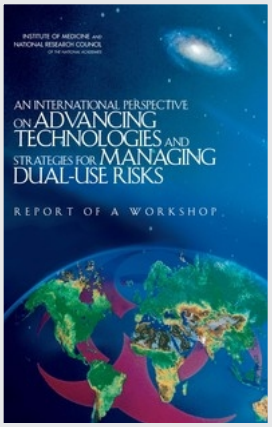

An International Perspective on Advancing Technologies and Strategies for Managing Dual-Use Risks: Report of a Workshop

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AN INTERNATIONAL PERSPECTIVE ON ADVANCING TECHNOLOGIES AND STRATEGIES FOR MANAGING DUAL-USE RISKS

REPORT OF A WORKSHOP

Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats

Development, Security, and Cooperation
Policy and Global Affairs
Board on Global Health

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This study was supported by contracts between the National Academies and the Department of Homeland Security; Centers for Disease Control; Food and Drug Administration; the NIAID; the National Science Foundation; and the Intelligence Technology Innovation Center. The views presented in this report are those of the National Research Council and Institute of Medicine Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats and are not necessarily those of the funding agencies.

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Preface

Life sciences knowledge, materials, and technologies are advancing worldwide at a dizzying and ever-accelerating rate.[1] It is undeniable that this new scientific knowledge and these advancing technologies hold extraordinary potential to improve public health and the quality of life for people worldwide, strengthen national economies, and close the development gap between the North and South. However, as with all scientific revolutions, there is a potential dark side to the advancing power and global spread of biotechnology. Every major new technology has been used for hostile purposes, and many experts believe it naive to think that the extraordinary growth in the life sciences and its associated technologies might not be similarly exploited for malevolent purposes.

The global spread of expertise in biotechnology and biological manufacturing processes raises concerns about how these advancing technological capabilities could not only alter the research and development landscape in the life sciences, but also enable the creation and production of new agents of biological origin with unique and unpredictable characteristics. The *Committee on Advances in Technology and the Prevention of Their*

[1]The pace of technological change has often been referred to as "Moore's-like." Moore's Law pertains to the rapid rate of technological development and advances in the semiconductor industry, specifically the doubling of the number of transistors on integrated circuits that occurs approximately every 18 months. Although advances in the life sciences occur in a discontinuous and random fashion and are driven by new conceptual breakthroughs in understanding of biological processes, it is a useful metaphor for the exponential growth of knowledge related to biology.

Application to Next Generation Biowarfare Threats, an ad hoc committee of the National Research Council and the Institute of Medicine, is examining current trends and future objectives of research in the life sciences, as well as converging technologies from other fields such as materials science, bioinformatics, and nanotechnology, that may enable the development of a new generation of biological threats over the next five to ten years, with the aim of identifying ways to anticipate, identify and mitigate this danger.

ABOUT THE WORKSHOP

As part of its study, the committee held a workshop at the *Instituto Nacional de Salud Publica* (National Institute of Public Health) in Cuernavaca, Mexico, in September 2004. The purpose of the workshop was to sample global perspectives on the current advancing technology landscape. Experts from different fields and from around the world presented their diverse outlooks on advancing technologies and forces that drive technological progress; local and regional capabilities for life sciences research, development, and application (both beneficial and malevolent); national perceptions and awareness of the risks associated with advancing technologies; and measures that have been taken, or could or should be taken, to reduce the potential for misapplication of technology(ies) for malevolent purposes. This report summarizes the formal and informal discussions held at the workshop.

Rather than an exhaustive analysis, the workshop was designed to take a limited number of snapshots of the current global technological landscape, the forces that drive it, and new capabilities that may emerge from it, particularly with respect to the dual-use risk of advancing technologies (as used in this discussion, "dual-use" refers to the potential of beneficial research advances to be exploited for malevolent purposes). The workshop was not intended to spawn recommendations or conclusions. The information summarized in these five chapters was gathered in the expectation that it would help inform the committee concerning the range of perspectives on this issue, which is of global importance and which can only be dealt with in a global context, as it seeks to develop its report on advancing technologies and the prevention of their application to next-generation bioterrorism and biological warfare threats. The final release of that report is planned for September 2005.

