code of Regulations § 100604(c)(1).

[53] 17 California Code of Regulations § 100604(e).

[54] 17 California Code of Regulations § 100604(d).

[55] 17 California Code of Regulations § 100604(f).

[56] 17 California Code of Regulations § 100603.

$500,000 in direct costs (NIH, 2003). NIH and the Association of University Technology Managers encourage universities to retain the right to share "research tools" for noncommercial purposes (AUTM, 2007).[57]

The provision on sharing biomedical materials for research purposes is the sole remaining vestige of an earlier proposal in draft intellectual property regulations for a broader research exemption for the use of all CIRM-funded intellectual property for research purposes. Many comments criticized this earlier proposal, arguing that it would undermine the commercial dissemination of research tools (ARI, 2007; CHI, 2007b; Invitrogen, 2007). CIRM responded with revisions that allow it to approve alternatives to the sharing requirement when the requirement is onerous and that allow grantees to discharge their sharing obligations by disclosing how to reconstruct the materials or by making them "broadly commercially available."[58]

Texas has a broader research exemption within the CPRIT program, requiring that patented inventions resulting from CPRIT funding be shared on reasonable terms with other CPRIT award recipients for noncommercial purposes. The comparable provisions of the Connecticut stem cell program are more similar to those of CIRM, setting an expectation that grant recipients and their institutions, hospitals, and companies will share reagents, data, and protocols developed as part of state-funded stem cell research. The Connecticut program specifies in its requests for proposals that such resources shall be made freely available to other Connecticut-based researchers. Similar to California and Connecticut, New York stipulates that resources, materials, and methods created through its sponsorship should be made easily available at reasonable cost to the research community. Maryland also requires grantees to share research results, including new cell lines as well as other materials developed with state funding, with qualified researchers. Grant recipients are permitted to request reasonable compensation for these materials.

More recently, CIRM has proposed Interim Regulations for the iPSC Banking Initiative to facilitate worldwide dissemination of a comprehensive collection of disease-specific human induced pluripotent stem (iPS) cell samples. These interim regulations would exempt grantees from the usual intellectual property and revenue-sharing regulations and provide for CIRM to own human iPS cell lines in the CIRM human iPS cell bank. The repository could charge a reasonable fee for the lines so that it could become self-sustaining, and CIRM could receive a share of revenues generated by the repository under the terms of a licensing agreement with the grantee (Baum, 2012).

[57] 64 Fed. Reg. 72090 (1999).

[58] 17 California Code of Regulations § 100607(c), (d), (e).

CONCLUSIONS AND RECOMMENDATIONS

CIRM's intellectual property policies reflect a reasonable effort to balance conflicting interests of different constituencies that each have a legitimate stake in these policies. The actual impact of the policies may not be clear for many years, but the concerns of stakeholders are already apparent. Some of the more contested provisions attempt to address competing views by leaving CIRM with discretion over implementation, but this flexibility cuts two ways: it provides for adaptation to particular circumstances, but it also creates uncertainty and risk for potential developers of commercial products.

Reliance on CIRM's discretion to mediate competing interests is problematic for two reasons. First, CIRM itself is a new institution with no track record to reassure stakeholders about how it is likely to exercise its discretion. Second, CIRM's future is uncertain given the time limits of its authorization and funding, yet its policies create obligations for the benefit of the State of California extending years into the future. It is not clear who will be responsible for overseeing these obligations on behalf of the state at the point of commercial product development, but it appears entirely possible that a future enforcer may be more concerned with revenue and access and less concerned with the interests of grantees and licensees than CIRM has been. This uncertainty may make commercial development of CIRM-funded inventions unattractive to grantees and licensees, especially if they have alternative opportunities that are not burdened with these risks and uncertainties.

CIRM might reduce some of the uncertainty arising from the unfamiliarity of its policies by modifying those policies to conform more closely to the more familiar Bayh-Dole approach. CIRM may have had more latitude to depart from this familiar approach in its early years when alternative sources of funding were unavailable. Departures from the Bayh-Dole approach may put CIRM-funded inventions at a growing disadvantage in the future as funding from other states and the federal government yield competing candidates for commercial development that are available for licensing on more favorable terms. The most significant departures from that approach from the perspective of grantees and licensees—those pertaining to revenue-sharing and access plans—are required by California law and evidently popular with the California legislature, posing a considerable political challenge if CIRM seeks to modify them at this point. Other departures from the Bayh-Dole approach, such as the broad definition of "CIRM-funded invention," may be less politically salient and easier to modify.

CIRM can and should address the uncertainty as to the future enforcement of its intellectual property policies by considering this issue as part of the sustainability platform recommended in Chapter 2. Innovators with a

long time horizon for product development are entitled to greater guidance on the allocation of institutional stewardship over the retained rights of the state in CIRM-funded intellectual property if and when CIRM itself ceases to exist. The notice and comment model used by CIRM to develop and revise its current intellectual property policies would be a good approach to provide useful feedback as the Institute thinks through this issue. Stakeholders would thereby have an opportunity to identify and explain their specific concerns about the long-term implications of rights created in the course of a time-limited research funding initiative. Perhaps stakeholders would have good ideas about how to minimize the resulting uncertainty for investors. In particular, the ICOC should reconsider whether, given the globalized nature of research and development in regenerative medicine there might be some advantage to California's long term interests to bring CIRM's IP policies into closer harmonization with the principles that are incorporated in Bayh-Dole. At this stage, however, it appears more likely that the limitations of the science and technology, rather than CIRM's intellectual property policies, are delaying the development of commercial products. It may be difficult to assess the impact of these policies until commercial prospects appear more realistic and imminent to product-developing firms.

Recommendation 5-1.[59] ***Incorporate Future Enforcement of Intellectual Property Policies in the Sustainability Platform.*** **As part of the plan maximizing the continued impact of CIRM's many achievements (see Recommendation 2-1), CIRM should propose regulations that specify who will have the power and authority to assert and enforce the future rights retained by the state in CIRM-funded intellectual property. CIRM should seek to clarify which state agencies and actors will be responsible for the exercise of discretion currently allocated to CIRM and the ICOC over future determinations on issues regarding march-in rights, access plans, and revenue-sharing rights that might arise years after CIRM's initial funding period has passed. As it has done in the past, CIRM should provide ample opportunity for public comment on proposed changes to its intellectual property policies that pertain to transition planning.**

Recommendation 5-2.[60] ***Consider Harmonizing Intellectual Property Policies with Policies of Bayh-Dole Act.*** **As other sources of funding for stem cell research become available and as the field of regenerative medicine advances from the laboratory to the clinic, the ICOC should**

[59]In the committee's view, this recommendation can be carried out by CIRM without legislative action.

[60]CIRM may need to work with the state legislature in order to fully implement this recommendation.

reconsider whether its goal of developing cures would be better served by harmonizing CIRM's IP policies wherever possible with the more familiar policies of the Bayh-Dole Act.

REFERENCES

ARI (Alliance for Research Innovation). 2007. *Comments to proposed CIRM regulation entitled: Intellectual property policy for for-profit organizations (IPPFPO)*. http://www.cirm.ca.gov/meetings/pdf/2007/052507_item_4a.pdf (accessed August 23, 2012).

AUTM (Association of University Technology Managers). 2007. *In the public interest: Nine points to consider in licensing university technology.* https://www.autm.net/Nine_Points_to_Consider.htm (accessed August 23, 2012).

Baum, E. 2012. *Proposed interim regulations for the iPSC banking initiative*. http://www.cirm.ca.gov/files/meetings/pdf/2012/052412_item_10b_Interim_Regulations_iPSC.pdf (accessed August 23, 2012).

BIMR (Burnham Institute for Medical Research). 2009.* *CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy*. Comments on proposed intellectual property regulations for non-profit and for-profit grantees (dated August 1, 2009).

BIOCOM. 2007a.* *Response to proposed IP and revenue sharing requirements for for-profit organizations*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated November 21, 2007).

BIOCOM. 2007b.* *Letter to members of the Independent Citizen's Oversight Committee*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated April 30, 2007).

CHI (California Healthcare Institute). 2006a. *Comments to proposed CIRM regulation entitled: Intellectual property policy for non-profit organizations [California Code of Regulations, Title 17—public health, division 4—California Institute for Regenerative Medicine, Chapter 3]* (dated June 15, 2006). http://www.chi.org/uploadedFiles/Legislative_Action/State_Issues/CHI%20IPPNPO%20comments.pdf (accessed August 23, 2012).

CHI. 2006b. *Comments to proposed changes to CIRM regulation entitled: Intellectual property policy for non-profit organizations, issued August 8, 2006* (dated August 22, 2006). http://www.chi.org/uploadedFiles/Legislative_Action/State_Issues/CHI%20comments%20to%20revised%20IPPNPO_082206.pdf (accessed August 23, 2012).

CHI. 2006c. *Comments to third set of proposed changes to the CIRM regulation entitled: Intellectual property policy for non-profit organizations, issued September 25, 2006* (dated October 4, 2006). http://www.chi.org/uploadedFiles/Legislative_Action/State_Issues/CHI%20comments%20to%20revised%20IPPNPO_100406.pdf (accessed August 23, 2012).

CHI. 2007a. *Comments to revised CIRM regulation entitled: Intellectual property policy for for-profit organizations (IPPFPO), issued September 20, 2007* (dated October 5, 2007). http://www.chi.org/uploadedFiles/CHI%20IPPFPO%20Comments_100507.pdf (accessed August 23, 2012).

CHI. 2007b. *Comments to third set of proposed changes to the CIRM regulation entitled: Intellectual property policy for for-profit organizations (IPPFPO), issued November 6, 2007* (dated November 21, 2007). http://www.chi.org/uploadedFiles/CHI%20IPPFPO%20Comments_112107.pdf (accessed August 23, 2012).

CNA (California Nurse Association). 2007.* *For profit IP, 3rd public comment*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated November 20, 2007).

Cohen, W. M., R. R. Nelson, and J. P. Walsh. 2000. *Protecting their intellectual assets: Appropriability conditions and why U.S. manufacturing firms patent (or not)*. Cambridge, MA: National Bureau of Economic Research.

Consolidated non-profit public comments on CIRM's IP policy. 2012.* *Entire first round non-profit comments: Letters dated May 10-June 17, 2006 to IP Task Force Members from James Salter, Roberta Froome, Charlene Chauvaux, Mark Pasley, Rohan Sabnis, Beverly Williamson-Pecori, John Lewis, Stephen Greenberg, Mark Reback, Georgina Celio, Arthur Dauer, Danila Oder, Sarah Keech, Nancy Kelly, Christine Gilbert, Carol Lowe, Virginia Downs, Maureen Fahlberg, Elisha Belmont, Delina Roberts, Jacques Couture, Michael Keenan, Sandusky Shelton, Jeff Barnard, Steve Walworth, Lou Edwards, Brad Dre, Jim Highfill, Stuart Bechman, Brian Zwetzig, and Kenneth Hoffman*. CIRM's response to IOM's data requests: Public comments on CIRM's IP policy (for-profit and non-profit) (dated March 16, 2012).

Consumer Watchdog. 2008.* *Comment on* § 100407. Access requirements for products developed by for-profit grantees. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated June 25, 2008).

Consumer Watchdog. 2009a.* *Comment on "proposed IP regulations: third round."* CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated August 18, 2009).

Consumer Watchdog. 2009b.* *Response to IP regulations, fourth version*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated September 11, 2009).

Eisenberg, R. S. 1996. Public research and private development: Patents and technology transfer in government-sponsored research. *Virginia Law Review* 82(8):1663-1727.

The Foundation for Taxpayer and Consumer Rights. 2006.* *Comment on the CIRM IP policy for non-profit regulations*. CIRM's response to IOM's data request: Non-profit public comments on CIRM's intellectual property policy (dated June 6, 2006).

Gavaghan, H. 1995. NIH drops reasonable pricing clause. *Nature* 374(6524):669.

Geron. 2007.* *Response to proposed regulations: Intellectual property and revenue sharing requirements for for-profit organizations*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated April 30, 2007).

Goldstein, L. 2009.* *Letter to Scott Tocher*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated July 31, 2009).

Invitrogen. 2007.* *Response to proposed adoption of the CIRM intellectual property and revenue sharing requirements for for-profit organizations (compiled 4th public comment)*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated December 11, 2007).

Kuehl, S. J., M. Dymally, N. Mcleod, K. Bass, D. Steinberg, P. Berg, L. Yee, D. L. Torre, N. Evans, M. Hayashi, R. Hernandez, D. Jones, and S. Lieber. 2007.* *CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy*. California legislature letter to Robert Klein (dated December 10, 2007).

LLUMC (Loma Linda University Medical Center). 2012. *Summary of NMTB activities*. http://lomalindahealth.org/medical-center//national-medical-technology-testbed/index.page (accessed August 30, 2012).

NIH (National Institutes of Health). 2003. *Final NIH statement on sharing research data*. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html (access August 23, 2012).

O'Connor, S. 2006.* *Email response to IPPNPO*. CIRM's response to IOM's data request: Non-profit public comments on CIRM's intellectual property policy (dated June 19, 2006).

Reynolds, J. 2006.* *Email to CIRM: Comment on intellectual property policy for non-profit organizations*. CIRM's response to IOM's data request: Non-profit public comments on CIRM's intellectual property policy (dated June 19, 2006).

Samuelson, P., B. Robert, and A. Centivany. 2006.* *Letter response to intellectual property policy for non-profit organizations*. CIRM's response to IOM's data request: Non-profit public comments on CIRM's intellectual property policy (dated June 19, 2006).

Schacht, W. H. 2011a. *The Bayh-Dole Act: Selected issues in patent policy and the commercialization of technology*. http://www.ieeeusa.org/policy/eyeonwashington/2011/documents/bayh.pdf (accessed August 23, 2012).

Schacht, W. H. 2011b. *Federal R&D, drug discovery, and pricing: Insights from the NIH-university-industry relationship*. http://www.fas.org/sgp/crs/misc/RL32324.pdf (accessed November 12, 2012).

Sholes, E. 2006.* *Proposed regulations on ownership and benefits of stem cell research*. CIRM's response to IOM's data request: Non-profit public comments on CIRM's intellectual property policy (dated June 12, 2006).

SRI (Scripps Research Institute). 2009.* *Comments on proposed adoption of revised IP regulations*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated July 31, 2009).

Stanford University Office of Technology Licensing. 2009.* *Comments on proposed intellectual property and revenue sharing requirements for non-profits and for-profit grantees*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated August 18, 2009).

StemCells. 2007a.* *Response to proposed CIRM regulations for intellectual property and revenue sharing by for-profit organizations*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated October 5, 2007).

StemCells. 2007b.* *Response to proposed CIRM regulations for intellectual property and revenue sharing by for-profit organizations*. CIRM's response to IOM's data request: For-profit public comments on CIRM's intellectual property policy (dated November 21, 2007).

Tocher, S. 2012. *Response to the consideration of proposed amendments to the intellectual property regulations—Additional amendments to revenue sharing and reporting requirements*. http://www.cirm.ca.gov/files/meetings/pdf/2012/072612_item_9_IP_Regs.pdf (accessed August 23, 2012).

UCOTT (University of California Office of Technology Transfer). 2006.* *CIRM's response to IOM's data request: Non-profit public comments on CIRM's intellectual property policy*. Comment on proposed CIRM regulation entitled: Intellectual property policy for non-profit organizations (dated June 16, 2006).

UCOTT. 2009a.* *Comments on proposed adoption of intellectual property regulations for non-profit and for profit grantees*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated February 2, 2009).

UCOTT. 2009b.* *Comments on proposed intellectual property regulations for non-profit and for-profit grantees*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated October 13, 2009).

UCOTT. 2009c.* *Comments on proposed intellectual property regulations for non-profit and for-profit grantees*. CIRM's response to IOM's data request: Consolidated public comments on CIRM's intellectual property policy (dated July 31, 2009).

References with an asterisk (*) are public access files. To access those documents, please contact The National Academies' Public Access Records Office at (202)334-3543 or paro@nas.edu.

Glossary

Allogenic stem cell transplantation: A procedure in which a person receives stem cells from a genetically similar but not identical donor. (1)

Blastocyst: A preimplantation embryo of about 150 cells produced by cell division following fertilization. The blastocyst is a sphere made up of an outer layer of cells (the trophoblast), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass). (2)

Differentiation: The process whereby an unspecialized embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell. Differentiation is controlled by the interaction of a cell's genes with the physical and chemical conditions outside the cell, usually through cellular signaling pathways. (3)

Embryo: In humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it is called a fetus. (4)

Embryonic stem cells: Primitive (undifferentiated) cells that are derived from preimplantation-stage embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. (5)

Human embryonic stem cell (hESC): A type of pluripotent stem cell derived from early-stage human embryos, up to and including the blastocyst stage, that is capable of dividing without differentiating for a prolonged period in culture, and is known to develop into cells and tissues of the three primary germ layers. (6)

Induced pluripotent stem cells (iPS) cell: A type of pluripotent stem cell, similar to an embryonic stem cell, formed by the introduction of certain embryonic genes into a somatic cell. (7)

Intellectual property (IP): Intangible property that is the result of creativity, such as patents, copyrights, etc. (8)

Investigational New Drug (IND): A new drug or biological drug that is used in a clinical investigation. (9)

Neurodegenerative disorder: A type of disease in which cells of the central nervous system stop working or die. Neurodegenerative disorders usually get worse over time and have no cure. They may be genetic or be caused by a tumor or stroke. Neurodegenerative disorders also occur in people who drink large amounts of alcohol or are exposed to certain viruses or toxins. (10)

Pluripotent: The state of a single cell that is capable of differentiating into all tissues of an organism, but not alone capable of sustaining full organismal development. (11)

Regenerative medicine: The process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. This can be done through a variety of approaches including the replacement of tissue function with synthetic constructs (artificial organs) and using cellular therapies such as stem cells or genetically modified cells to generate new tissues and organs. (12)

Request for Applications (RFAs): An RFA is a formal statement that solicits grant or cooperative agreement applications in a well-defined scientific area to accomplish specific program objectives. An RFA indicates the estimated amount of funds set aside for the competition, the estimated number of awards to be made, whether cost sharing is required, and the application submission date(s). (13)

Somatic cell: Any body cell other than gametes (egg or sperm); sometimes referred to as "adult" cells. (14)

Stem cells: Cells with the ability to divide for indefinite periods in culture and to give rise to specialized cells. (15)

Venture capital: Investment in a project in which there is a substantial element of risk, a new or expanding business. (16)

REFERENCES

(1) National Cancer Institute. 2012. *NCI dictionary of cancer terms*. http://www.cancer.gov/dictionary?cdrid=270732 (accessed August 23, 2012).

(2) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#blastocyst (accessed March 16, 2012).
(3) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#differentiation (accessed March 16, 2012).
(4) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#embryo (accessed March 16, 2012).
(5) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#embryonicsc (accessed March 16, 2012).
(6) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#hesc (accessed March 16, 2012).
(7) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#ips (accessed March 16, 2012).
(8) Oxford Dictionaries. 2012. *Intellectual property*. http://oxforddictionaries.com/definition/english/intellectual%2Bproperty (accessed August 23, 2012).
(9) National Institutes of Health. 2012. *Glossary & acronym list*. http://grants.nih.gov/grants/glossary.htm#I (accessed August 23, 2012).
(10) National Cancer Institute. 2012. *Dictionary of cancer terms*. http://www.cancer.gov/dictionary?cdrid=687218 (accessed March 16, 2012).
(11) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#pluripotent (accessed March 16, 2012).
(12) European Science Foundation. 2012. *Regenerative Medicine (REMEDIC)*. http://www.esf.org/nc/activities/research-networking-programmes/medical-sciences-emrc/current-esf-research-networking-programmes/regenerative-medicine-remedic.html (accessed November 15, 2012).
(13) National Institutes of Health. 2012. *Glossary & acronym list*. http://grants.nih.gov/grants/glossary.htm#R (accessed August 23, 2012)

(14) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#Somaticcell (accessed March 16, 2012).
(15) National Institutes of Health. 2011. *Resource for stem cell research: Glossary.* http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={3C35BAB6-0FE6-4C4E-95F2-2CB61B58D96D}&NRORIGINALURL=%2finfo%2fglossary.asp&NRCACHEHINT=NoModifyGuest#stemcells (accessed March 16, 2012).
(16) Oxford Dictionaries. 2012. *Venture capital*. http://oxforddictionaries.com/definition/english/venture%2Bcapital (accessed August 23, 2012).

Appendix A

Data Sources and Methods

The Committee on a Review of the California Institute for Regenerative Medicine (CIRM) was asked to assess CIRM's initial processes, programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies. To respond comprehensively to its charge, the committee examined data from a variety of sources. These sources included documents pertaining to the establishment and initial operation of CIRM and numerous evaluation reports commissioned during the Institute's initial 5- to 6-year period of operation. Valuable input also was obtained through CIRM's responses to the committee's data requests, three public meetings, two adjunct meetings, site visits to CIRM-funded research facilities, telephone interviews, and written public comments in response to online questionnaires targeting various stakeholders. The study was conducted over a 17-month period.

STUDY COMMITTEE

The study committee comprised 13 individuals with expertise in stem cell research, developmental biology, bioethics, research administration, financial structures for biomedical research, program evaluation, economics and finance, business administration, and intellectual property. Appendix E provides biographical sketches of the committee members. The committee convened for a total of 10 days on five different occasions in October 2011, January 2012, April 2012, June 2012, and August 2012.

DOCUMENT REVIEW

The committee reviewed background documents and evaluation reports pertaining to CIRM, including Proposition 71 and Senate Bill (SB) 1064; 2004 Economic Impact Analysis reports; the 2006 CIRM Scientific Strategic Plan; CIRM annual reports from 2007 through 2010; the 2008 Interim Economic Impact Review and addendum; the 2009 Strategic Plan Update; the 2009 Little Hoover Commission Review of CIRM; 2010 External Advisory Panel (EAP) evaluation reports; the 2011 CIRM publication on the economic impact of research funded by CIRM; and the 2012 CIRM transition plan. The committee also reviewed published reports on stem cell research.

DATA REQUESTS TO CIRM

The committee made a total of 79 requests for data, reports, and information from CIRM. These requests were on topics related to CIRM's initial processes and planning, grants and programs, grant management and resources, reviews and evaluations, governance and management, finances, collaborations, intellectual property policies, and conflict of interest policies.

PUBLIC MEETINGS

The committee hosted three public meetings to obtain additional information on specific aspects of the study charge. These meetings were held in conjunction with the committee's October (Washington, DC), January (San Francisco, California), and April (Irvine, California) meetings. The committee determined the topics and speakers for these public meetings. As part of the two public meetings in California, the committee held open forums at which members of the public were invited to provide testimony on any topics related to the study charge.

At the first public meeting, CIRM delivered the charge to the committee and provided a general overview of its structure and programs. At the second meeting, representatives from CIRM's leadership and governing board provided information on the Institute's scientific priorities and transition plan, standards working group, and intellectual property policies. In addition, CIRM principal investigators provided their perspectives on the Institute. The third public meeting included presentations from individuals with varying perspectives on CIRM—investigators who applied for but did not receive funding from the Institute, current Disease Team grantees, industry representatives, and a technology transfer officer. The agendas for the public meetings are presented in Boxes A-1 through A-3.

ADJUNCT MEETINGS

A subgroup of the committee hosted two meetings with stem cell scientists outside of California to obtain their perspectives on the work funded by CIRM and the Institute's scientific impact. Discussions centered on the scientists' view of CIRM's accomplishments and goals as articulated in the 2012 Strategic Plan. The first meeting was held May 30, 2012, in Toronto, Canada, and the second in Boston, Massachusetts, on June 26, 2012. These sites were selected as the committee considered them to be major hubs of activity in stem cell research. Scientists participating in these meeting are listed below.

Toronto

Mick Bhatia, Stem Cell and Cancer Research Institute, McMaster University (by phone)
James Ellis, Department of Molecular Genetics, University of Toronto
Andras Nagy, Samuel Lunenfeld Research Institute, Mount Sinai Hospital
Janet Rossant, Department of Medical Genetics and Microbiology, University of Toronto
Molly Shoichet, Department of Chemical Engineering and Applied Chemistry, University of Toronto (by phone)
William Stanford, Department of Cellular and Molecular Medicine, University of Ottawa
Peter Zandstra, Institute of Biomaterials and Biomedical Engineering, University of Toronto

Boston

Fernando Camargo, Stem Cell and Regenerative Biology, Harvard University
Konrad Hochedlinger, Stem Cell and Regenerative Biology, Harvard University
Jerome Ritz, Connell O'Reilly Cell Manipulation and Gene Transfer Laboratory, Dana-Farber Cancer Institute, Harvard Medical School
Anthony Rosenzweig, Beth Israel Deaconess Medical Center, Harvard Medical School
David Scadden, Stem Cell and Regenerative Biology, Harvard University
Ramesh Shivdasani, School of Medicine, and Dana-Farber Cancer Institute, Harvard Medical School
Les Silberstein, Joint Program in Transfusion Medicine, Harvard Medical School
Amy Wagers, Stem Cell and Regenerative Biology, Harvard University

Clifford Woolf, FM Kirby Neurobiology Center, Children's Hospital, Harvard Medical School
Leonard Zon, Stem Cell and Regenerative Biology, Harvard University

SITE VISITS

Individual members of the committee conducted three site visits to CIRM-funded research facilities to obtain information about stem cell programs funded by the Institute. The committee selected one private university, one medical school, and one public university to visit. In January 2012, committee members visited CIRM facilities at the University of California, Davis (UC Davis), the University of California, San Francisco (UCSF), and Stanford University. The visits included tours of the stem cell facilities and discussions with principal investigators about the CIRM-funded work being conducted at the institutions. Investigators and university leadership who participated in each site visit are listed below. In addition, in August 2012, the committee chair and vice chair visited Celgene, a biopharmaceutical company in Summit, New Jersey. The purpose of this visit was to help the committee better understand the process of discovery, development, and commercialization of products to treat disease.

UC Davis

Gerhard Bauer, Stem Cell Research Program, UC Davis Institute for Regenerative Cures (IRC)
Paul Knoepfler, Department of Cell Biology and Human Anatomy, School of Medicine
Kit Lam, Department of Biochemistry and Molecular Medicine, UC Davis Comprehensive Cancer Center
Claire Pomeroy, CEO, UC Davis Health System and Dean of School of Medicine
Mark Zern, Transplant Research Institute
Min Zhao, Department of Dermatology, School of Medicine

UCSF

Arturo Alvarez-Bullya, Department of Neurological Surgery, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research
Sam Hawgood, Dean of the UCSF School of Medicine and Vice Chancellor for Medical Affairs
Diana Laird, Department of Obstetrics, Gynecology and Reproductive Sciences, UCSF Medical Center
Daniel Lim, Department of Neurological Surgery, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research

Emmanuelle Passegue, Division of Hematology/Oncology, Department of Medicine, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research
Holger Willenbring, Department of Surgery, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research

Stanford University

Michael Longaker, Department of Surgery
Ravi Majeti, Division of Hematology, School of Medicine
Norma Neff, Research Technical Manager
Renee A. Reijo-Pera, Center for Human Embryonic Stem Cell Research and Education
Yuval Rinkevich, Institute for Stem Cell Biology and Regenerative Medicine
Chris Shay, Space and Renovations Project Management
Judy Shizuru, Department of Blood & Marrow Transplantation, School of Medicine
Irving Weissman, Department of Pathology, Institute for Stem Cell Biology and Regenerative Medicine, School of Medicine
Marius Wernig, Department of Pathology, Institute for Stem Cell Biology and Regenerative Medicine, School of Medicine
Joanna Wysocka, Department of Chemical and System Biology

INTERVIEWS

Committee members spoke with many individuals during the course of this study. These formal and informal conversations, which took place by phone between the committee's in-person meetings, were intended to gather information to inform the committee's deliberations and to clarify questions. The individuals who provided this information are listed below.

Cindy Bell, Genome Canada and former Director of Cancer Stem Cell Consortium
Alan Bernstein, former Executive Director, Global HIV Vaccine Enterprise
Genc Bülent, Bundesministerium für Bildung und Forschung (BMBF) (Federal Ministry of Education and Research), Germany
George Daley, Stem Cell Transplantation at the Children's Hospital
Kristen Doyle, Cancer Prevention and Research Institute of Texas
Bill Gimson, Cancer Prevention and Research Institute of Texas
Dan Gincel, Maryland Stem Cell Research Fund
Zach W. Hall, former president, CIRM
Marianne Horn, Connecticut Department of Public Health

Richard Klausner, The Column Group
Bob Klein, former board chair, CIRM
Bernard Lo, UCSF School of Medicine, CIRM Standards Working Group
Jeff Lomax, CIRM
Bert Lubin, Children's Hospital and Research Center Foundation
David Magnus, Stanford University School of Medicine
Ed Penhoet, Alta Partners, former vice chair of CIRM's Governing Board
Mahendra S. Rao, National Institutes of Health (NIH) Intramural Center for Regenerative Medicine
Beth Roxland, New York State Task Force on Life and the Law
Christopher Scott, Stanford University School of Medicine
Michael Stöcker, BMBF
Lawrence S. Sturman, New York State Stem Cell Science
Alan Trounson, CIRM

BOX A-1
Committee on a Review of the California Institute for Regenerative Medicine (CIRM)

The National Academies Keck Building
500 Fifth Street, NW
Washington, DC 20001
Room 110

AGENDA FOR PUBLIC SESSION
October 19, 2011

11:15 a.m. **WELCOME AND COMMITTEE INTRODUCTIONS**

Harold T. Shapiro, Ph.D.
OM Committee Chair

11:25 a.m. **OVERVIEW OF CIRM: INITIAL PROCESSES, FUNDING MODEL, ORGANIZATION, AND MANAGEMENT SYSTEMS**

Robert Klein II, J.D.
Chair Emeritus, CIRM Governing Board

ONLINE QUESTIONNAIRES

The committee used online questionnaires to obtain public input from a variety of stakeholders on topics related to the study charge. A total of seven questionnaires in different topic areas targeting different stakeholders were placed on the Institute of Medicine (IOM) website. These questionnaires were intended to help the committee understand perspectives of a variety of stakeholders on CIRM and its work. The questionnaires were constructed for CIRM Independent Citizens Oversight Committee (ICOC) members, leadership from CIRM-funded institutions, CIRM principal investigators, university technology transfer professionals, investigators who applied for but did not receive funding from CIRM, CIRM for-profit industry partners, CIRM international partners, and stakeholders and members of the general public. A summary of themes from the responses to the questionnaires can be found in Appendix B.

12:30 p.m.	**LUNCH**
1:15 p.m.	**OVERVIEW OF THE SCIENCE AND CIRM'S PROGRAMMATIC AND SCIENTIFIC SCOPE** *Ellen G. Feigal, M.D.* Senior Vice President, Research and Development, CIRM
2:00 p.m.	**INTELLECTUAL PROPERTY AND BUSINESS DEVELOPMENT** *Elona Baum, J.D.* General Counsel and Vice President, Business Development, CIRM
2:20 p.m.	**CHARGE TO THE COMMITTEE** *Jonathan Thomas, J.D., D.Phil.* Chair, CIRM Governing Board
2:35 p.m.	**QUESTIONS AND DISCUSSION OF STUDY CHARGE**
3:30 p.m.	**ADJOURN OPEN SESSION**

BOX A-2
Committee on a Review of the California Institute for Regenerative Medicine (CIRM)

South San Francisco Conference Center
255 South Airport Boulevard
South San Francisco, CA 94080

AGENDA FOR PUBLIC SESSION
January 24, 2012

9:00 a.m. **WELCOME AND COMMITTEE INTRODUCTIONS**

Harold T. Shapiro, Ph.D.
IOM Committee Chair

9:10 a.m. **EVOLVING SCIENTIFIC PRIORITIES AT CIRM**

Alan Trounson, Ph.D.
CIRM President

10:10 a.m. **OVERVIEW OF CIRM SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP**

Bernard Lo, M.D.
Standards Working Group Co-Chair

10:50 a.m. **BREAK**

11:00 a.m. **CIRM INTELLECTUAL PROPERTY POLICIES**

Duane J. Roth
CIRM Governing Board Vice Chair and Intellectual Property/Industry Subcommittee Member

11:40 a.m. **OVERVIEW OF CIRM TRANSITION PLAN**

Jonathan Thomas, J.D., D.Phil.
Chair, CIRM Governing Board

12:20 p.m. **LUNCH**

1:15 p.m. **PERSPECTIVES ON CIRM FROM THE PATIENT ADVOCACY COMMUNITY**

Jeff Sheehy
Co-Vice Chair of the Scientific and Medical Research Funding Working Group and CIRM Patient Advocate Board Member
Director of Communications
AIDS Research Institute
University of California, San Francisco

1:50 p.m. **PERSPECTIVES ON CIRM FROM PRINCIPAL INVESTIGATORS**

Irina Conboy, Ph.D.
Assistant Professor, Department of Bioengineering
University of California, Berkeley

John P. Murnane, Ph.D.
Professor, Department of Radiation Oncology
University of California, San Francisco

Howard Y. Chang, M.D., Ph.D.
Stanford University School of Medicine, Howard Hughes Medical Institute

Helen M. Blau, Ph.D.
Donald E. and Delia B. Baxter Professor
Director, Baxter Laboratory for Stem Cell Biology
Stanford University School of Medicine

Frederick J. Meyers, M.D., M.A.C.P. (by phone—invited)
Executive Associate Dean, University of California, Davis, School of Medicine

Alice F. Tarantal, Ph.D. (by phone)
Professor and Vice-Chair for Research, Department of Pediatrics
University of California, Davis, School of Medicine

3:15 p.m. **BREAK**

continued

BOX A-2 Continued

3:30 p.m.	**RECAP/DISCUSSION OF MORNING AND AFTERNOON PRESENTATIONS**
4:00 p.m.	**PUBLIC COMMENT**
	Individuals register for a slot and have 5 minutes for comments on any topic related to the study charge.
5:00 p.m.	**ADJOURN OPEN SESSION**

BOX A-3
Committee on a Review of the California Institute for Regenerative Medicine (CIRM)

Arnold and Mabel Beckman Center
of the National Academies of Sciences and Engineering
Huntington Room
100 Academy
Irvine, CA 92617

AGENDA FOR PUBLIC SESSION
April 10, 2012

9:00 a.m. **WELCOME AND COMMITTEE INTRODUCTIONS**

Harold T. Shapiro, Ph.D.
IOM Committee Chair

9:10 a.m. **OVERVIEW OF LITTLE HOOVER COMMISSION REPORT**

Stuart Drown (*by phone*)
Executive Director, Little Hoover Commission

10:00 a.m. **PERSPECTIVES ON CIRM FROM STAKEHOLDERS**

Ruth Holton-Hodson
California Deputy State Controller

Ken Taymor, J.D. (by phone)
Executive Director, Berkeley Center for Law, Business and Economy

John Simpson (*by phone*)
Director, Stem Cell Oversight and Accountability Project
Consumer Watchdog

Marcy Darnovsky, Ph.D. (by phone)
Associate Executive Director, Center for Genetics and Society

David Jensen
Publisher-Editor, *California Stem Cell Report*

continued

BOX A-3 Continued

11:30 a.m. **LUNCH**

12:00 p.m. **PERSPECTIVES FROM CIRM APPLICANTS**

Leonard H. Rome, Ph.D. (by phone)
Senior Associate Dean for Research and Professor of Biological Chemistry, David Geffen School of Medicine
University of California, Los Angeles

Xuejun H. Parsons, Ph.D.
Associate Professor of Regenerative Medicine and Scientific Director in Cardiovascular and Neural Regeneration
San Diego Regenerative Medicine Institute

12:45 p.m. **PERSPECTIVES ON CIRM FROM DISEASE TEAM INVESTIGATORS**

Donald Kohn, M.D.
Professor, Department of Microbiology, Immunology, and Molecular Genetics and Department of Pediatrics
University of California, Los Angeles

Larry Goldstein, Ph.D.
Professor, Department of Cellular and Molecular Medicine and Department of Neurosciences
University of California, San Diego School of Medicine

Dennis Clegg, Ph.D.
Professor, Molecular, Cellular, and Developmental Biology
University of California, Santa Barbara

Catriona Jamieson, M.D., Ph.D.
Associate Professor, Division of Hematology-Oncology
University of California, San Diego Moores Cancer Center

2:00 p.m. **PERSPECTIVES ON CIRM FROM INDUSTRY**

Gregory A. Bonfiglio, J.D., Panel Moderator
Managing Partner, Proteus Venture Partners

Michael D. West, Ph.D.
Chief Executive Officer, BioTime, Inc.

Allan Robins, Ph.D.
Acting Chief Executive Officer, Vice President and Chief Technical Officer, ViaCyte, Inc.

Gail K. Naughton, Ph.D.
CEO, Chairman of the Board, Histogen, Inc.

3:30 p.m. **BREAK**

3:45 p.m. **PERSPECTIVES ON CIRM FROM TECHNOLOGY TRANSFER OFFICERS**

Casie Kelly, Ph.D.
Technology Transfer Officer, Life Sciences, Office of Intellectual Property & Industry Sponsored Research
University of California, Los Angeles

4:30 p.m. **PUBLIC COMMENT**

Individuals register for a slot and have 5 minutes for comments on any topic related to the study charge.