The workshop provided strong evidence that the global technology landscape is shifting dramatically and rapidly, in terms of the types of technological advances being made, the capabilities being acquired, and the geographical spread and distribution of these advances and capabilities. While some of the most recent advances in biotechnology, such as

control of gene expression through RNA interference or the development of entirely new genes using combinatorial approaches coupled with biological selection, have remained relatively restricted in their use, the proceedings from this workshop make it abundantly clear that advances in genomic sequencing, DNA synthesis, computing, and bioinformatic techniques have already profoundly shaped the international technology landscape of today. As highlighted in Cuernavaca, the global spread of these technologies has led to the establishment of globally dispersed, national genomic medicine platforms; high throughput microbial sequencing; efforts to develop novel high capacity, low cost production methods, such as plant-based manufacturing of vaccines, antibodies, and other pharmaceuticals; and advances in transgenic crop bioengineering.

This burgeoning genetic knowledge base and technological growth is unequivocally global. China has some 20,000 people working in 200 biotechnology laboratories nationwide, has created 150 transgenic crops, and is a world leader in the production of protein-enhanced materials. Cuba supports a major drug and biotechnology program, which includes the production of a meningococcal serotype B vaccine and a number of other pharmaceuticals that are being sold worldwide. South Korea performed what may be the world's first successful human cloning experiment, and is positioning itself as a leader in stem cell research. Singapore is investing billions of dollars in biotechnology, declaring it to be the "fourth pillar" of its economy. More than 76 sequencing centers worldwide, including centers in Brazil and China, have participated in sequencing at least one complete microbial genome.

The global dissemination of life sciences knowledge and advancing technological capacity is being driven not only by the growing use of international subcontracting and technology cooperation agreements but, as much or more by national decisions to strengthen economy, public health, and national security, as well as international decisions to close the development gap between developed and less developed economies. It is accelerated by both long-term and short-term exchanges of life scientists between lesser developed countries and countries such as the United States and those in Western Europe and Asia.

This rapid growth and dispersion of tools, technology, and knowledge in the life sciences enterprise will likely accelerate in the first decade of the 21st century. This phenomenon is to be expected and welcomed, since the application of these advancing technologies research and development activities in the life sciences holds tremendous potential for ensuring the security of the global food supply and advancing human health worldwide.

As with all technological revolutions, the potential always exists for intentional or inadvertent misapplication. It is inevitable that these rapid

technological advances, accompanied by a growing understanding of human life at the level of systems biology, will place the potential for greater destructive power into the hands of the technologically able and point the way to dangerous, subtle, and insidious novel ways to cause human, animal, and plant disease, create economic and political chaos, and catalyze societal disruption. The United States, and the global community, need to consider in a collective fashion how they may best cope with the increasing risks posed by the global proliferation of knowledge, technology, equipment, and materials.

Some analysts argue that the difficulties inherent in creating, manufacturing, and delivering bioweapons are prohibitive and limit the utility (and thus the threat) of such weapons.[2] Others argue that, on the contrary, bioweapons are the "poor man's atomic bomb" and thus have the potential to create as much, if not more, human misery and terror than any other weapon of mass destruction (WMD).[3] Either way, the unpredictability of future state and non-state efforts to acquire and employ biological weapons poses a serious vulnerability to national and global stability and security.

On the first day of the workshop, presentations and discussions were divided into two sessions. In the first session, "Drivers of Global Technological Development," the goal was to address the following questions: Why have advancing technologies grown in the directions that they have, and what are some of the obstacles that groups, nations, and regions face in their pursuit of the positive aspects of technology growth? In the second session, "The Global Landscape of Technology/Efforts to Mitigate Risks for Misapplication," presentations and discussion focused on how advancing technological opportunities are being exploited for beneficial purposes.