5:30 p.m. **ADJOURN OPEN SESSION**

Appendix B

Summary of Questionnaires

As described in Appendix A, the committee solicited testimony in multiple forms from a variety stakeholders on topics related to the study charge. In addition to direct testimony given at three public meetings, the committee asked for comments through seven online questionnaires (see Boxes B-1 to B-7 for questionnaire items) from members of the Independent Citizens Oversight Committee (ICOC), the leadership of California Institute for Regenerative Medicine (CIRM)-funded institutions, principal investigators who were recipients of CIRM grants, investigators who applied for but did not receive CIRM funding, university technology transfer professionals, CIRM industry partners, CIRM international partners, and stakeholders and members of the general public.

Each questionnaire was posted on the committee's Institute of Medicine (IOM) project website. IOM staff contacted individuals and groups in each category by e-mail to provide information about the study, the purpose of the questionnaires, and links to each questionnaire. Only aggregated responses—without information identifying individual respondents—were presented to the committee and placed in the public access file for the project.

The questionnaire responses were used to inform the committee's deliberations. The results were not obtained through random sampling, but through targeting of specific audiences. The information obtained through these seven questionnaires was in no way determinative of or the sole basis for the committee's recommendations.

DESCRIPTION OF QUESTIONNAIRES

The committee received 220 responses in total, from 12 of 29 members of the ICOC, 8 of 18 invited individuals from the leadership of CIRM-funded institutions, 120 of 340 CIRM principal investigators, 30 investigators not funded by CIRM, 4 of 21 technology transfer professionals, 1 of 20 individuals representing CIRM industry partners, and 45 individuals from the general public. Although these comments helped inform the committee's deliberations, the committee recognizes that the response rate to the questionnaires was low and that the responses cannot be considered representative of the targeted groups.

The remainder of this appendix provides brief summaries and highlights of the thoughts, perspectives, and concerns articulated by various respondents on CIRM's organizational processes, its programmatic and scientific scope, its organizational and management systems, its funding model, and its intellectual property policies.

RESPONSES TO QUESTIONNAIRE FOR MEMBERS OF THE INDEPENDENT CITIZENS OVERSIGHT COMMITTEE

There is little question that members of the ICOC are proud of CIRM's overall record of accomplishment in establishing California as one of the key worldwide hubs of research in regenerative medicine. Moreover, given the complex nature of mobilizing an expert staff to allocate thoughtfully funds entrusted to them by the state, they believe CIRM has done a remarkable job in a very short period of time. Those board members responding to the questionnaire did have some concerns, which focused on the working relationship between the chair and the president, the size of the board (too large), and the challenge of meeting various state requirements that apply to all state agencies. Finally, for the most part, respondents thought the board operated effectively and focused on the right issues. As a group of respondents, they are aware of the transition challenges that lie ahead, including the potential expiration of state funds, the need to produce clinical outcomes, and the desire and need to work more effectively with industry. Most respondents believe that personal interests have not played a role in their work on the ICOC and that conflicts of interest have not affected the ICOC's effectiveness.

RESPONSES TO QUESTIONNAIRE FOR LEADERSHIP OF CIRM-FUNDED INSTITUTIONS

To gauge the impact of CIRM and CIRM funding on research institutions in California, the committee selected those institutions with the high-

est CIRM funding levels and invited the deans of seven medical schools, research deans at three universities lacking medical schools, research directors at two independent hospitals, and research directors at six independent research institutes to complete the questionnaire. Three respondents were members of the CIRM board, and all three felt they were able to balance their responsibilities as a board member with their institutional responsibilities. Respondents were unanimous in indicating that CIRM's intellectual property policies had not influenced their decision to pursue CIRM funding. The greatest diversity of responses was elicited by the question: "In what ways can CIRM be improved?" Two respondents alluded to the need for greater transparency, and two felt that a more clearly articulated strategic plan was needed. Two expressed concerns about CIRM staff turnover and other indications of administrative "dysfunction." One mentioned a need to involve clinicians earlier in the planning stages of research to "ascertain the realistic translational potential" of basic research projects.

Overall, based on a fairly limited set of responses, CIRM appears to have had a positive impact on research institutions in California, especially with respect to increased space for stem cell research, enhanced training opportunities, and retention of faculty. Responses suggest that the overall institutional impact of CIRM has been a function of success in obtaining CIRM funding. There have clearly been big "winners" in this competition, and those institutions are the ones for which CIRM funding has had the largest positive impact, including recruiting faculty from outside California and building entirely new buildings for stem cell research funded by a combination of CIRM facilities awards and private gifts.

RESPONSES TO QUESTIONNAIRE FOR PRINCIPAL INVESTIGATORS FUNDED BY CIRM

Most principal investigators who responded to the questionnaire felt that CIRM's priorities were clearly articulated, that the requests for applications (RFAs) were clear regarding the scope and purpose of the research, and that the pre-application review was helpful. Most also felt that the CIRM scientific staff were very helpful, although at times were somewhat inflexible regarding adaptation to emerging findings. Those principal investigators that were also funded by the National Institutes of Health (NIH) felt that overall, the CIRM process compared favorably. On the other hand, some expressed the sentiment that the grant management process could be more flexible and streamlined and that the pre-application process could be more transparent.

RESPONSES TO QUESTIONNAIRE FOR CALIFORNIA STEM CELL INVESTIGATORS WHO APPLIED FOR AND DID NOT RECEIVE FUNDING FROM CIRM

Principal investigators that were not successful in obtaining funding from CIRM were more critical of CIRM's processes. Even in this group, however, most respondents felt CIRM's priorities were clear, as were the RFAs. This group of unsuccessful applicants for CIRM funding was less sanguine about the fairness of the overall program and the responsiveness of the CIRM staff. Most of these respondents felt that the feedback from CIRM staff and/or reviewers was not helpful and said they were unaware of the appeal process.

RESPONSES TO QUESTIONNAIRE FOR TECHNOLOGY TRANSFER PROFESSIONALS

Given that there were only four responses to this questionnaire, the committee could not draw definitive inferences. All respondents considered themselves to be familiar with CIRM's intellectual property policies. Most offered unfavorable comments about these policies. They felt that the policies are adequate but confusing, seem overly burdensome to licensees, and in some cases are too aggressive.

Only one respondent felt that CIRM's intellectual property policies were similar to other such policies. Others felt that CIRM's policies are complex and "place more burdens on potential licensees." One respondent indicated that "implementation guidelines useful for instructing practice are virtually nonexistent. For example, CIRM requires an annual utilization report but does not cite a due date or what kinds of information such a report should contain."

Most respondents have received invention disclosures involving CIRM-funded research; the number of invention disclosures received varied from 4 to 35. These respondents had filed patent applications for CIRM-funded inventions, and the number of inventions they sought to patent or license ranged from 4 to 12. These respondents all felt that CIRM policies were more complex to administer than others. None are currently in licensing discussions concerning any such inventions.

Respondents made several suggestions for improving CIRM's intellectual property policies. They include reducing burdens on grant recipients and potential licensees; clarifying regulations and policy definitions; clarifying guidelines for implementation and for compliance; holding quarterly videoconferencing; networking to identify possible licensees; and modifying licensing sections, especially in drug pricing and royalty sharing with the state.

RESPONSES TO QUESTIONNAIRE FOR INDUSTRY PARTNERS

The committee received only one response to this questionnaire and did not believe it was appropriate to draw even very tentative inferences from that response.

RESPONSES TO QUESTIONNAIRE FOR THE GENERAL PUBLIC

The committee was eager to receive input from the California public and grateful to those that took advantage of the open questionnaire. However, the committee recognizes the difficulty of assessing this input given the small number of responses and with little knowledge of the backgrounds of the respondents themselves.

Most respondents to the public questionnaire felt that CIRM took a leadership role in establishing infrastructures for biomedical research, providing funding for a research area that lacked federal financial support, attracting and retaining distinguished stem cell scientists, creating important partnerships with many countries, promoting collaboration among researchers around the world, and stimulating similar programs in other states. Several made comments, however, about CIRM's having spent too much on infrastructure and basic research with no clinical outcomes/products. Some respondents felt the California taxpayers were "misled" and their money "wasted." There was some expression of concern that CIRM was providing insufficient support for work with human embryonic stem cells. There were many complaints about transparency.

Most respondents felt that information on CIRM's website was sufficient, useful, and up to date, and the monthly newsletter and e-mail updates were very helpful. Others felt that the materials were too scientific for the public to understand.

BOX B-1
Questionnaire for Members of the Independent Citizens Oversight Committee (ICOC)

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies.

To help the committee address its charge, it would like to obtain input from members of the Independent Citizens Oversight Committee (ICOC).

Question 1: What are CIRM's most significant accomplishments?
Question 2: What features of CIRM have contributed most to its successes?
Question 3: What features have been most challenging or have impeded accomplishments?
Question 4: What do you think are CIRM's greatest challenges and opportunities in the future?
Question 5: How well do the varying constituents of the ICOC work together?
Question 6: In what ways does the ICOC agree on the direction the organization should take? In what ways do they disagree?
Question 7: In what ways are you productively involved in strategic planning for CIRM?
Question 8: Are there elements of the strategic planning that you are not part of? Should you be?
Question 9: Do you find the work of the ICOC (including sub-committees, work groups, etc.) appropriate, and do ICOC members have appropriate input to board decisions?

Question 10: Are ICOC meetings focused on the right issues and do they make good use of time?

Question 11: Is the required time commitment as an ICOC member appropriate?

Question 12: Do you feel valued as an ICOC member? How has this been demonstrated (or not)?

Question 13: In what ways do the structure and composition of the ICOC impact its effectiveness?

Question 14: How effectively does the ICOC work with CIRM Board Chair and President? Are roles and responsibilities clearly defined?

Question 15: What is your perspective on the balance of responsibilities between the Chairperson and the President?

Question 16: What would you change to make the ICOC more effective?

Question 17: Do you believe that board members, in their work on the ICOC, are influenced by their personal or private interests, apart from and potentially different from the broader interests of the people of California as sponsors of CIRM? Please elaborate.

Question 18: Does conflict of interest affect the ICOC's effectiveness?

Question 19: What are the strengths of the ICOC organizational structure? Weaknesses?

Question 20: How does the structure, level of transparency, and oversight of the ICOC contribute to the effectiveness of CIRM (e.g., driving excellent science, achieving clinical outcomes, engaging the scientific community and other stakeholders, and improving California's status in the field)?

Question 21: Please feel free to share any further thoughts with us. You may also e-mail documents or other information to jxi@nas.edu.

BOX B-2
Questionnaire for Leadership of CIRM-funded Institutions

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies.

To help the committee address its charge, the leadership from institutions and organizations that receive funding from CIRM are invited to share their thoughts and concerns about CIRM.

Question 1: How has CIRM funding affected your ability to increase space for stem cell research?

Question 2: How has CIRM funding enabled you to recruit new faculty from outside California?

Question 3: How has CIRM funding enabled you to retain faculty who might otherwise be recruited outside California, including both senior faculty and trainees who have joined your faculty?

Question 4: How has CIRM funding provided new training opportunities for students; postdoctoral fellows?

Question 5: How has CIRM funding affected your ability to raise philanthropic funds?

Question 6: How has CIRM funding affected your faculty's ability to obtain National Institutes of Health grant funding?

Question 7: Given that CIRM funding likely provides lower indirect costs than National Institutes of Health funding, what effect has this had on overall financial status of the research enterprise?

Question 8: What has been the effect of CIRM funding on setting research directions and priorities?

Question 9: If you are a member of the CIRM Board, how have you balanced your responsibilities as a member of the board with your responsibilities as a leader of your own institution?

Question 10: In what ways can CIRM be improved?

Question 11: Have CIRM intellectual property policies influenced your decision to pursue CIRM funding?

Question 12: What type of organization do you represent (e.g., medical school, research institute, hospital, university without a medical school)?

Question 13: If you have additional thoughts about how CIRM can improve its programs and initiatives to meet its scientific goals or would like to share information related to the committee's work, please use the space provided below to do so. You may also e-mail documents or articles to support your testimony to jxi@nas.edu.

BOX B-3
Questionnaire for CIRM Principal Investigators

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies.

To help the committee address its charge, investigators who receive funding from CIRM are invited to share their thoughts and concerns about CIRM.

Question 1: Are CIRM funding priorities clearly articulated?

Question 2: Are CIRM-initiated requests for applications clear regarding scope and purpose of the research for which they were requesting proposals?

Question 3: Was the pre-application and proposal review process helpful and fair?

Question 4: Was CIRM program staff accessible, responsive, and helpful once a grant was awarded?

Question 5: Was CIRM willing to allow appropriate modification of research aims and budget allocations when results [in your lab or elsewhere] indicated some change in direction was advisable?

Question 6: How does the CIRM proposal and grants management process compare to other agencies such as the National Institutes of Health? Is it more or less efficient or about the same?

Question 7: In what ways can CIRM be improved?

Question 8: If you have additional thoughts about how CIRM can improve its programs and initiatives to meet its scientific goals or would like to share information related to the committee's work, please use the space provided below to do so. You may also e-mail documents or articles to support your testimony to jxi@nas.edu.

BOX B-4
Questionnaire for California Stem Cell Investigators Who Applied for and Did Not Receive Funding from CIRM

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies.

To help the committee address its charge, investigators who applied for but did not receive funding from CIRM are invited to share their thoughts about CIRM.

Question 1: Are CIRM funding priorities clearly articulated?

Question 2: Are CIRM-initiated requests for applications clear regarding scope and purpose of the research for which CIRM was requesting proposals?

Question 3: Was the pre-application and proposal review process helpful and fair?

Question 4: Was CIRM program staff accessible, responsive, and helpful in providing feedback regarding the specific aims of the RFA prior to submission?

Question 5: Were reviewer critiques helpful in revising proposals for a second submission? Was CIRM program staff accessible, responsive, and helpful in providing additional feedback that helped to understand the critiques?

Question 6: Is it possible to appeal a funding decision? If so, was the process for appeal clearly defined and did it appear to be a fair process?

Question 7: How does the CIRM proposal process compare to other agencies such as the National Institutes of Health? Is it more or less efficient or about the same?

Question 8: In what ways can the CIRM-initiated RFA proposal process be improved?

Question 9: If you have additional thoughts about how CIRM can improve its programs and initiatives to meet its scientific goals or would like to share information related to the committee's work, please use the space provided below to do so. You may also e-mail documents or articles to support your testimony to jxi@nas.edu.

BOX B-5
Questionnaire for the General Public

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. In 2005, CIRM was created and began its operations following the 2004 adoption of Proposition 71 (the California Stem Cell Research and Cures Act). Proposition 71 charged CIRM with determining the most effective means of distributing $3 billion in state funds over at least 10 years in order to accelerate the science of regenerative medicine and its translation into health and economic benefits for the State of California.

The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies. To help the committee address its charge, members of the public are invited to share their thoughts, perspectives and/or concerns about CIRM.

Question 1: Please share your opinion about the continued importance of stem cell research and the role of CIRM's work/contribution in this area.

Question 2: What particular or specific impact has CIRM had on the biomedical research community both in California and elsewhere since its inception in 2005?

Question 3: If you are an individual or know an individual with a chronic, debilitating disease what do you see as potentially the biggest benefit you or they might receive from CIRM's work?

Question 4: Do you think CIRM has provided to the public transparent, up-to-date, and sufficient information about its organization and activities? Do you find the information helpful?

Question 5: How should information about CIRM's organization, activities, and programs be shared with the public?

Question 6: What is your opinion about CIRM's portfolio of projects and its grant programs? Do you think it is necessary that CIRM meet its scientific goal of developing stem cell and related research for the diagnosis, prevention and treatment of disease and injury within its initial timeline of 10 years?

Question 7: If you have additional thoughts about how CIRM can improve its programs and initiatives to meet its scientific goals or would like to share information related to the committee's work, please use the space provided below to do so. You may also e-mail documents or articles to support your testimony to jxi@nas.edu.

BOX B-6
Questionnaire for Technology Transfer Professionals

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies.

To help the committee address its charge, the committee has a very particular interest in how technology transfer professionals at institutions that perform CIRM-funded research assess CIRM's intellectual property policies.

Question 1: Are you familiar with the intellectual property (IP) policies of CIRM? If so, please complete the remaining questions.
Question 2: Overall what do you think of the CIRM IP policies?
Question 3: Do CIRM's IP policies differ in important respects from those of other sponsors of research? If so, please explain.
Question 4: Compared to other sponsors of research, does CIRM provide adequate support for the technology transfer activities of its grantees?
Question 5: Has your office received any invention disclosures involving CIRM-funded research in your institution?
Question 6: How many such disclosures has your office received?
Question 7: Have you filed patent applications or sought to license IP rights for any CIRM-funded inventions?
Question 8: How many CIRM-funded inventions have you sought to patent and/or license?
Question 9: Are you currently in licensing discussion concerning any such inventions?
Question 10: Have the CIRM IP policies played a significant role in considerations of how your office will handle inventions arising from CIRM-funded research?
Question 11: To your knowledge, have the CIRM IP policies had any impact on your ability to find licensees for CIRM-funded inventions?
Question 12: How in your view could CIRM IP policies be enhanced or improved?
Question 13: Please feel free to share any further thoughts you might have on IP policies and technology transfer related to CIRM-funded research. You may also e-mail documents or other information to jxi@nas.edu.

BOX B-7
Questionnaire for CIRM Industry Partners

The California Institute for Regenerative Medicine (CIRM) has asked the Institute of Medicine (IOM) to provide an independent assessment of CIRM's programs, operations, and performance. The IOM Committee on a Review of the California Institute for Regenerative Medicine will assess the organization's initial processes, its programmatic and scientific scope, organizational and management systems, funding model, and intellectual property policies.

To help the committee address its charge, entities in current partnership with CIRM are invited to share their thoughts and concerns about CIRM.

Question 1: What is the nature of your partnership(s) with CIRM? How/why was the partnership initiated? Who initiated it? If the partnership involves collaborating with academic scientists in California, how critical was CIRM to forming the partnership?

Question 2: Was the process of assembling the partnership easy to arrange relative to other partnerships in which you have participated?

Question 3: How critical is the research being conducted to your business? Does the partnership fill a gap in funding unmet by other sources?

Question 4: What, if anything, is unique about partnering with CIRM?

Question 5: Are you satisfied with the ongoing management of the partnership? How could management be improved?

Question 6: Would you expect your partnerships with CIRM to grow, remain at current levels or decline?

Question 7: Have the intellectual property (IP) and revenue sharing policies and the Consumer Access requirements of CIRM been a significant consideration in entering into partnership with CIRM? What do you think of those policies? Have you licensed CIRM-funded IP? Are you in discussions to license IP arising from your partnership with CIRM or other CIRM-funded research?

Question 8: How could existing CIRM programs and processes be enhanced or improved?

Question 9: Have CIRM funding and projects enhanced the biotech industry in California? How could CIRM engage/support industry better?

Question 10: If you have additional thoughts about how CIRM can improve its programs and initiatives to meet its scientific goals or would like to share information related to the committee's work, please use the space provided below to do so. You may also e-mail documents or articles to support your testimony to jxi@nas.edu.

Appendix C

Proposition 71

Proposition 71

This initiative measure is submitted to the people in accordance with the provisions of Section 8 of Article II of the California Constitution.

This initiative measure expressly amends the California Constitution by adding an article thereto; and amends a section of the Government Code, and adds sections to the Health and Safety Code; therefore, new provisions proposed to be added are printed in *italic type* to indicate that they are new.

PROPOSED LAW

CALIFORNIA STEM CELL RESEARCH AND CURES INITIATIVE

SECTION 1. Title

This measure shall be known as the "California Stem Cell Research and Cures Act."

SEC. 2. Findings and Declarations

The people of California find and declare the following:

Millions of children and adults suffer from devastating diseases or injuries that are currently incurable, including cancer, diabetes, heart disease, Alzheimer's, Parkinson's, spinal cord injuries, blindness, Lou Gehrig's disease, HIV/AIDS, mental health disorders, multiple sclerosis, Huntington's disease, and more than 70 other diseases and injuries.

Recently medical science has discovered a new way to attack chronic diseases and injuries. The cure and treatment of these diseases can potentially be accomplished through the use of new regenerative medical therapies including a special type of human cells, called stem cells. These life-saving medical breakthroughs can only happen if adequate funding is made available to advance stem cell research, develop therapies, and conduct clinical trials.

About half of California's families have a child or adult who has suffered or will suffer from a serious, often critical or terminal, medical condition that could potentially be treated or cured with stem cell therapies. In these cases of chronic illness or when patients face a medical crisis, the health care system may simply not be able to meet the needs of patients or control spiraling costs, unless therapy focus switches away from maintenance and toward prevention and cures.

Unfortunately, the federal government is not providing adequate funding necessary for the urgent research and facilities needed to develop stem cell therapies to treat and cure diseases and serious injuries. This critical funding gap currently prevents the rapid advancement of research that could benefit millions of Californians.

The California Stem Cell Research and Cures Act will close this funding gap by establishing an institute which will issue bonds to support stem cell research, emphasizing pluripotent stem cell and progenitor cell research and other vital medical technologies, for the development of life-saving regenerative medical treatments and cures.

SEC. 3. Purpose and Intent

It is the intent of the people of California in enacting this measure to:

Authorize an average of $295 million per year in bonds over a 10-year period to fund stem cell research and dedicated facilities for scientists at California's universities and other advanced medical research facilities throughout the state.

Maximize the use of research funds by giving priority to stem cell research that has the greatest potential for therapies and cures, specifically focused on pluripotent stem cell and progenitor cell research among other vital research opportunities that cannot, or are unlikely to, receive timely or sufficient federal funding, unencumbered by limitations that would impede the research. Research shall be subject to accepted patient disclosure and patient consent standards.

Assure that the research is conducted safely and ethically by including provisions to require compliance with standards based on national models that protect patient safety, patient rights, and patient privacy.

Prohibit the use of bond proceeds of this initiative for funding for human reproductive cloning.

Improve the California health care system and reduce the long-term health care cost burden on California through the development of therapies that treat diseases and injuries with the ultimate goal to cure them.

Require strict fiscal and public accountability through mandatory independent audits, open meetings, public hearings. and annual reports to the public. Create an Independent Citizen's Oversight Committee composed of representatives of the University of California campuses with medical schools; other California universities and California medical research institutions; California disease advocacy groups; and California experts in the development of medical therapies.

Protect and benefit the California budget: by postponing general fund payments on the bonds for the first five years; by funding scientific and medical research that will significantly reduce state health care costs in the future; and by providing an opportunity for the state to benefit from royalties, patents, and licensing fees that result from the research.

Benefit the California economy by creating projects, jobs, and therapies that will generate millions of dollars in new tax revenues in our state.

Advance the biotech industry in California to world leadership, as an economic engine for California's future.

SEC. 4. Article XXXV is added to the California Constitution, to read:

Article XXXV. Medical Research

SECTION 1. There is hereby established the California Institute for Regenerative Medicine.

SEC. 2. The Institute shall have the following purposes:

(a) To make grants and loans for stem cell research, for research facilities, and for other vital research opportunities to realize therapies, protocols, and/or medical procedures that will result in, as speedily as possible, the cure for, and/or substantial mitigation of, major diseases, injuries, and orphan diseases.

(b) To support all stages of the process of developing cures, from laboratory research through successful clinical trials.

(c) To establish the appropriate regulatory standards and oversight bodies for research and facilities development.

SEC. 3. No funds authorized for, or made available to, the institute shall be used for research involving human reproductive cloning.

SEC. 4. Funds authorized for, or made available to, the institute shall be continuously appropriate without regard to fiscal year, be available and used only for the purposes provided in this article, and shall not be subject to appropriation or transfer by the Legislature of the Governor for any other purpose.

SEC. 5. There is herby established a right to conduct stem cell research which includes research involving adult stem cells, cord blood stem cells, pluripotent stem cells, and/or progenitor stem cells. Pluripotent stem cells are cells that are capable of self-renewal, and have broad potential to differentiate into multiple adult cell types. Pluripotent stem cells may be derived from somatic cell nuclear transfer or from surplus products of in vitro fertilization treatment when such products are donated under appropriate informed consent procedures. Progenitor cells are multipotent or precursor cells that are partially differentiated, but retain the ability to divide and give rise to differentiated cells.

SEC. 6. Notwithstanding any other provision of this Constitution or any law, the institute, which is established in state government, may utilize state issues tax-exempt and taxable bonds to fund its operations, medical and scientific research, including therapy development through clinical trials, and facilities.

SEC. 7. Notwithstanding any other provision of this Constitution, including Article VII, or any law, the institute and its employees are exempt from civil service.

SEC. 5. Chapter 3 (commencing with Section 125290.10) is added to Part 5 of Division 106 of the Health and Safety Code, to read:

CHAPTER 3. CALIFORNIA STEM CELL RESEARCH AND CURES BOND ACT

Article 1. California Stem Cell Research and Cures Act

125290.10. General—Independent Citizen's Oversight Committee (ICOC)

This chapter implements Article XXXV of the California Constitution, which established the California Institute for Regenerative Medicine (institute).

125290.15. Creation of the ICOC

There is hereby created the Independent Citizen's Oversight Committee, hereinafter, the ICOC, which shall govern the institute and is herby vested with full power, authority, and jurisdiction over the institute.

125290.20. ICOC Membership; Appointment; Terms of Office

(a) ICOC Membership

The ICOC shall have 29 members, appointed as follows:

(1) The Chancellors of the University of California at San Francisco, Davis, San Diego, Los Angeles, and Irvine, shall each appoint an executive officer from his or her campus.

(2) The Governor, the Lieutenant Governor, the Treasurer, and the Controller shall each appoint an executive officer from the following three categories:

(A) A California university, excluding the five campuses of the University of California described in paragraph (1), that has demonstrated success and leadership in stem cell research, and that has:

(i) A nationally ranked research hospital and medical school; this criteria will apply to only two of the four appointments.

(ii) A recent proven history of administering scientific and/or medical research grants and contracts in an average annual range exceeding one hundred million dollars ($100,000,000).

(iii) A ranking, within the past five years, in the top 10 United States universities with the highest number of life science patents or that has research or clinical faculty who are members of the National Academy of Sciences.

(B) A California nonprofit academic and research institution that is not a part of the University of California, that has demonstrated success and leadership in stem cell research, and that has:

(i) A nationally ranked research hospital or that has research or clinical faculty who are members of the National Academy of Sciences.

(ii) A proven history in the last five years of managing a research budget in the life sciences exceeding twenty million dollars ($20,000,000).

(C) A California life science commercial entity that is not actively engaged in researching or developing therapies with pluripotent or progenitor stem cells, that has a background in implementing successful experimental medical therapies, and that has not been awarded, or applied for, funding by the institute at the time of appointment. A board member of that entity with a successful history of developing innovative medical therapies may be appointed in lieu of an executive officer.

(D) Only one member shall be appointed from a single university, institution, or entity. The executive officer of a California university, a nonprofit research institution or life science commercial entity who is appointed as a member, may from time to time delegate those duties to an executive officer of the entity or to the dean of the medical school, if applicable.

(3) The Governor, the Lieutenant Governor, the Treasurer, and the Controller shall appoint members from among California representatives of California regional, state, or national disease advocacy groups, as follows:

(A) The Governor shall appoint two members, one from each of the following disease advocacy groups: spinal cord injury and Alzheimer's disease.

(B) The Lieutenant Governor shall appoint two members, one from each of the following disease advocacy groups: type II diabetes and multiple sclerosis or amyotrophic lateral sclerosis.

(C) The Treasurer shall appoint two members, one from each of the following disease groups: type I diabetes and heart disease.

(D) The Controller shall appoint two members, one from each of the following disease groups: cancer and Parkinson's disease.

(4) The Speaker of the Assembly shall appoint a member from among California representatives of a California regional, state, or national mental health disease advocacy group.

(5) The President pro Tempore of the Senate shall appoint a member from among California representatives of a California regional, state, or national HIV/AIDS disease advocacy group.

(6) A chairperson and vice chairperson who shall be elected by the ICOC members. Within 40 days of the effective date of this act, each constitutional officer shall nominate a candidate for chairperson and another candidate for vice chairperson. The chairperson and vice chairperson shall each be elected for a term of six years. The chairperson and vice chairperson of ICOC shall be full or part time employees of the institute and shall meet the following criteria:

(A) Mandatory Chairperson Criteria

(i) Documented history in successful stem cell research advocacy.

(ii) Experience with state and federal legislative processes that must include some experience with medical legislative approvals of standards and/or funding.

(iii) Qualified for appointment pursuant to paragraph (3), (4), or (5) of subdivision (a).

(iv) Cannot be concurrently employed by or on leave from any prospective grant or loan recipient institutions in California.

(B) Additional Criteria for Consideration:

(i) Experience with governmental agencies or institutions (either executive or board position).

(ii) Experience with the process of establishing government standards and procedures.

(iii) Legal experience with the legal review of proper governmental authority for the exercise of government agency or government institutional powers.

(iv) Direct knowledge and experience in bond financing.

The vice chairperson shall satisfy clauses (i), (iii), and (iv) of subparagraph (A). The vice chairperson shall be selected from among individuals who have attributes and experience complementary to those of the chairperson, preferably covering the criteria not represented by the chairperson's credentials and experience.

(b) Appointment of ICOC Members

(1) All appointments shall be made within 40 days of the effective date of this act. In the event that any of the appointments are not completed within the permitted timeframe, the ICOC shall proceed to operate with the appointments that are in place, provided that at least 60 percent of the appointments have been made.

(2) Forty-five days after the effective date of the measure adding this chapter, the State Controller and the Treasurer, or if only one is available within 45 days, the other shall convene a meeting of the appointed members of the ICOC to elect a chairperson and vice chairperson from among the individuals nominated by the constitutional officers pursuant to paragraph (6) of subdivision (a).

(c) ICOC Member Terms of Office

(1) The members appointed pursuant to paragraphs (1), (3), (4), and (5) of subdivision (a) shall serve eight-year terms, and all other members shall serve six-year terms. Members shall serve a maximum of two terms.

(2) If a vacancy occurs within a term, the appointing authority shall appoint a replacement member within 30 days to serve the remainder of the term.

(3) When a term expires, the appointing authority shall appoint a member within 30 days. ICOC members shall continue to serve until their replacements are appointed.

125290.25. Majority Vote of Quorum

Actions of the ICOC may be taken only by a majority vote of a quorum of the ICOC.

125290.30. Public and Financial Accountability Standards

(a) Annual Public Report

The institute shall issue an annual report to the public which sets forth its activities, grants awarded, grants in progress, research accomplishments, and future program directions. Each annual report shall include, but not be limited to, the following: the number and dollar amounts of research and facilities grants; the grantees for the prior year; the institute's administrative expenses; an assessment of the availability of funding for stem cell research from sources other than the institute; a summary of research findings, including promising new research areas; an assessment of the relationship between the institute's grants and the overall strategy of its research program; and a report of the institute's strategic research and financial plans.

(b) Independent Financial Audit for Review by State Controller

The institute shall annually commission an independent financial audit of its activities from a certified public accounting firm, which shall be provided to the State Controller, who shall review the audit and annually issue a public report of that review.

(c) Citizen's Financial Accountability Oversight Committee

There shall be a Citizen's Financial Accountability Oversight Committee chaired by the State Controller. This committee shall review the annual financial audit, the State Controller's report and evaluation of that audit, and the financial practices of the institute. The State Controller, the State Treasurer, the President pro Tempore of the Senate, the Speaker of the Assembly, and the Chairperson of the ICOC shall each appoint a public member of the committee. Committee members shall have medical backgrounds and knowledge of relevant financial matters. The committee shall provide recommendations on the institute's financial practices and performance. The State Controller shall provide staff support. The committee shall hold a public meeting, with appropriate notice, and with a formal public comment period. The committee shall evaluate public comments and include appropriate summaries in its annual report. The ICOC shall provide funds for the per diem expenses of the committee members and for publication of the annual report.

(d) Public Meeting Laws

(1) The ICOC shall hold at least two public meetings per year, one of which will be designated as the institute's annual meeting. The ICOC may hold additional meetings as it determines are necessary or appropriate.

(2) The Bagley-Keene Open Meeting Act, Article 9 (commencing with Section 11120) of Chapter 1 of Part 1 of Division 3 of Title 2 of the Government Code, shall apply to all meetings of the ICOC, except as otherwise provided in this section. The ICOC shall award all grants, loans, and contracts in public meetings and shall adopt all governance, scientific, medical, and regulatory standards in public meetings.

(3) The ICOC may conduct closed sessions as permitted by the Bagley-Keene Open Meeting Act, under Section 11126 of the Government Code. In addition, the ICOC may conduct closed sessions when it meets to consider or discuss:

(A) Matters involving information relating to patients or medical subjects, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(B) Matters involving confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user an opportunity to obtain a business advantage over competitors who do not know it or use it.

(C) Matters involving prepublication, confidential scientific research or data.

(D) Matters concerning the appointment, employment, performance, compensation, or dismissal of institute officers and employees. Action on compensation of the institute's officers and employees shall only be taken in open session.

(4) The meeting required by paragraph (2) of subdivision (b) of Section 125290.20 shall be deemed to be a special meeting for the purposes of Section 11125.4 of the Government Code.

(e) Public Records

(1) The California Public Records Act, Article 1 (commencing with Section 6250) of Chapter 3.5 of Division 7 of Title 1 of the Government Code, shall apply to all records of the institute, except as otherwise provided in this section.

(2) Nothing in this section shall be construed to require disclosure of any records that are any of the following:

(A) Personnel, medical, or similar files, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(B) Records containing or reflecting confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user an opportunity to obtain a business advantage over competitors who do not know it or use it.

(C) Prepublication scientific working papers or research data.

(f) Competitive Bidding

(1) The institute shall, except as otherwise provided in this section, be governed by the competitive bidding requirements applicable to the University of California, as set forth in Article 1 (commencing with Section 10500) of Chapter 2.1 of Part 2 of Division 2 of the Public Contract Code.

(2) For all institute contracts, the ICOC shall follow the procedures required of the Regents by Article 1 (commencing with Section 10500) of Chapter 2.1 of Part 2 of Division 2 of the Public Contract Code with respect to contracts let by the University of California.

(3) The requirements of this section shall not be applicable to grants or loans approved by the ICOC.

(4) Except as provided in this section, the Public Contract Code shall not apply to contracts let by the institute.

(g) Conflicts of Interest

(1) The Political Reform Act, Title 9 (commencing with Section 81000) of the Government Code, shall apply to the institute and to the ICOC, except as provided in this section and in subdivision (e) of Section 125290.50.

(A) No member of the ICOC shall make, participate in making, or in any way attempt to use his or her official position to influence a decision to approve or award a grant, loan, or contract to his or

her employer, but a member may participate in a decision to approve or award a grant, loan, or contract to a nonprofit entity in the same field as his or her employer.

(B) A member of the ICOC may participate in a decision to approve or award a grant, loan, or contract to an entity for the purpose of research involving a disease from which a member or his or her immediate family suffers or in which the member has an interest as a representative of a disease advocacy organization.

(C) The adoption of standards is not a decision subject to this section.

(2) Service as a member of the ICOC by a member of the faculty or administration of any system of the University of California shall not, by itself, be deemed to be inconsistent, incompatible, in conflict with, or inimical to the duties of the ICOC member as a member of the faculty or administration of any system of the University of California and shall not result in the automatic vacation of either such office. Service as a member of the ICOC by a representative or employee of a disease advocacy organization, a nonprofit academic and research institution, or a life science commercial entity shall not be deemed to be inconsistent, incompatible, in conflict with, or inimical to the duties of the ICOC member as a representative or employee of that organization, institution, or entity.

(3) Section 1090 of the Government Code shall not apply to any grant, loan, or contract made by the ICOC except where both of the following conditions are met:

(A) The grant, loan, or contract directly relates to services to be provided by any member of the ICOC or the entity the member represents or financially benefits the member or the entity he or she represents.

(B) The member fails to recuse himself or herself from making, participating in making, or in any way attempting to use his or her official position to influence a decision on the grant loan or contract.

(h) Patent Royalties and License Revenues Paid to the State of California

The ICOC shall establish standards that require that all grants and loan awards be subject to intellectual property agreements that balance the opportunity of the State of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements.

(i) Preference for California Suppliers

The ICOC shall establish standards to ensure that grantees purchase goods and services from California suppliers to the extent reasonably possible, in a good faith effort to achieve a goal of more than 50 percent of such purchases from California suppliers.

125290.35. Medical and Scientific Accountability Standards

(a) Medical Standards

In order to avoid duplication or conflicts in technical standards for scientific and medical research, with alternative state programs, the institute will develop its own scientific and medical standards to carry out the specific controls and intent of the act, notwithstanding subdivision (b) of Section 125300, Sections 125320, 125118, 125118.5, 125119, 125119.3 and 125119.5, or any other current or future state laws or regulations dealing with the study and research of pluripotent stem cells and/or progenitor cells, or other vital research opportunities, except Section 125315. The ICOC, its working committees, and its grantees shall be governed solely by the provisions of this act in the establishment of standards, the award of grants, and the conduct of grants awarded pursuant to this act.

(b) The ICOC shall establish standards as follows:

(1) Informed Consent

Standards for obtaining the informed consent of research donors, patients, or participants, which initially shall be generally based on the standards in place on January 1, 2003, for all research funded by the National Institutes of Health, with modifications to adapt to the mission and objectives of the institute.

(2) Controls on Research Involving Humans

Standards for the review of research involving human subjects which initially shall be generally based on the Institutional Review Board standards promulgated by the National Institutes of Health and in effect on January 1, 2003, with modifications to adapt to the mission and objectives of the institute.

(3) Prohibition on Compensation

Standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses.

(4) Patient Privacy Laws

Standards to assure compliance with state and federal patient privacy laws.