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[2]Guillemin, J. 2005. *Biological Weapons: From the Invention of State-Sponsored Programs to Contemporary Bioterrorism*; Columbia University Press, New York; Cohen, H. W. 2004. "The pitfalls of bioterrorism preparedness: the anthrax and smallpox experiences." *American Journal of Public Health* 94:1667-71, October; *Combating Terrorism: Need for Comprehensive Threat and Risk Assessments of Chemical and Biological Attacks: Report to Congressional Requesters.* Washington, DC: US General Accounting Office; 1999:1-35. GAO publication NSIAS-99-163; Squassoni, S. 2004. "Nuclear, Biological, and Chemical Weapons and Missiles: Status and Trends." CRS Report for Congress, July 2 (RL30699).

[3]S. Squassoni et al., "Proliferation Control Regimes: Background and Status," Report for Congress RL31559. The term "weapons of mass destruction" has been defined by the United Nations to include "atomic explosive weapons, radio-active materials weapons, lethal chemical and biological weapons, and any weapons developed in the future which have characteristics comparable in destructive effect to those of the atomic bomb. . . ." United Nations Security Council, Commission for Conventional Armaments: "Resolution Adopted by the Commission at its Thirteenth Meeting, 12 August 1948, and a Second Progress Report of the Commission," S/C.3/32/Rev.1; 12 August 1948, at page 2.

On the second day of the workshop there were also two sessions: "Safeguarding the Benefits of Technology—Addressing the Dual-Use Dilemma" and "Emerging and Converging Technologies." The goal of the former was to provide a global perspective on the wide range of measures currently being implemented or explored as viable strategies for managing the dual-use dilemma. The goal of the latter was to explore some emerging technologies, future technological trajectories, and the dynamic evolution of new dual-use risks with time.

ACKNOWLEDGMENTS

The *Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats*, an ad hoc committee of the National Research Council and the Institute of Medicine, wishes to express its warmest appreciation to the individuals and organizations who gave valuable time to provide information and advice to the Committee through their participation in the workshop. A full list of presenters can be found in Appendix B. The Committee is also indebted to the NRC and IOM staff who contributed during the course of the workshop and to the production of this workshop summary. On behalf of the Committee we gratefully acknowledge the efforts led by Eileen Choffnes and Stacey Knobler, co-Study Directors of the Committee, Elizabeth Kitchens, research associate, and Kate Giamis, senior program assistant, who dedicated much effort and time to developing this workshop's agenda and final report of the workshop, and our technical writer Leslie Pray, for her thoughtful and insightful approach and skill in translating the workshop proceedings and discussion into this workshop summary. We would also like to thank the following staff at the Instituto National de Salud Publica: Mauricio Hernandez Ávila, Executive Director of the National Institute of Public Health; Jaime Sepúlveda Amor, Director of the National Institutes of Health; and Juan Manuel Álvarez Iraizos, Logistics Coordinator. Without their generous offer of a venue for this meeting and logistical support throughout the planning and execution of this activity the workshop would not have been possible.

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 NRC'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 quality and objectivity. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We wish to thank the following individuals for their review of this

report: Uri Dadush, The World Bank; Stephen Johnston, University of Texas; Michael Oborne, Organisation for Economic Co-operation and Development; and Terry Taylor, The International Institute for Strategic Studies.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the content of the report, nor did they see the final draft before its release. The review of this report was overseen by Gail Cassell, Eli Lilly and Company. Appointed by the National Research Council, she was 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.

Finally, the Committee also thanks sponsors that supported this activity. Financial support for this project was provided by the U.S. Department of Health and Human Services' National Institutes of Health, Centers for Disease Control and Prevention, and Food and Drug Administration; the Intelligence Technology Innovation Center; the Department of Homeland Security; and the National Science Foundation. The views presented in this workshop summary are those of the editors and workshop participants and are not necessarily those of the funding organizations.

Stanley M. Lemon
Co-Chair

David A. Relman
Co-Chair

Contents

1 INTRODUCTION 1
About the Workshop, 2
Organization of This Report, 5

2 THE INTERNATIONAL PERSPECTIVE ON THE BIOTECHNOLOGY LANDSCAPE 7
Genomic Technology, 8
Plants as a Manufacturing Platform, 19
Transgenic Crops, 28

3 DRIVERS OF INTERNATIONAL BIOTECHNOLOGY DEVELOPMENT 25
Economic Drivers, 36
Social Drivers, 43
Political Drivers, 51

4 EMERGING AND CONVERGING TECHNOLOGIES 57
Bioregulators and Innate Immunity, 59
DNA Nanotechnology, 64
Converging Technologies, 67

5 MODELS FOR MANAGING CHANGE 73
Arms Control, 75
Non-BWC Tools, 92
Informal Strategies, 95

APPENDIXES

A WORKSHOP AGENDA 113
B PARTICIPANTS LIST 119
C COMMITTEE MEMBER AND PARTICIPANTS BIOSKETCHES 121

1

Introduction

Life sciences knowledge, materials, and technologies are advancing worldwide with Moore's Law-like speed.[1] It is undeniable that this new scientific knowledge and these advancing technologies hold extraordinary potential to improve public health and the quality of life for people worldwide, strengthen national economies, and close the development gap between the North and South. However, as with all scientific revolutions, there is a potential dark side to the advancing power and global spread of biotechnology. Every major new technology has been used for hostile purposes, and many experts believe it naive to think that the extraordinary growth in the life sciences and its associated technologies might not be similarly exploited for nefarious purposes.

The threat of bioterrorism, coupled with the global spread of expertise in biotechnology and biological manufacturing processes, raise concerns about how this advancing technological prowess could enable the creation and production of new agents of biological terrorism with unique and unpredictable characteristics. The *Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats*,

[1]Moore's Law pertains to the rapid rate of technological development and advances in the semiconductor industry, specifically the doubling of the number of transistors on integrated circuits that occurs approximately every 18 months. Although advances in the life sciences occur at more random intervals and are driven by new conceptual breakthroughs in understanding of biological processes, it is a useful metaphor for the exponential growth of knowledge related to biology.

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Rather than an exhaustive analysis, the workshop was designed to take a limited number of snapshots of the current global technological landscape, the forces that drive it, and new capabilities that may emerge from it, particularly with respect to the dual-use risk of advancing technologies (as used in this discussion, the "dual-use risk" refers to beneficial applications that have the potential to be exploited for malevolent purposes). The workshop was not intended to spawn recommendations or conclusions. The information gathered, as summarized in these five chapters, will inform the committee in developing its report on advancing technologies and the prevention of their application to next-generation bioterrorism and biological warfare threats. The final release of that report is planned for late 2005.

The global technology landscape is shifting dramatically and rapidly, both in terms of the types of technological advances being made and the geographical spread and distribution of these advances. Although some of the most recent advances in biotechnology, such as control of gene expression through RNA interference or the development of entirely new genes using combinatorial approaches coupled with biological selection, remain relatively restricted in their use, the proceedings from this workshop made it abundantly clear that advances in genomic sequencing, com-

puting, and bioinformatic techniques have already profoundly shaped the international technology landscape of today. As highlighted in Cuernavaca, the global spread of these technologies has led to the establishment of national genomic medicine platforms; high throughput microbial sequencing; the development of novel production methods, such as plant-based manufacturing of vaccines, antibodies, and other pharmaceuticals; and advances in transgenic crop bioengineering.

This burgeoning genetic knowledge base and technological growth is unequivocally global. China has some 20,000 people working in 200 biotechnology laboratories nationwide, has created 150 transgenic crops, and is a world leader in the production of protein-enhanced materials. Cuba boasts a major drug and biotechnology program, including the production of a meningococcal serotype B vaccine and a number of other pharmaceuticals that are being sold worldwide. South Korea performed what may be the world's first successful therapeutic cloning experiment and is positioning itself as a leader in stem cell research. Singapore is investing billions of dollars in biotechnology, declaring it to be the "fourth pillar" of its economy. More than 76 sequencing centers worldwide, including centers in Brazil and China, have participated in sequencing at least one complete microbial genome.