(5) Limitations on Payments for Cells

Standards limiting payments for the purchase of stem cells or stem cell lines to reasonable payment for the removal, processing, disposal, preservation, quality control, storage, transplantation, or implantation or legal transaction or other administrative costs associated with these medical procedures and specifically including any required payments for medical or scientific technologies, products, or processes for royalties, patent, or licensing fees or other costs for intellectual property.

(6) Time Limits for Obtaining Cells

Standards setting a limit on the time during which cells may be extracted from blastocysts, which shall initially be 8 to 12 days after cell division begins, not counting any time during which the blastocysts and/or cells have been stored frozen.

125290.40. ICOC Functions

The ICOC shall perform the following functions:

(a) Oversee the operations of the institute.

(b) Develop annual and long-term strategic research and financial plans for the institute.

(c) Make final decisions on research standards and grant awards in California.

(d) Ensure the completion of an annual financial audit of the institute's operations.

(e) Issue public reports on the activities of the institute.

(f) Establish policies regarding intellectual property rights arising from research funded by the institute.

(g) Establish rules and guidelines for the operation of the ICOC and its working groups.

(h) Perform all other acts necessary or appropriate in the exercise of its power, authority, and jurisdiction over the institute.

(i) Select members of the working groups.

(j) Adopt, amend, and rescind rules and regulations to carry out the purposes and provisions of this chapter, and to govern the procedures of the ICOC. Except as provided in subdivision (k), these rules and regulations shall be adopted in accordance with the Administrative Procedure Act (Government Code, Title 2, Division 3, Part 1, Chapter 4.5, Sections 11371 et seq.).

(k) Notwithstanding the Administrative Procedure Act (APA), and in order to facilitate the immediate commencement of research covered by this chapter, the ICOC may adopt interim regulations without compliance with the procedures set forth in the APA. The interim regulations shall remain in effect for 270 days unless earlier superseded by regulations adopted pursuant to the APA.

(l) Request the issuance of bonds from the California Stem Cell Research and Cures Finance Committee and loans from the Pooled Money Investment Board.

(m) May annually modify its funding and finance programs to optimize the institute's ability to achieve the objective that its activities be revenue-positive for the State of California during its first five years of operation without jeopardizing the progress of its core medical and scientific research program.

(n) Notwithstanding Section 11005 of the Government Code, accept additional revenue and real and personal property, including, but not limited to, gifts, royalties, interest, and appropriations that may be used to supplement annual research grant funding and the operations of the institute.

125290.45. ICOC Operations

(a) Legal Actions and Liability

(1) The institute may sue and be sued.

(2) Based upon ICOC standards, institute grantees shall indemnify or insure and hold the institute harmless against any and all losses, claims, damages, expenses, or liabilities, including attorneys' fees, arising from research conducted by the grantee pursuant to the grant, and/or, in the alternative, grantees shall name the institute as an additional insured and submit proof of such insurance.

(3) Given the scientific, medical, and technical nature of the issues facing the ICOC, and notwithstanding Section 11042 of the Government Code, the institute is authorized to retain outside counsel when the ICOC determines that the institute requires specialized services not provided by the Attorney General's office.

(4) The institute may enter into any contracts or obligations which are authorized or permitted by law.

(b) Personnel

(1) The ICOC shall from time to time determine the total number of authorized employees for the institute, up to a maximum of 50 employees,

excluding members of the working groups, who shall not be considered institute employees. The ICOC shall select a chairperson, vice chairperson and president who shall exercise all of the powers delegated to them by the ICOC. The following functions apply to the chairperson, vice chairperson, and president:

(A) The chairperson's primary responsibilities are to manage the ICOC agenda and work flow including all evaluations and approvals of scientific and medical working group grants, loans, facilities, and standards evaluations, and to supervise all annual reports and public accountability requirements; to manage and optimize the institute's bond financing plans and funding cash flow plan; to interface with the California Legislature, the United States Congress, the California health care system, and the California public; to optimize all financial leverage opportunities for the institute; and to lead negotiations for intellectual property agreements, policies, and contract terms. The chairperson shall also serve as a member of the Scientific and Medical Accountability Standards Working Group and the Scientific and Medical Research Facilities Working Group and as an ex-officio member of the Scientific and Medical Research Funding Working Group. The vice chairperson's primary responsibilities are to support the chairperson in all duties and to carry out those duties in the chairperson's absence.

(B) The president's primary responsibilities are to serve as the chief executive of the institute; to recruit the highest scientific and medical talent in the United States to serve the institute on its working groups; to serve the institute on its working groups; to direct ICOC staff and participate in the process of supporting all working group requirements to develop recommendations on grants, loans, facilities, and standards as well as to direct and support the ICOC process of evaluating and acting on those recommendations, the implementation of all decisions on these and general matters of the ICOC; to hire, direct, and manage the staff of the institute; to develop the budgets and cost control programs of the institute; to manage compliance with all rules and regulations on the ICOC, including the performance of all grant recipients; and to manage and execute all intellectual property agreements and any other contracts pertaining to the institute or research it funds.

(2) Each member of the ICOC except, the chairperson, vice chairperson, and president, shall receive a per diem of one hundred dollars ($100) per day (adjusted annually for cost of living) for each day actually spent in the discharge of the member's duties, plus reasonable and necessary travel and other expenses incurred in the performance of the member's duties.

(3) The ICOC shall establish daily consulting rates and expense reimbursement standards for the non-ICOC members of all of its working groups.

(4) Notwithstanding Section 19825 of the Government Code, the ICOC shall set compensation for the chairperson, vice chairperson, and president and other officers, and for the scientific, medical, technical, and administrative staff of the institute within the range of compensation levels for executive officers and scientific, medical, technical, and administrative staff of medical schools within the University of California system and the nonprofit academic and research institutions described in paragraph (2) of subdivision (a) of Section 125290.20.

125290.50. Scientific and Medical Working Groups-General

(a) The institute shall have, and there is hereby established, three separate scientific and medical working groups as follows:

(1) Scientific and Medical Research Funding Working Group.

(2) Scientific and Medical Accountability Standards Working Group.

(3) Scientific and Medical Research Facilities Working Group.

(b) Working Group Members

Appointments of scientific and medical working group members shall be made by a majority vote of a quorum of the ICOC, within 30 days of the election and appointment of the initial ICOC members. The working group members' terms shall be six years except that, after the first six-year terms, the members' terms will be staggered so that one-third of the members shall be elected for a term that expires two years later, one-third of the members shall be elected for a term that expires four years later, and one-third of the members shall be elected for a term that expires six years later. Subsequent terms are for six years. Working group members may serve a maximum of two consecutive terms.

(c) Working Group Meetings

Each scientific and medical working group shall hold at least four meetings per year, one of which shall be designated as its annual meeting.

(d) Working Group Recommendations to the ICOC

Recommendations of each of the working groups may be forwarded to the ICOC only by a vote of a majority of a quorum of the members of each working group. If 35 percent of the members of any working group join together in a minority position, a minority report may be submitted to the ICOC. The ICOC shall consider the recommendations of the working groups in making its decisions on applications for research and facility grants and loan awards and in adopting regulatory standards. Each working group shall recommend to ICOC rules, procedures, and practices for that working group.

(e) Conflict of Interest

(1) The ICOC shall adopt conflict of interest rules, based on standards applicable to members of scientific review committees of the National Institutes of Health, to govern the participation of non-ICOC working group members.

(2) The ICOC shall appoint an ethics officer from among the staff of the institute.

(3) Because the working groups are purely advisory and have no final decisionmaking authority, members of the working groups shall not be considered public officials, employees, or consultants for purposes of the Political Reform Act (Title 9 (commencing with Section 81000) of the Government Code), Sections 1090 and 19990 of the Government Code, and Sections 10516 and 10517 of the Public Contract Code.

(f) Working Group Records

All records of the working groups submitted as part of the working groups' recommendations to the ICOC for approval shall be subject to the Public Records Act. Except as provided in this subdivision, the working groups shall not be subject to the provisions of Article 9 (commencing with Section 11120) of Chapter 1 of Part 1 of Division 3 of Title 2 of the Government Code, or Article 1 (commencing with Section 6250) of Chapter 3.5 of Division 7 of Title 1 of the Government Code.

125290.55. Scientific and Medical Accountability Standards Working Group

(a) Membership

The Scientific and Medical Accountability Standards Working Group shall have 19 members as follows:

(1) Five ICOC members from the 10 groups that focus on disease-specific areas described in paragraphs (3), (4), and (5) of subdivision (a) of Section 125290.20.

(2) Nine scientists and clinicians nationally recognized in the field of pluripotent and progenitor cell research.

(3) Four medical ethicists.

(4) The Chairperson of the ICOC.

(b) Functions

The Scientific and Medical Accountability Standards Working Group shall have the following functions:

(1) To recommend to the ICOC scientific, medical, and ethical standards.

(2) To recommend to the ICOC standards for all medical, socioeconomic, and financial aspects of clinical trials and therapy delivery to patients, including, among others, standards for safe and ethical procedures for obtaining materials and cells for research and clinical efforts for the appropriate treatment of human subjects in medical research consistent with paragraph (2) of subdivision (b) of Section 125290.35, and to ensure compliance with patient privacy laws.

(3) To recommend to the ICOC modification of the standards described in paragraphs (1) and (2) as needed.

(4) To make recommendations to the ICOC on the oversight of funded research to ensure compliance with the standards described in paragraphs (1) and (2).

(5) To advise the ICOC, the Scientific and Medical Research Funding Working Group, and the Scientific and Medical Research Facilities Working Group, on an ongoing basis, on relevant ethical and regulatory issues.

125290.60. Scientific and Medical Research Funding Working Group

(a) Membership

The Scientific and Medical Research Funding Working Group shall have 23 members as follows:

(1) Seven ICOC members from the 10 disease advocacy group members described in paragraphs (3), (4), and (5) of subdivision (a) of Section 125290.20.

(2) Fifteen scientists nationally recognized in the field of stem cell research.

(3) The Chairperson of the ICOC.

(b) Functions

The Scientific and Medical Research Funding Working Group shall perform the following functions:

(1) Recommend to the ICOC interim and final criteria, standards, and requirements for considering funding applications and for awarding research grants and loans.

(2) Recommend to the ICOC standards for the scientific and medical oversight of awards.

(3) Recommend to the ICOC any modifications of the criteria, standards, and requirements described in paragraphs (1) and (2) above as needed.

(4) Review grant and loan applications based on the criteria, requirements, and standards adopted by the ICOC and make recommendations to the ICOC for the award of research, therapy development, and clinical trial grants and loans.

(5) Conduct peer group progress oversight reviews of grantees to ensure compliance with the terms of the award, and report to the ICOC any recommendations for subsequent action.

(6) Recommend to the ICOC standards for the evaluation of grantees to ensure that they comply with all applicable requirements. Such standards shall mandate periodic reporting by grantees and shall authorize the Scientific and Medical Research Funding Working Group to audit a grantee and forward any recommendations for action to the ICOC.

(7) Recommend its first grant awards within 60 days of the issuance of the interim standards.

(c) Recommendations for Awards

Award recommendations shall be based upon a competitive evaluation as follows:

(1) Only the 15 scientist members of the Scientific and Medical Research Funding Working Group shall score grant and loan award applications for scientific merit. Such scoring shall be based on scientific merit in three separate classifications—research, therapy development, and clinical trials, on criteria including the following:

(A) A demonstrated record of achievement in the areas of pluripotent stem cell and progenitor cell biology and medicine, unless the research is determined to be a vital research opportunity.

(B) The quality of the research proposal, the potential for achieving significant research, or clinical results, the timetable for realizing such significant results, the importance of the research objectives, and the innovativeness of the proposed research.

(C) In order to ensure that institute funding does not duplicate or supplant existing funding, a high priority shall be placed on funding pluripotent stem cell and progenitor cell research that cannot, or is unlikely to, receive timely or sufficient federal funding, unencumbered by limitations that would impede the research. In this regard, other research categories funded by the National Institutes of Health shall not be funded by the institute.

(D) Notwithstanding subparagraph (C), other scientific and medical research and technologies and/or any stem cell research proposal not actually funded by the institute under subparagraph (C) may be funded by the institute if at least two-thirds of a quorum of the members of the Scientific and Medical Research Funding Working Group recommend to the ICOC that such a research proposal is a vital research opportunity.

125290.65. Scientific and Medical Facilities Working Group

(a) Membership

The Scientific and Medical Research Facilities Working Group shall have 11 members as follows:

(1) Six members of the Scientific and Medical Research Funding Working Group.

(2) Four real estate specialists. To be eligible to serve on the Scientific and Medical Research Facilities Working Group, a real estate specialist shall be a resident of California, shall be prohibited from receiving compensation from any construction or development entity providing specialized services for medical research facilities, and shall not provide real estate facilities brokerage services for any applicant for, or any funding by the Scientific and Medical Research Facilities Working Group and shall not receive compensation from any recipient of institute funding grants.

(3) The Chairperson of the ICOC.

(b) Functions

The Scientific and Medical Research Facilities Working Group shall perform the following functions:

(1) Make recommendations to the ICOC on interim and final criteria requirements, and standards for applications for, and the awarding of, grants and loans for buildings, building leases, and capital equipment; those standards and requirements shall include, among others:

(A) Facility milestones and timetables for achieving such milestones.

(B) Priority for applications that provide for facilities that will be available for research no more than two years after the grant award.

(C) The requirement that all funded facilities and equipment be located solely within California.

(D) The requirement that grantees comply with reimbursable building cost standards, competitive building leasing standards, capital equipment cost standards, and reimbursement standards and terms recommended by the Scientific and Medical Facilities Funding Working Group, and adopted by the ICOC.

(E) The requirement that grantees shall pay all workers employed on construction or modification of the facility funded by facilities grants or loans of the institute, the general prevailing rate of per diem wages for work of a similar character in the locality in which work on the facility is performed, and not less than the general prevailing rate of per diem wages for holiday and overtime work fixed as provided in Chapter 1 (commencing with Section 1720) of Part 7 of Division 2 of the Labor Code.

(F) The requirement that grantees be not-for-profit entities.

(G) The requirement that awards be made on a competitive basis, with the following minimum requirements:

(i) That the grantee secure matching funds from sources other than the institute equal to at least 20 percent of the award. Applications of equivalent merit, as determined by the Scientific and Medical Research Funding Working Group, considering research opportunities to be conducted in the proposed research facility, shall receive priority to the extent that they provide higher matching fund amounts. The Scientific and Medical Research Facilities Working Group may recommend waiving the matching fund requirement in extraordinary cases of high merit or urgency.

(ii) That capital equipment costs and capital equipment loans be allocated when equipment costs can be recovered in part by the grantee from other users of the equipment.

(2) Make recommendations to the ICOC on oversight procedures to ensure grantees' compliance with the terms of an award.

125290.70. Appropriation and Allocation of Funding

(a) Moneys in the California Stem Cell Research and Cures Fund shall be allocated as follows:

(1) (A) No less than 97 percent of the proceeds of the bonds authorized pursuant to Section 125291.30, after allocation of bond proceeds to purposes described in paragraphs (4) and (5) of subdivision (a) of Section 125291.20, shall be used for grants and grant oversight as provided in this chapter.

(B) Not less than 90 percent of the amount used for grants shall be used for research grants, with no more than the following amounts as stipulated below to be committed during the first 10 years of grant making by the institute, with each year's commitments to be advanced over a period of one to seven years, except that any such funds that are not committed may be carried over to one or more following years. The maximum amount of research funding to be allocated annually as follows: Year 1, 5.6 percent; Year 2, 9.4 percent; Year 3, 9.4 percent; Year 4, 11.3 percent; Year 5, 11.3 percent; Year 6, 11.3 percent; Year 7, 11.3 percent; Year 8, 11.3 percent; Year 9, 11.3 percent; and Year 10, 7.5 percent.

(C) Not more than 3 percent of the proceeds of bonds authorized by Section 125291.30 may be used by the institute for research and research facilities implementation costs, including the development, administration, and oversight of the grant making process and the operations of the working groups.

(2) Not more than 3 percent of the proceeds of the bonds authorized pursuant to Section 125291.30 shall be used for the costs of general administration of the institute.

(3) In any single year any new research funding to any single grantee for any program year is limited to no more than 2 percent of the total bond authorization under this chapter. This limitation shall be considered separately for each new proposal without aggregating any prior year approvals that may fund research activities. This requirement shall be determinative, unless 65 percent of a quorum of the ICOC approves a higher limit for that grantee.

(4) Recognizing the priority of immediately building facilities that ensure the independence of the scientific and medical research of the institute, up to 10 percent of the proceeds of the bonds authorized pursuant to Section 125291.30, net of costs described in paragraphs (2), (4), and (5) of subdivision (a) of Section 125291.20 shall be allocated for grants to build scientific and medical research facilities of nonprofit entities which are intended to be constructed in the first five years.

(5) The institute shall limit indirect costs to 25 percent of a research award, excluding amounts included in a facilities award, except that the indirect cost limitation may be increased by that amount by which the grantee provides matching funds in excess of 20 percent of the grant amount.

(b) To enable the institute to commence operating during the first six months following the adoption of the measure adding this chapter, there is hereby appropriated from the General Fund as a temporary start-up loan to the institute three million dollars ($3,000,000) for initial administrative and implementation costs. All loans to the institute pursuant to this appropriation shall be repaid to the General Fund within 12 months of each loan draw from the proceeds of bonds sold pursuant to Section 125291.30.

(c) The institute's funding schedule is designed to create a positive tax revenue stream for the State of California during the institute's first five calendar years of operations, without drawing funds from the General Fund for principal and interest payments for those first five calendar years.

Article 2. California Stem Cell Research and Cures Bond Act of 2004

125291.10. This article shall be known, and may be cited, as the California Stem Cell Research and Cures Bond Act of 2004.

125291.15. As used in this article, the following terms have the following meaning:

(a) "Act" means the California Stem Cell Research and Cures Bond Act constituting Chapter 3 (commencing with Section 125290.10) of Part 5 of Division 106.

(b) "Board" or "institute" means the California Institute for Regenerative Medicine designated in accordance with subdivision (b) of Section 125291.40.

(c) "Committee" means the California Stem Cell Research and Cures Finance Committee created pursuant to subdivision (a) of Section 125291.40.

(d) "Fund" means the California Stem Cell Research and Cures Fund created pursuant to Section 125291.25.

(e) "Interim debt" means any interim loans pursuant to subdivision (b) of Section 125290.70, and Sections 125291.60 and 125291.65, bond anticipation notes or commercial paper notes issued to make deposits into the fund and which will be paid from the proceeds of bonds issued pursuant to this article.

125291.20. (a) Notwithstanding Section 13340 of the Government Code or any other provision of law, moneys in the fund are appropriated without regard to fiscal years to the institute for the purpose of (1) making grants or loans to fund research and construct facilities for research, all as described in and pursuant to the act, (2) paying general administrative costs of the institute (not to exceed 3 percent of the net proceeds of each sale of bonds), (3) paying the annual administration costs of the interim debt or bonds after December 31 of the fifth full calendar year after this article takes effect, (4) paying the costs of issuing interim debt, paying the annual administration costs of the interim debt until and including December 31 of the fifth full calendar year after this article takes effect, and paying interest on interim debt, if such interim debt is incurred or issued on or prior to December 31 of the fifth full calendar year after this article takes effect, and (5) paying the costs of issuing bonds, paying the annual administration costs of the bonds until and including December 31 of the fifth full calendar year after this article takes effect, and paying interest on bonds that accrues on or prior to December 31 of the fifth full calendar year after this article takes effect (except that such limitation does not apply to premium and accrued interest as provided in Section 125291.70). In addition, moneys in the fund or other proceeds of the sale of bonds authorized by this article may be used to pay principal of or redemption premium on any interim debt issued prior to the issuance of bonds authorized by this article. Moneys deposited in the fund from the proceeds of interim debt may be used to pay general administrative costs of the institute without regard to the 3 percent limit set forth in (2) above, so long as such 3 percent limit is satisfied for each issue of bonds.

(b) Repayment of principal and interest on any loans made by the institute pursuant to this article shall be deposited in the fund and used to make additional grants and loans for the purposes of this act or for paying continuing costs of the annual administration of outstanding bonds.

125291.25. The proceeds of interim debt and bonds issued and sold pursuant to this article shall be deposited in the State Treasury to the credit of the California Stem Cell Research and Cures Fund, which is hereby created in the State Treasury, except to the extent that proceeds of the issuance of bonds are used directly to repay interim debt.

125291.30. Bonds in the total amount of three billion dollars ($3,000,000,000), not including the amount of any refunding bonds issued in accordance with Section 125291.75, or as much thereof as is

necessary, may be issued and sold to provide a fund to be used for carrying out the purposes expressed in this article and to be used and sold for carrying out the purposes of Section 125291.20 and to reimburse the General Obligation Bond Expense Revolving Fund pursuant to Section 16724.5 of the Government Code. The bonds, when sold, shall be and shall constitute a valid and binding obligation of the State of California, and the full faith and credit of the State of California is hereby pledged for the punctual payment of both the principal of, and interest on, the bonds as the principal and interest become due and payable.

125291.35. The bonds authorized by this article shall be prepared, executed, issued, sold, paid, and redeemed as provided in the State General Obligation Bond Law (Chapter 4 (commencing with Section 16720) of Part 3 of Division 4 of Title 2 of the Government Code), and all of the provisions of that law except Section 16727 apply to the bonds and to this article and are hereby incorporated in this article as though set forth in full in this article.

125291.40. (a) Solely for the purpose of authorizing the issuance and sale, pursuant to the State General Obligation Bond Law, of the bonds and interim debt authorized by this article, the California Stem Cell Research and Cures Finance Committee is hereby created. For purposes of this article, the California Stem Cell Research and Cures Finance Committee is "the committee" as that term is used in the State General Obligation Bond Law. The committee consists of the Treasurer, the Controller, the Director of Finance, the Chairperson of the California Institute for Regenerative Medicine, and two other members of the Independent Citizens Oversight Committee (as created by the act) chosen by the Chairperson of the California Institute for Regenerative Medicine, or their designated representatives. The Treasurer shall serve as chairperson of the committee. A majority of the committee may act for the committee.

(b) For purposes of the State General Obligation Bond Law, the California Institute for Regenerative Medicine is designated the "board."

125291.45. (a) The committee shall determine whether or not it is necessary or desirable to issue bonds authorized pursuant to this article in order to carry out the actions specified in this article and, if so, the amount of bonds to be issued and sold. Successive issues of bonds may be authorized and sold to carry out those actions progressively, and it is not necessary that all of the bonds authorized to be issued be sold at any one time. The bonds may bear interest which is includable in gross income for federal income tax purposes if the committee determines that such treatment is necessary in order to provide funds for the purposes of the act.

(b) The total amount of the bonds authorized by Section 125291.30 which may be issued in any calendar year, commencing in 2005, shall not exceed three hundred fifty million dollars ($350,000,000). If less than this amount of bonds is issued in any year, the remaining permitted amount may be carried over to one or more subsequent years.

(c) An interest-only floating rate bond structure will be implemented for interim debt and bonds until at least December 31 of the fifth full calendar year after this article takes effect, with all interest to be paid from proceeds from the sale of interim debt or bonds, to minimize debt service payable from the General Fund during the initial period of basic research and therapy development, if the committee determines, with the advice of the Treasurer, that this structure will result in the lowest achievable borrowing costs for the state during that five-year period considering the objective of avoiding any bond debt service payments, by the General Fund, during that period. Upon such initial determination, the committee may delegate, by resolution, to the Treasurer such authority in connection with issuance of bonds as it may determine, including, but not limited to, the authority to implement and continue this bond financing structure (including during any time following the initial five-year period) and to determine that an alternate financing plan would result in significant lower borrowing costs for the state consistent with the objectives related to the General Fund and to implement such alternate financing plan.

125291.50. There shall be collected each year and in the same manner and at the same time as other state revenue is collected, in addition to the ordinary revenues of the state, a sum in an amount required to pay the principal of, and interest on, the bonds maturing each year. It is the duty of all officers charged by law with any duty in regard to the collection of the revenue to do and perform each and every act that is necessary to collect that additional sum.

125291.55. Notwithstanding Section 13340 of the Government Code, there is hereby appropriated from the General Fund in the State Treasury, for the purposes of this article, an amount that will equal the total of the following:

(a) The sum annually necessary to pay the principal of, and interest on, bonds issued and sold

pursuant to this article, as the principal and interest become due and payable.

(b) The sum necessary to carry out Section 125291.60 appropriated without regard to fiscal years.

125291.60. The Director of Finance may authorize the withdrawal from the General Fund of an amount or amounts, not to exceed the amount of the unsold bonds that have been authorized by the committee, to be sold for the purpose of carrying out this article. Any amount withdrawn shall be deposited in the fund. Any money made available under this section shall be returned to the General Fund, plus an amount equal to the interest that the money would have earned in the Pooled Money Investment Account, from money received from the sale of bonds for the purpose of carrying out this article.

125291.65. The institute may request the Pooled Money Investment Board to make a loan from the Pooled Money Investment Account in accordance with Section 16312 of the Government Code for the purposes of carrying out this article. The amount of the request shall not exceed the amount of the unsold bonds that the committee, by resolution, has authorized to be sold for the purpose of carrying out this article. The institute shall execute any documents required by the Pooled Money Investment Board to obtain and repay the loan. Any amounts loaned shall be deposited in the fund to be allocated by the institute in accordance with this article.

125291.70. All money deposited in the fund that is derived from premium and accrued interest on bonds sold shall be reserved in the fund and shall be available for transfer to the General Fund as a credit to expenditures for bond interest.

125291.75. The bonds may be refunded in accordance with Article 6 (commencing with Section 16780) of Chapter 4 of Part 3 of Division 4 of Title 2 of the Government Code, which is a part of the State General Obligation Bond Law. Approval by the voters of the state for the issuance of the bonds described in this article includes the approval of the issuance of any bonds issued to refund any bonds originally issued under this article or any previously issued refunding bonds.

125291.80. Notwithstanding any provision of this article or the State General Obligation Bond Law, if the Treasurer sells bonds pursuant to this article that include a bond counsel opinion to the effect that the interest on the bonds is excluded from gross income for federal tax purposes, subject to designated conditions, the Treasurer may maintain separate accounts for the investment of bond proceeds and the investment earnings on those proceeds. The Treasurer may use or direct the use of those proceeds or earnings to pay any rebate, penalty, or other payment required under federal law or to take any other action with respect to the investment and use of bond proceeds required or desirable under federal law to maintain the tax-exempt status of those bonds and to obtain any other advantage under federal law on behalf of the funds of this state.

125291.85. Inasmuch as the proceeds from the sale of bonds authorized by this article are not "proceeds of taxes" as that term is used in Article XIII B of the California Constitution, the disbursement of these proceeds is not subject to the limitations imposed by that article.

Article 3. Definitions

125292.10. As used in this chapter and in Article XXXV of the California Constitution, the following terms have the following meanings:

(a) "Act" means the California Stem Cell Research and Cures Bond Act constituting Chapter 3 (commencing with Section 125290.10) of Part 5 of Division 106 of the Health and Safety Code.

(b) "Adult stem cell" means an undifferentiated cell found in a differentiated tissue in an adult organism that can renew itself and may, with certain limitations, differentiate to yield all the specialized cell types of the tissue from which it originated.

(c) "Capitalized interest" means interest funded by bond proceeds.

(d) "Committee" means the California Stem Cell Research and Cures Finance Committee created pursuant to subdivision (a) of Section 125291.40.

(e) "Constitutional officers" means the Governor, Lieutenant Governor, Treasurer, and Controller of California.

(f) "Facilities" means buildings, building leases, or capital equipment.

(g) "Floating-rate bonds" means bonds which do not bear a fixed rate of interest until their final maturity date, including commercial paper notes.

(h) "Fund" means the California Stem Cell Research and Disease Cures Fund created pursuant to Section 125291.25.

(i) "Grant" means a grant, loan, or guarantee.

(j) "Grantee" means a recipient of a grant from the institute. All University of California grantee

institutions shall be considered as separate and individual grantee institutions.

(k) "Human reproductive cloning" means the practice of creating or attempting to create a human being by transferring the nucleus from a human cell into an egg cell from which the nucleus has been removed for the purpose of implanting the resulting product in a uterus to initiate a pregnancy.

(l) "Indirect costs" mean the recipient's costs in the administration, accounting, general overhead, and general support costs for implementing a grant or loan of the institute. NIH definitions of indirect costs will be utilized as one of the bases by the Scientific and Medical Research Standards Working Group to create a guideline for recipients on this definition, with modifications to reflect guidance by the ICOC and this act.

(m) "Institute" means the California Institute for Regenerative Medicine.

(n) "Interim standards" means temporary standards that perform the same function as "emergency regulations" under the Administrative Procedure Act (Government Code, Title 2, Division 3, Part 1, Chapter 4.5, Sections 11371 et seq.) except that in order to provide greater opportunity for public comment on the permanent regulations, remain in force for 270 days rather than 180 days.

(o) "Life science commercial entity" means a firm or organization, headquartered in California, whose business model includes biomedical or biotechnology product development and commercialization.

(p) "Medical ethicist" means an individual with advanced training in ethics who holds a Ph.D., MA, or equivalent training and who spends or has spent substantial time (1) researching and writing on ethical issues related to medicine, and (2) administering ethical safeguards during the clinical trial process, particularly through service on institutional review boards.

(q) "Pluripotent cells" means cells that are capable of self-renewal, and have broad potential to differentiate into multiple adult cell types. Pluripotent stem cells may be derived from somatic cell nuclear transfer or from surplus products of in vitro fertilization treatments when such products are donated under appropriate informed consent procedures. These excess cells from in vitro fertilization treatments would otherwise be intended to be discarded if not utilized for medical research.

(r) "Progenitor cells" means multipotent or precursor cells that are partially differentiated but retain the ability to divide and give rise to differentiated cells.

(s) "Quorum" means at least 65 percent of the members who are eligible to vote.

(t) "Research donor" means a human who donates biological materials for research purposes after full disclosure and consent.

(u) "Research funding" includes interdisciplinary scientific and medical funding for basic research, therapy development, and the development of pharmacologies and treatments through clinical trials. When a facility's grant or loan has not been provided to house all elements of the research, therapy development, and/or clinical trials, research funding shall include an allowance for a market lease rate of reimbursement for the facility. In all cases, operating costs of the facility, including, but not limited to, library and communication services,utilities, maintenance, janitorial, and security, shall be included as direct research funding costs. Legal costs of the institute incurred in order to negotiate standards with federal and state governments and research institutions; to implement standards or regulations; to resolve disputes; and/or to carry out all other actions necessary to defend and/or advance the institute's mission shall be considered direct research funding costs.

(v) "Research participant" means a human enrolled with full disclosure and consent, and participating in clinical trials.

(w) "Revenue positive" means all state tax revenues generated directly and indirectly by the research and facilities of the institute are greater than the debt service on the state bonds actually paid by the General Fund in the same year.

(x) "Stem cells" mean nonspecialized cells that have the capacity to divide in culture and to differentiate into more mature cells with specialized functions.

(y) "Vital research opportunity" means scientific and medical research and technologies and/or any stem cell research not actually funded by the institute under subparagraph (C) of paragraph (1) of subdivision (c) of Section 125290.60 which provides a substantially superior research opportunity vital to advance medical science as determined by at least a two-thirds vote of a quorum of the members of the Scientific and Medical Research Funding Working Group and recommended as such by that working group to the ICOC. Human reproductive cloning shall not be a vital research opportunity.

SEC. 6. Section 20069 of the Government Code is amended to read:

(a) "State service" means service rendered as an employee or officer (employed, appointed or elected) of the state, *the California Institute for Regenerative Medicine and the officers and employees of its governing body,* the university, a school employer, or a contracting agency, for compensation, and only while he or she is receiving compensation from that employer therefor, except as provided in Article 4 (commencing with Section 20990) of Chapter 11.

(b) "State service," solely for purposes of qualification for benefits and retirement allowances under this system, shall also include service rendered as an officer or employee of a county if the salary for the service constitutes compensation earnable by a member of this system under Section 20638.

SEC. 7. Severability

If any provision of this act, or part thereof, is for any reason held to be invalid or unconstitutional, the remaining provisions shall not be affected, but shall remain in full force and effect, and to this end the provisions of this act are severable.

SEC. 8. Amendments

The statutory provisions of this measure, except the bond provisions, may be amended to enhance the ability of the institute to further the purposes of the grant and loan programs created by the measure, by a bill introduced and passed no earlier than the third full calendar year following adoption, by 70 percent of the membership of both houses of the Legislature and signed by the Governor, provided that at least 14 days prior to passage in each house, copies of the bill in final form shall be made available by the clerk of each house to the public and news media.

Appendix D

Senate Bill 1064

Senate Bill No. 1064

CHAPTER 637

An act to amend Sections 125290.20, 125290.30, 125290.40, 125290.45, and 125290.60 of, and to add Sections 125290.71 and 125290.80 to, the Health and Safety Code, relating to stem cells.

[Approved by Governor September 30, 2010.
Filed with Secretary of State September 30, 2010.]

LEGISLATIVE COUNSEL'S DIGEST

SB 1064, Alquist. California Stem Cell Research and Cures Act.

The California Stem Cell Research and Cures Act, an initiative measure approved by the voters at the November 2, 2004, statewide general election as Proposition 71, establishes the California Institute for Regenerative Medicine (CIRM), the purpose of which is, among other things, to make grants and loans for stem cell research, for research facilities, and for other vital research opportunities to realize therapies, protocols, and medical procedures that will result in the cure for, or substantial mitigation of, diseases and injuries. Existing law establishes the Independent Citizens Oversight Committee (ICOC) composed of appointed members, that is required to perform various functions and duties with regard to the operation of the institute, including, but not limited to, establishing standards applicable to research funded by the institute. Existing law prohibits amendment of Proposition 71 by the Legislature unless the amendment is approved by the voters, or the amendment is accomplished by a bill introduced after the first 2 full calendar years and approved by a vote of 70% of both houses, and only if the amendment enhances the ability of the institute to further the purposes of the grant and loan programs.

Existing law specifies the appointment process for the members of the ICOC, including the chairperson and vice chairperson who are employees of the ICOC, and provides that the chairperson and vice chairperson serve 6-year terms. Existing law defines the duties of the chairperson and the president of the ICOC and limits the total number of authorized employees of the CIRM to 50.

This bill would require the CIRM, under the guidance of the ICOC, to create a succession plan addressing changes in leadership in the CIRM and ICOC, as specified. The bill would eliminate the 50-employee maximum for the CIRM.

The bill would also require the CIRM, under the guidance of the ICOC, to create, by January 31, 2012, a transition plan to address the expiration

of current bond funding and to submit that plan to the Governor, the Controller, and the Legislature.

Existing law requires the CIRM to commission an independent financial audit, which is provided to the Controller for review and reported in the annual public report. Existing law establishes the Citizen's Financial Accountability Oversight Committee, chaired by the Controller, to review the annual audit and financial practices of the CIRM.

This bill would, additionally, require a performance audit to be conducted every 3 years, as specified. Existing law contains provisions relating to the extent to which requirements relating to the disclosure of public records applied to records of the CIRM.

This bill would require the ICOC to disclose, in all meeting minutes, a summary of vote tallies, including each board member's votes and recusals.

The act provides that the ICOC shall establish standards that require that all grants and loan awards under the act shall be subject to intellectual property agreements that balance the opportunity of the state to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and

clinical trials with the need to ensure that essential medical research is not unreasonably hindered by the intellectual property agreements.

This bill would require that intellectual property standards that the ICOC develops include a requirement that each grantee and the exclusive licensees of the grantee submit to the CIRM a plan that will afford Californians access to any drug that is, in whole or in part, the result of research funded by the CIRM, except when the ICOC adopts a waiver, as specified. The bill would also require specified grant recipients to share a fraction of the revenue they receive from licensing or self-commercialization of an invention or technology that arises from research funded by CIRM, as specified.

Existing law establishes the procedure by which grant and loan applications are processed and scored by the 15 scientist members of the Scientific and Medical Research Funding Working Group.

This bill would remove the 15 member limit, and would instead require that a peer review panel consist of both scientists and patient advocates and require that there be 15 scientists on a peer review panel.

The people of the state of California do enact as follows:

SECTION 1. The Legislature finds and declares the following:

(a) The California Institute for Regenerative Medicine was established in 2004, through the passage of Proposition 71, for the purposes of implementing and managing a $3 billion investment in stem cell research on behalf of the state.

(b) Stem cell research is a promising area of research aimed at finding breakthrough cures for currently incurable diseases and injuries affecting millions of people. This investment, as stated in the proposition, would protect and benefit the California budget by funding scientific and medical research that will significantly reduce state health care costs in the future.

(c) Furthermore, the Legislative Analyst, in its official ballot information, stated that the state would "receive payments from patents, royalties, and licenses resulting from the research funded by the institute" through institute-established standards "requiring that all grants and loans be subject to agreements allowing the state to financially benefit from patents, royalties, and licenses resulting from the research activities funded under the measure."

(d) Since its inception, questions and concerns have been raised about the institute's practices, its governing board, and how the state directly and financially benefits through this sizeable investment. These criticisms divert the attention and focus of the institute to drive transformational scientific research and find cures.

(e) It is the intent of the Legislature to further enhance the ability of the institute to manage this investment made with public funds by addressing public concerns regarding oversight and transparency.

(f) It is further the intent of this act to ensure that California maximizes its receipt of revenues generated through grants or loans made through the institute and with state funds.

(g) It is in the best interests of the state that therapies that are created in whole or in part by funding from the institute be made available to Californians who have no other means of purchasing those therapies for reasons that include, but are not limited to, low income or the lack of available health insurance coverage.

(h) It is in the best interests of the state that the leadership of the institute, including the ICOC and the officers of the institute, possess the qualities necessary to serve the needs of the institute, and that the chairperson of the ICOC and the president of the institute have well defined and complementary duties.

SEC. 2. Section 125290.20 of the Health and Safety Code is amended to read:

125290.20. ICOC Membership; Appointments; Terms of Office

(a) ICOC Membership

The ICOC shall have 29 members, appointed as follows:

(1) The Chancellors of the University of California at San Francisco, Davis, San Diego, Los Angeles, and Irvine shall each appoint an executive officer from his or her campus.

(2) The Governor, the Lieutenant Governor, the Treasurer, and the

Controller shall each appoint an executive officer from the following three categories:

(A) A California university, excluding the five campuses of the University of California described in paragraph (1), that has demonstrated success and leadership in stem cell research, and that has:

(i) A nationally ranked research hospital and medical school; this criteria will apply to only two of the four appointments.

(ii) A recent proven history of administering scientific and/or medical research grants and contracts in an average annual range exceeding one hundred million dollars ($100,000,000).

(iii) A ranking, within the past five years, in the top 10 United States universities with the highest number of life science patents or that has research or clinical faculty who are members of the National Academy of Sciences.

(B) A California nonprofit academic and research institution that is not a part of the University of California, that has demonstrated success and leadership in stem cell research, and that has:

(i) A nationally ranked research hospital or that has research or clinical faculty who are members of the National Academy of Sciences.

(ii) A proven history in the last five years of managing a research budget in the life sciences exceeding twenty million dollars ($20,000,000).

(C) A California life science commercial entity that is not actively engaged in researching or developing therapies with pluripotent or progenitor stem cells, that has a background in implementing successful experimental medical therapies, and that has not been awarded, or applied for, funding by the institute at the time of appointment. A board member of that entity with a successful history of developing innovative medical therapies may be appointed in lieu of an executive officer.

(D) Only one member shall be appointed from a single university, institution, or entity. The executive officer of a California university, a nonprofit research institution or life science commercial entity who is appointed as a member, may from time to time delegate those duties to an executive officer of the entity or to the dean of the medical school, if applicable.

(3) The Governor, the Lieutenant Governor, the Treasurer, and the Controller shall appoint members from among California representatives of California regional, state, or national disease advocacy groups, as follows:

(A) The Governor shall appoint two members, one from each of the following disease advocacy groups: spinal cord injury and Alzheimer's disease.

(B) The Lieutenant Governor shall appoint two members, one from each of the following disease advocacy groups: type II diabetes and multiple sclerosis or amyotrophic lateral sclerosis.

(C) The Treasurer shall appoint two members, one from each of the following disease groups: type I diabetes and heart disease.

(D) The Controller shall appoint two members, one from each of the following disease groups: cancer and Parkinson's disease.

(4) The Speaker of the Assembly shall appoint a member from among California representatives of a California regional, state, or national mental health disease advocacy group.

(5) The President pro Tempore of the Senate shall appoint a member from among California representatives of a California regional, state, or national HIV/AIDS disease advocacy group.

(6) A chairperson and vice chairperson who shall be elected by the ICOC members. Each constitutional officer shall nominate a candidate for chairperson and another candidate for vice chairperson. The chairperson and vice chairperson shall each be elected for a term of six years. The chairperson and vice chairperson of ICOC shall be full- or part-time employees of the institute and shall meet the following criteria:

(A) Mandatory Chairperson Criteria

(i) Documented history in successful stem cell research advocacy.

(ii) Experience with state and federal legislative processes that must include some experience with medical legislative approvals of standards and/or funding.

(iii) Qualified for appointment pursuant to paragraph (3), (4), or (5) of subdivision (a).

(iv) Cannot be concurrently employed by or on leave from any prospective grant or loan recipient institutions in California.

(B) Additional Criteria for Consideration:

(i) Experience with governmental agencies or institutions (either executive or board position).

(ii) Experience with the process of establishing government standards and procedures.

(iii) Legal experience with the legal review of proper governmental authority for the exercise of government agency or government institutional powers.

(iv) Direct knowledge and experience in bond financing.

The vice chairperson shall satisfy clauses (i), (iii), and (iv) of subparagraph (A). The vice chairperson shall be selected from among individuals who have attributes and experience complementary to those of the chairperson, preferably covering the criteria not represented by the chairperson's credentials and experience.

(b) Appointment of ICOC Members

(1) All appointments shall be made within 40 days of the effective date of this act. In the event that any of the appointments are not completed within the permitted timeframe, the ICOC shall proceed to operate with the appointments that are in place, provided that at least 60 percent of the appointments have been made.

(2) Forty-five days after the effective date of the measure adding this chapter, the Controller and the Treasurer, or if only one is available within 45 days, the other shall convene a meeting of the appointed members of the ICOC to elect a chairperson and vice chairperson from among the individuals nominated by the constitutional officers pursuant to paragraph (6) of subdivision (a).

(c) ICOC Member Terms of Office

(1) The members appointed pursuant to paragraphs (1), (3), (4), and (5) of subdivision (a) shall serve eight-year terms, and all other members shall serve six-year terms. Members shall serve a maximum of two terms.

(2) If a vacancy occurs within a term, the appointing authority shall appoint a replacement member within 30 days to serve the remainder of the term.

(3) When a term expires, the appointing authority shall appoint a member within 30 days. ICOC members shall continue to serve until their replacements are appointed.

SEC. 3. Section 125290.30 of the Health and Safety Code is amended to read:

125290.30. Public and Financial Accountability Standards

(a) Annual Public Report

The institute shall issue an annual report to the public which sets forth its activities, grants awarded, grants in progress, research accomplishments, and future program directions. Each annual report shall include, but not be limited to, the following: the number and dollar amounts of research and facilities grants; the grantees for the prior year; the institute's administrative expenses; an assessment of the availability of funding for stem cell research from sources other than the institute; a summary of research findings, including promising new research areas; an assessment of the relationship between the institute's grants and the overall strategy of its research program; and a report of the institute's strategic research and financial plans.

(b) Independent Financial Audit for Review by Controller

The institute shall annually commission an independent financial audit of its activities from a certified public accounting firm, which shall be provided to the Controller, who shall review the audit and annually issue a public report of that review.

(c) A performance audit shall be commissioned by the institute every three years beginning with the audit for the 2010-11 fiscal year. The performance audit, which may be performed by the Bureau of State Audits, shall examine the functions, operations, management systems, and policies and procedures of the institute to assess whether the institute is achieving economy, efficiency, and

effectiveness in the employment of available resources. The performance audit shall be conducted in accordance with government auditing

standards, and shall include a review of whether the institute is complying with ICOC policies and procedures. The performance audit shall not be required to include a review of

scientific performance. The first performance audit shall include, but not be limited to, all of the following:

(1) Policies and procedures for the issuance of contracts and grants and a review of a representative sample of contracts, grants, and loans executed by the institute.

(2) Policies and procedures relating to the protection or treatment of intellectual property rights associated with research funded or commissioned by the institute.

(d) All administrative costs of the audits required by subdivisions (b) and (c) shall be paid by the institute.

(e) Citizen's Financial Accountability Oversight Committee

There shall be a Citizen's Financial Accountability Oversight Committee chaired by the Controller. This committee shall review the annual financial audit, the Controller's report and evaluation of that audit, and the financial practices of the institute. The Controller, the Treasurer, the President pro Tempore of the Senate, the Speaker of the Assembly, and the Chairperson of the ICOC shall each appoint a public member of the committee. Committee members shall have medical backgrounds and knowledge of relevant financial matters. The committee shall provide recommendations on the institute's financial practices and performance. The Controller shall provide staff support. The committee shall hold a public meeting, with appropriate notice, and with a formal public comment period. The committee shall evaluate public comments and include appropriate summaries in its annual report. The ICOC shall provide funds for all costs associated with the per diem expenses of the committee members and for publication of the annual report.

(f) Public Meeting Laws

(1) The ICOC shall hold at least two public meetings per year, one of which will be designated as the institute's annual meeting. The ICOC may hold additional meetings as it determines are necessary or appropriate.

(2) The Bagley-Keene Open Meeting Act, Article 9 (commencing with Section 11120) of Chapter 1 of Part 1 of Division 3 of Title 2 of the Government Code, shall apply to all meetings of the ICOC, except as otherwise provided in this section. The ICOC shall award all grants, loans, and contracts in public meetings and shall adopt all governance, scientific, medical, and regulatory standards in public meetings.

(3) The ICOC may conduct closed sessions as permitted by the Bagley-Keene Open Meeting Act, under Section 11126 of the Government Code. In addition, the ICOC may conduct closed sessions when it meets to consider or discuss:

(A) Matters involving information relating to patients or medical subjects, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(B) Matters involving confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user an opportunity to obtain a business advantage over competitors who do not know it or use it.

(C) Matters involving prepublication, confidential scientific research or data.

(D) Matters concerning the appointment, employment, performance, compensation, or dismissal of institute officers and employees. Action on compensation of the institute's officers and employees shall only be taken in open session.

(4) The meeting required by paragraph (2) of subdivision (b) of Section 125290.20 shall be deemed to be a special meeting for the purposes of Section 11125.4 of the Government Code.

(g) Public Records

(1) The California Public Records Act, Article 1 (commencing with Section 6250) of Chapter 3.5 of Division 7 of Title 1 of the Government Code, shall apply to all records of the institute, except as otherwise provided in this section.

(2) Nothing in this section shall be construed to require disclosure of any records that are any of the following:

(A) Personnel, medical, or similar files, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(B) Records containing or reflecting confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user an opportunity to obtain a business advantage over competitors who do not know it or use it.

(C) Prepublication scientific working papers or research data.

(3) The institute shall include, in all meeting minutes, a summary of vote tallies and disclosure of each board member's votes and recusals on all action items.

(h) Competitive Bidding

(1) The institute shall, except as otherwise provided in this section, be

governed by the competitive bidding requirements applicable to the University of California, as set forth in Article 1 (commencing with Section 10500) of Chapter 2.1 of Part 2 of Division 2 of the Public Contract Code.

(2) For all institute contracts, the ICOC shall follow the procedures required of the Regents by Article 1 (commencing with Section 10500) of Chapter 2.1 of Part 2 of Division 2 of the Public Contract Code with respect to contracts let by the University of California.

(3) The requirements of this section shall not be applicable to grants or loans approved by the ICOC.

(4) Except as provided in this section, the Public Contract Code shall not apply to contracts let by the institute.

(i) Conflicts of Interest

(1) The Political Reform Act, Title 9 (commencing with Section 81000) of the Government Code, shall apply to the institute and to the ICOC, except as provided in this section and in subdivision (e) of Section 125290.50.

(A) No member of the ICOC shall make, participate in making, or in any way attempt to use his or her official position to influence a decision to approve or award a grant, loan, or contract to his or her employer, but a member may participate in a decision to approve or award a grant, loan, or contract to a nonprofit entity in the same field as his or her employer.

(B) A member of the ICOC may participate in a decision to approve or award a grant, loan, or contract to an entity for the purpose of research involving a disease from which a member or his or her immediate family suffers or in which the member has an interest as a representative of a disease advocacy organization.

(C) The adoption of standards is not a decision subject to this section.

(2) Service as a member of the ICOC by a member of the faculty or administration of any system of the University of California shall not, by itself, be deemed to be inconsistent, incompatible, in conflict with, or inimical to the duties of the ICOC member as a member of the faculty or administration of any system of the University of California and shall not result in the automatic vacation of either such office. Service as a member of the ICOC by a representative or employee of a disease advocacy organization, a nonprofit academic and research institution, or a life science commercial entity shall not be deemed to be inconsistent, incompatible, in conflict with, or inimical to the duties of the ICOC member as a representative or employee of that organization, institution, or entity.

(3) Section 1090 of the Government Code shall not apply to any grant, loan, or contract made by the ICOC except where both of the following conditions are met:

(A) The grant, loan, or contract directly relates to services to be provided by any member of the ICOC or the entity the member represents or financially benefits the member or the entity he or she represents.

(B) The member fails to recuse himself or herself from making, participating in making, or in any way attempting to use his or her official position to influence a decision on the grant loan or contract.

(j) Patent Royalties and License Revenues Paid to the State of California

(1) The ICOC shall establish standards that require that all grants and loan awards be subject to intellectual property agreements that balance the opportunity of the State of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to ensure that essential medical research is not unreasonably hindered by the intellectual property agreements. All revenues received through the intellectual property agreements established pursuant to this subdivision shall be deposited into the General Fund.

(2) These standards shall include, at a minimum, a requirement that CIRM grantees, other than loan recipients and facilities grant recipients, share a fraction of the revenue they receive from licensing or self-commercializing an invention or technology that arises from research funded by CIRM, as set forth below. All revenues received pursuant to this paragraph or regulations adopted to implement this paragraph shall be deposited in the General Fund for use consistent with Section 202(c)(7) of Title 35 of the United States Code, if applicable.

(A) (i) A grantee that licenses an invention or technology that arises from research funded by CIRM shall pay 25 percent of the revenues it receives in excess of five hundred thousand dollars ($500,000), in the aggregate, to the General Fund. The threshold amount of five hundred thousand dollars ($500,000) shall be adjusted annually by a multiple of a fraction, the denominator of which is the Consumer Price Index, All Urban Consumers, All Items (San Francisco-Oakland-San Jose; 1982-84=100) as prepared by the Bureau of Labor Statistics of the United States Department of Labor and published for the month of October 2009, and the numerator of which is that index published for the month in which the grantee accepts the grant.

(ii) If funding sources other than CIRM directly contributed to the development of the invention or technology, then the return to the General Fund shall be calculated as follows: The amount of CIRM funding for the invention or technology shall be divided by the total of funding provided by all sources, and that fraction shall be multiplied by 25. That numeral is the percentage due to the General Fund.

(B) (i) A grantee that self-commercializes a product that results from an invention or technology that arises from research funded by CIRM shall pay an amount to the General Fund equal to three times the total amount of the CIRM grant or grants received by the grantee in support of the research that contributed to the creation of the product. The rate of payback of the royalty shall be at a rate of 3 percent of the annual net revenue received by the grantee from the product.

(ii) In addition to the payment required by clause (i), the first time that net commercial revenues earned by the grantee from the product exceed two hundred fifty million dollars ($250,000,000) in a calendar year, the grantee shall make a one-time payment to the General Fund equal to three times the total amount of the grant or grants awarded by CIRM to the grantee in support of the research that contributed to the creation of the product.

(iii) In addition to the payments required by clauses (i) and (ii), the first time that net commercial revenues earned by the grantee from the product exceed five hundred million dollars ($500,000,000) in a calendar year, the grantee shall make an additional one-time payment to the General Fund equal to three times the total amount of the grant or grants awarded by CIRM to the grantee in support of the research that contributed to the creation of the product.

(iv) In addition to the payments required by clauses (i), (ii), and (iii), the first time that net commercial revenues earned by the grantee from the product equal or exceed five hundred million dollars ($500,000,000) in a calendar year, the grantee shall pay the General Fund 1 percent annually of net commercial revenue in excess of five hundred million dollars ($500,000,000) for the life of any patent covering the invention or technology, if the grantee patented its invention or technology and received a CIRM grant or grants amounting to more than five million dollars ($5,000,000) in support of the research that contributed to the creation of the product.

(3) The ICOC shall have the authority to adopt regulations to implement this subdivision. The ICOC shall also have the authority to modify the formulas specified in subparagraphs (A) and (B) of paragraph (2) through regulations if the ICOC determines pursuant to paragraph (1) that a modification is required either in order to ensure that essential medical research, including, but not limited to, therapy development and the broad delivery of therapies to patients, is not unreasonably hindered, or to ensure that the State of California has an opportunity to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials. The ICOC shall notify the appropriate fiscal and policy committees of the Legislature 10 calendar days before exercising its authority to vote on the modification of the formulas specified in subparagraphs (A) and (B) of paragraph (2).

(k) Preference for California Suppliers

The ICOC shall establish standards to ensure that grantees purchase goods and services from California suppliers to the extent reasonably possible, in a good faith effort to achieve a goal of more than 50 percent of such purchases from California suppliers.

SEC. 4. Section 125290.40 of the Health and Safety Code is amended to read:

125290.40. ICOC Functions

The ICOC shall perform the following functions:

(a) Oversee the operations of the institute.

(b) Develop annual and long-term strategic research and financial plans for the institute.

(c) Make final decisions on research standards and grant awards in California.

(d) Ensure the completion of an annual financial audit of the institute's operations.

(e) Issue public reports on the activities of the institute.

(f) Establish policies regarding intellectual property rights arising from research funded by the institute.

(g) Establish rules and guidelines for the operation of the ICOC and its working groups.

(h) Perform all other acts necessary or appropriate in the exercise of its power, authority, and jurisdiction over the institute.

(i) Select members of the working groups.

(j) Adopt, amend, and rescind rules and regulations to carry out the purposes and provisions of this chapter, and to govern the procedures of the ICOC. Except as provided in subdivision (k), these rules and regulations shall be adopted in accordance with the Administrative Procedure Act (Government Code, Title 2, Division 3, Part 1, Chapter 4.5, Sections 11371 et seq.).

(k) Notwithstanding the Administrative Procedure Act (APA), and in order to facilitate the immediate commencement of research covered by this chapter, the ICOC may adopt interim regulations without compliance with the procedures set forth in the APA. The interim regulations shall remain in effect for 270 days unless earlier superseded by regulations adopted pursuant to the APA.

(l) Request the issuance of bonds from the California Stem Cell Research and Cures Finance Committee and loans from the Pooled Money Investment Board.

(m) May annually modify its funding and finance programs to optimize the institute's ability to achieve the objective that its activities be revenue-positive for the State of California during its first five years of operation without jeopardizing the progress of its core medical and scientific research program.

(n) Notwithstanding Section 11005 of the Government Code, accept additional revenue and real and personal property, including, but not limited to, gifts, royalties, interest, and appropriations that may be used to supplement annual research grant funding and the operations of the institute.

(o) Under the guidance of the ICOC, the institute shall create a succession plan addressing changes in leadership of both the institute and the

ICOC designed to minimize disruption and adverse impacts to the activities of the institute. A copy of the succession plan shall be transmitted to the Governor, Controller, and the Legislature within 30 days of its completion. The succession plan should include, but is not limited to:

(1) An assessment of leadership needs before beginning a search.

(2) An outline of succession procedures.

(3) Strategies to ensure successful knowledge transfer.

SEC. 5. Section 125290.45 of the Health and Safety Code is amended to read:

125290.45. ICOC Operations

(a) Legal Actions and Liability

(1) The institute may sue and be sued.

(2) Based upon ICOC standards, institute grantees shall indemnify or insure and hold the institute harmless against any and all losses, claims, damages, expenses, or liabilities, including attorneys' fees, arising from research conducted by the grantee pursuant to the grant, and/or, in the alternative, grantees shall name the institute as an additional insured and submit proof of such insurance.

(3) Given the scientific, medical, and technical nature of the issues facing the ICOC, and notwithstanding Section 11042 of the Government Code, the institute is authorized to retain outside counsel when the ICOC determines that the institute requires specialized services not provided by the Attorney General's office.

(4) The institute may enter into any contracts or obligations which are authorized or permitted by law.

(b) Personnel

(1) The ICOC shall from time to time determine the total number of authorized employees for the institute, excluding members of the working groups who shall not be considered institute employees. The ICOC shall select a chairperson, vice chairperson, and president who shall exercise all of the powers delegated to them by the ICOC. The following functions apply to the chairperson, vice chairperson, and president:

(A) The chairperson's primary responsibilities are to manage the ICOC agenda and workflow including all evaluations and approvals of scientific and medical working group grants, loans, facilities, and standards evaluations, and to supervise all annual reports and public accountability requirements; to manage and optimize the institute's bond financing plans and funding cashflow plan; to interface with the California Legislature, the United States Congress, the California health care system, and the California public; to optimize all financial leverage opportunities for the institute; and to lead negotiations for intellectual property agreements, policies, and contract terms. The chairperson shall also serve as a member of the Scientific and Medical Accountability Standards Working Group and the Scien-

tific and Medical Research Facilities Working Group and as an ex officio member of the Scientific and Medical Research Funding Working Group. The vice chairperson's primary responsibilities are to support the chairperson in all duties and to carry out those duties in the chairperson's absence.

(B) The president's primary responsibilities are to serve as the chief executive of the institute; to recruit the highest scientific and medical talent in the United States to serve the institute on its working groups; to serve the institute on its working groups; to direct ICOC staff and participate in the process of supporting all working group requirements to develop recommendations on grants, loans, facilities, and standards as well as to direct and support the ICOC process of evaluating and acting on those recommendations, the implementation of all decisions on these and general matters of the ICOC; to hire, direct, and manage the staff of the institute; to develop the budgets and cost control programs of the institute; to manage compliance with all rules and regulations of the ICOC, including the performance of all grant recipients; and to manage and execute all intellectual property agreements and any other contracts pertaining to the institute or research it funds.

(2) Each member of the ICOC except, the chairperson, vice chairperson, and president, shall receive a per diem of one hundred dollars ($100) per day (adjusted annually for cost of living) for each day actually spent in the discharge of the member's duties, plus reasonable and necessary travel and other expenses incurred in the performance of the member's duties.

(3) The ICOC shall establish daily consulting rates and expense reimbursement standards for the members of all of its working groups.

(4) Notwithstanding Section 19825 of the Government Code, the ICOC shall set compensation for the chairperson, vice chairperson, and president and other officers, and for the scientific, medical, technical, and administrative staff of the institute within the range of compensation levels for executive officers and scientific, medical, technical, and administrative staff of medical schools within the University of California system and the nonprofit academic and research institutions described in paragraph (2) of subdivision (a) of Section 125290.20.

SEC. 6. Section 125290.60 of the Health and Safety Code is amended to read:

125290.60. Scientific and Medical Research Funding Working Group

(a) Membership

The Scientific and Medical Research Funding Working Group shall have at least 23 members as follows:

(1) Seven ICOC members from the 10 disease advocacy group members described in paragraphs (3), (4), and (5) of subdivision (a) of Section 125290.20.

(2) At least 15 scientists nationally recognized in the field of stem cell research.

(3) The Chairperson of the ICOC.

(b) Functions

The Scientific and Medical Research Funding Working Group shall perform the following functions:

(1) Recommend to the ICOC interim and final criteria, standards, and requirements for considering funding applications and for awarding research grants and loans.

(2) Recommend to the ICOC standards for the scientific and medical oversight of awards.

(3) Recommend to the ICOC any modifications of the criteria, standards, and requirements described in paragraphs (1) and (2) above as needed.

(4) Review grant and loan applications based on the criteria, requirements, and standards adopted by the ICOC and make recommendations to the ICOC for the award of research, therapy development, and clinical trial grants and loans.

(5) Conduct peer group progress oversight reviews of grantees to ensure compliance with the terms of the award, and report to the ICOC any recommendations for subsequent action.

(6) Recommend to the ICOC standards for the evaluation of grantees to ensure that they comply with all applicable requirements. Such standards shall mandate periodic reporting by grantees and shall authorize the Scientific and Medical Research Funding Working Group to audit a grantee and forward any recommendations for action to the ICOC.

(7) Recommend its first grant awards within 60 days of the issuance of the interim standards.

(c) Recommendations for Awards

Award recommendations shall be based upon a competitive evaluation as follows:

A peer review panel shall consist of both scientists and patient advocates. There shall be 15 scientists on a peer review panel. Only the scientist members of the Scientific and Medical Research Funding Working Group shall score grant and loan award applications for scientific merit. Such scoring shall be based on scientific merit in three separate classifications--research, therapy development, and clinical trials, on criteria including the following:

(1) A demonstrated record of achievement in the areas of pluripotent stem cell and progenitor cell biology and medicine, unless the research is determined to be a vital research opportunity.

(2) The quality of the research proposal, the potential for achieving significant research, or clinical results, the timetable for realizing such

significant results, the importance of the research objectives, and the innovativeness of the proposed research.

(3) In order to ensure that institute funding does not duplicate or supplant existing funding, a high priority shall be placed on funding pluripotent stem cell and progenitor cell research that cannot, or is unlikely to, receive timely or sufficient federal funding, unencumbered by limitations that would impede the research. In this regard, other research categories funded by the National Institutes of Health shall not be funded by the institute.

(4) Notwithstanding paragraph (3), other scientific and medical research and technologies and/or any stem cell research proposal not actually funded by the institute under paragraph (3) may be funded by the institute if at least two-thirds of a quorum of the members of the Scientific and Medical Research Funding Working Group recommend to the ICOC that such a research proposal is a vital research opportunity.

SEC. 7. Section 125290.71 is added to the Health and Safety Code, to read:

125290.71. Under the guidance of the ICOC, the institute shall, by January 31, 2012, create a transition plan addressing the expiration of current bond funding. A copy of the transition plan shall be transmitted to the Governor, the Controller, and the Legislature within 30 days of its completion.

SEC. 8. Section 125290.80 is added to the Health and Safety Code, to read:

125290.80. The intellectual property standards that the ICOC develops shall include:

(a) A requirement that each grantee or the exclusive licensee of the grantee submit a plan to CIRM to afford access to any drug that is, in whole or in part, the result of research funded by CIRM to Californians who have no other means to purchase the drug. The access plan must be consistent with industry standards at the time of commercialization in California, accounting for the size of the market for the drug, and the resources of the grantee or exclusive licensee.

(b) A requirement that the grantee or exclusive licensee either submit the plan required by subdivision (a), seek an extension from CIRM, or notify CIRM of its intention to seek a waiver, within 10 business days following final approval of the drug by the federal Food and Drug Administration. If the grantee seeks an extension, the plan must be submitted within 30 business days following final approval of the drug by the federal Food and Drug Administration. The plan shall be subject to the approval of CIRM, after a public hearing and opportunity for public comment.

(c) A process by which the ICOC may waive the requirement in subdivision (a) if the ICOC determines, after a public hearing, that in the absence

of the waiver, development and broad delivery of the drug will be unreasonably hindered or that the waiver will provide significant benefits that equal or exceed the benefits that would otherwise flow to the state pursuant to subdivision (a). The process shall include the requirement that a request for a waiver shall be posted on CIRM's Internet Web site for a minimum of 10 business days in advance of the public hearing and that CIRM shall notify the Legislature if the ICOC grants a waiver request, including the reasons that justified the waiver request.

(d) Procedures to protect from public disclosure proprietary information submitted by grantees and exclusive licensees to CIRM pursuant to this section.

Appendix E

Committee Biographies

Harold T. Shapiro, Ph.D. (*Chair*), currently holds a faculty appointment as professor of economics and public affairs at Princeton University. He served as the university's 18th president from 1988 until 2001. He came to Princeton from the University of Michigan, where he served on the faculty for 24 years as professor of economics and public policy and as president from 1980 to 1988. He also served as chairman of the executive board of the University of Michigan Hospitals from 1977 to 1988. His fields of special interest have included econometrics; mathematical economics; science policy; the evolution of higher education as a social institution; and, more recently, bioethics. From July 1996 to October 2001, Dr. Shapiro served as chair of the National Bioethics Advisory Commission, which issued six major reports in the period 1996-2001. From 1990 to 1992, he served as a member and vice chair of President Bush's Council of Advisors on Science and Technology. Dr. Shapiro received his bachelor's degree from McGill University in 1956. Then, after 5 years in business, he enrolled in the Graduate School at Princeton and earned his Ph.D. in 1964.

Terry Magnuson, Ph.D. (*Vice Chair*), is vice dean for research of the School of Medicine, S.G. Kenan professor and chair of the Department of Genetics, and director of the Cancer Genetics Program of the Lineberger Comprehensive Cancer Center at the University of North Carolina (UNC) at Chapel Hill. Dr. Magnuson was recruited to UNC in 2000 as founding chair of the Department of Genetics and director of the newly established Carolina Center for Genome Sciences. He also created the Cancer Genetics Program in the UNC Lineberger Comprehensive Cancer Center. He was appointed

vice dean for research in the School of Medicine in July 2010. The work in the Magnuson laboratory focuses on the role of mammalian genes in unique epigenetic phenomena such as genomic imprinting, X-chromosome inactivation, and stem cell pluripotency. The laboratory also studies the tumor suppressor role of the BAF/PBAF chromatin remodeling complexes and has developed a novel genome-wide mutagenesis strategy. Dr. Magnuson received his Ph.D. from Cornell University and was a postdoctoral fellow at the University of California, San Francisco (UCSF).

Richard R. Behringer, Ph.D., is professor and Ben F. Love chair in cancer research in the Department of Genetics at The University of Texas MD Anderson Cancer Center. His research focuses on the molecular and cellular mechanisms that lead to the formation of the mammalian body plan, the genesis of tissues and organs during embryogenesis, and the pathology of developmental defects. He also studies the genetic mechanisms that result in organ morphology and physiology differences that have evolved among species. Dr. Behringer obtained his Ph.D. in biology from University of South Carolina and completed his postdoctoral training at the University of Pennsylvania and the University of Washington.

Rebecca S. Eisenberg, J.D., is Robert and Barbara Luciano professor of law at the University of Michigan School of Law. She began her career following law school as law clerk for Chief Judge Robert F. Peckham on the U.S. District Court for the Northern District of California and then practiced law as a litigator in San Francisco. She joined the Michigan School of Law faculty in 1984. Professor Eisenberg regularly teaches courses in patent law, trademark law, and U.S. Food and Drug Administration (FDA) law, and runs workshops on intellectual property and student scholarship. She has previously taught courses on torts, legal regulation of science, and legal issues in biopharmaceutical research. She has written and lectured extensively about the role of intellectual property in biopharmaceutical research, publishing in scientific journals as well as law reviews. Dr. Eisenberg received her J.D. from Boalt Hall School of Law at the University of California, Berkeley.

Insoo Hyun, Ph.D., is associate professor of bioethics and philosophy at Case Western Reserve University School of Medicine. His research interests include ethical and policy issues in stem cell research, social justice, medical decision making, and health resource allocation. In 2005, Dr. Hyun was awarded a Fulbright Research Award by the U.S. Department of State to study the ethical, legal, and cultural dynamics of human research cloning in South Korea. In 2006 he chaired the Subcommittee on Human Biological Materials Procurement for the International Embryonic Stem Cell Guidelines Task Force, a multinational, multidisciplinary working group for the

International Society for Stem Cell Research (ISSCR). In 2007 he served as co-chairperson of the ISSCR Task Force on International Guidelines for the Clinical Translation of Stem Cells. Dr. Hyun is the past chairperson of the ISSCR's Ethics and Public Policy Committee. He received his B.A. and M.A. in philosophy from Stanford University and his Ph.D. in philosophy from Brown University.

Gary A. Koretzky, M.D., Ph.D., is Francis C. Wood professor of medicine, vice chair for research, and chief scientific officer, Perelman School of Medicine at the University of Pennsylvania. He also serves as co-program leader of the Immunobiology Research Program in the Abramson Cancer Center. Dr. Koretzky is recognized for his research contributions to the understanding of the development and mechanisms of activation of cells of the immune system. His laboratory has identified a number of novel proteins that regulate signals downstream of key immune cell receptors and has demonstrated their critical importance using in vitro and in vivo approaches. Dr. Koretzky also has interest and experience in developing new and evaluating existing research programs. He graduated from the University of Pennsylvania School of Medicine M.D./Ph.D. program. He then completed his residency in internal medicine and fellowship training in rheumatology at the University of California, San Francisco.

Cato T. Laurencin, M.D., Ph.D., is a university professor at the University of Connecticut (the seventh in that institution's history). In addition, he is the Albert and Wilda Van Dusen distinguished endowed professor of orthopaedic surgery and professor of chemical, materials, and biomolecular engineering. Dr. Laurencin is director of the Institute for Regenerative Engineering and director of the Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Science. In addition, he serves as chief executive officer of the Connecticut Institute for Clinical and Translational Science at the University of Connecticut. He earned his B.S.E. in chemical engineering from Princeton University, his M.D. magna cum laude from Harvard Medical School, and his Ph.D. in biochemical engineering/biotechnology from the Massachusetts Institute of Technology. Dr. Laurencin completed his residency in orthopaedic surgery at the Harvard Combined Orthopaedic Surgery Program. He completed a fellowship at Cornell University Medical Center/The Hospital for Special Surgery in sports medicine and shoulder surgery. An expert in shoulder and knee surgery, Dr. Laurencin is an international leader in musculoskeletal regenerative research. He is an elected member of both the Institute of Medicine and the National Academy of Engineering. Internationally, he is a fellow of the African Academy of Sciences. Dr. Laurencin has been heavily involved in mentoring activities. In recognition of his work, he received the Presidential

Award for Excellence in Science, Mathematics and Engineering Mentoring in ceremonies at the White House in 2010.

Aaron D. Levine, Ph.D., M.Phil., is assistant professor in the School of Public Policy at the Georgia Institute of Technology. His research focuses on understanding how the policy environment influences the development of ethically contentious new technologies, particularly in the life sciences. His recent work has focused on both stem cell policy and the fertility industry. Dr. Levine is the author of *Cloning: A Beginner's Guide*, an introduction to the science of cloning and embryonic stem cells and the ethical and policy debates this science inspires. He completed his Ph.D. in public affairs at the Woodrow Wilson School at Princeton University. He also holds an M.Phil. in biological sciences from the University of Cambridge.

Michael H. May, Ph.D., is chief executive officer of the Centre for Commercialization of Regenerative Medicine (CCRM) in Canada. Hosted by the University of Toronto, CCRM brings together leading regenerative medicine experts from the University of Toronto and McMaster University with researchers from the Hospital for Sick Children, the University Health Network, the Ottawa Hospital Research Institute, and Mount Sinai Hospital to accelerate research and development in regenerative medicine and create a commercialization pipeline that rapidly brings regenerative medicine technologies to market. Previously, he was president and chief operating officer of Rimon Therapeutics Ltd., a Toronto-based regenerative medicine company developing novel medical polymers with drug-like activity. Dr. May completed his Ph.D. in chemical engineering at the University of Toronto.

Cheryl A. Moore is executive vice president and chief operating officer of the Howard Hughes Medical Institute (HHMI). She leads collaborative strategic efforts and oversees key operational functions including communications, facilities, finance, human resources, information technology, and procurement. Formerly chief operating officer at the Institute's Janelia Farm Research Campus, she played a pivotal role in Janelia's development and was responsible for all operational aspects of the campus and its $100 million annual budget. Prior to joining HHMI, Ms. Moore served as senior vice president and chief operating officer of what is now known as the Sanford-Burnham Institute for Medical Research in La Jolla, California. Ms. Moore spent much of her professional career in the San Diego area, where she also held top management positions with an international financial services firm and both startup and public health care companies. She received her B.S. in business administration from the University of San Diego.

Stuart H. Orkin, M.D., is chairman of Department of Pediatric Oncology at Dana-Farber Cancer Institute (DFCI); associate chief of the Division of Hematology-Oncology at the Children's Hospital, Boston; and David G. Nathan professor of pediatrics at Harvard Medical School. Dr. Orkin is a Howard Hughes Medical Institute investigator. His research focuses on stem cell biology, particularly the development and function of the blood system, the relationship between cancer and stem cells, and the mechanisms responsible for self-renewal of stem cells. Dr. Orkin received his M.D. degree from Harvard Medical School, followed by postdoctoral research at the National Institutes of Health and clinical training in pediatrics and hematology-oncology at Children's Hospital Boston and DFCI. He is a member of the National Academy of Sciences and the Institute of Medicine.

Allen M. Spiegel, M.D., is Marilyn and Stanley M. Katz Dean, Albert Einstein College of Medicine of Yeshiva University. He began his career at the National Institutes of Health (NIH) in 1973 as a clinical associate in its Endocrinology Training program. He then served as a senior investigator in the Metabolic Disease Branch from 1977 to 1984. In 1985, he was appointed chief of molecular pathophysiology, and he then became chief of the Metabolic Diseases Branch. In 1990, he was appointed director of the National Institute of Diabetes and Digestive and Kidney Disorders' (NIDDKs') Division of Intramural Research. From 1999 to 2006, he served as director of NIDDK. In that capacity, he served as vice chair of the NIH Stem Cell Task Force and testified on numerous occasions in Congress at hearings related to NIH support for stem cell research. Currently, he serves on the medical advisory board of the NY Stem Cell Foundation and on the Empire State Stem Cell Funding Board. Dr. Spiegel earned his bachelor's degree from Columbia University and his M.D. degree from Harvard Medical School. He completed his clinical training at Massachusetts General Hospital.

Sharon Terry, M.A., is president and chief executive officer of Genetic Alliance, a network transforming health by promoting openness as process and product, centered on the health of individuals, families, and communities. She is also the founding chief executive officer of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). Following the diagnosis of their two children with PXE in 1994, Ms. Terry, a former college chaplain, and her husband, Patrick, founded and built a dynamic organization that enables ethical research and policies and provides support and information to members and the public. She co-directs a 33-laboratory research consortium and manages 52 offices worldwide for PXE International. Ms. Terry is also a co-founder of the Genetic Alliance Biobank, a centralized biological and data reposi-

tory catalyzing translational genomic research on genetic diseases. She is at the forefront of consumer participation in genetics research, services, and policy and serves as a member of many of the major governmental advisory committees on biomedical research. In 2005, she received an honorary doctorate from Iona College for her work in community engagement and haplotype mapping. She was elected an Ashoka Fellow in 2009 and received the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011.