The global dissemination of life sciences knowledge and advancing technological capacity is being driven not only by the growing use of international subcontracting and technological cooperation agreements, but also by national decisions to strengthen economy, public health, and national security, as well as international decisions to close the development gap between the North and South. It is accelerated by both long-term and short-term exchanges of biological scientists between lesser developed countries and countries such as the United States and those in Western Europe and Asia. This rapid growth and dissemination of biotechnology is unstoppable, as it should be, since advancing technologies holds tremendous potential for advancing the human security[2] of the global population.

As with all technological revolutions, the potential always exists for intentional or inadvertent misapplication. These rapid technological advances, accompanied by a growing understanding of the molecular, biochemical, and physiological pathways of living organisms, particularly with respect to innate immunity, and the control of gene expression, almost inevitably place greater destructive power into the hands of the

[2]Human security, as distinct from national or state security, is the condition or state of being characterized by freedom from pervasive threats to people's rights; these threats include economic, food-security, health, environmental, and political situations. "Human Security Now," *http://www.humansecurity-chs.org/*. Accessed November 1, 2004.

technologically able and point the way to dangerous, subtle, and insidious ways to cause human disease and catalyze economic and political consequences. The United States and the world need a new way of thinking about how to live with the increasing risks posed by the global proliferation of knowledge, technology, equipment, and materials.

Some analysts argue that the inherent difficulties in obtaining and handling the materials necessary to create, manufacture, and disseminate bioweapons are prohibitive and limit the utility (and threat) of such weapons.[3] Others argue that, on the contrary, bioweapons are the "poor man's atomic bomb" and thus have the potential to create as much, if not more, human misery and terror than any other weapon of mass destruction (WMD).[4] Either way, the unpredictability of state and non-state efforts to acquire and employ biological weapons poses a serious vulnerability to national, and global, stability and security.

On the first day of the workshop, presentations and discussions were divided into two sessions. In the first session, "Drivers of Global Technological Development," the goal was to address the following questions: Why have advancing technologies grown in the directions that they have, and what are some of the obstacles that groups, nations, and regions face in their pursuit of the positive aspects of technology growth? In the second session, "The Global Landscape of Technology/Efforts to Mitigate Risks for Misapplication," presentations and discussion focused on how advancing technological opportunities are being exploited for beneficial purposes.

On the second day of the workshop there were, again, two sessions: "Safeguarding the Benefits of Technology—Addressing the Dual-Use Dilemma" and "Emerging and Converging Technologies." The goal of the former was to provide a global perspective on the wide range of measures currently being implemented or explored as viable strategies for managing the dual-use dilemma. The goal of the latter was to explore some emerging technologies, future technological trajectories, and the dynamic evolution of new dual-use risks with time.

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[3]Guillemin, J. 2005. *Biological Weapons: From the Invention of State-Sponsored Programs to Contemporary Bioterrorism*; Columbia University Press, New York; Cohen, H. W. 2004. "The pitfalls of bioterrorism preparedness: the anthrax and smallpox experiences." *American Journal of Public Health* 94:1667-71, October; *Combating Terrorism: Need for Comprehensive Threat and Risk Assessments of Chemical and Biological Attacks: Report to Congressional Requesters.* Washington, DC: US General Accounting Office; 1999:1-35. GAO publication NSIAS-99-163; Squassoni, S. 2004. "Nuclear, Biological, and Chemical Weapons and Missiles: Status and Trends." CRS Report for Congress, July 2 (RL30699).

[4]Squassoni, S. et al. 2005. "Proliferation Control Regimes: Background and Status." Report for Congress, February 10 (RL31559).

ORGANIZATION OF THIS REPORT

Chapter 2 of this report summarizes workshop presentations on several features of the global advancing technologies landscape, with a focus on genomic medicine in Mexico and Singapore; microbial genomic sequencing; plant-derived pharmaceuticals; and transgenic crop bioengineering. Again, the workshop presentations and dialogue summarized here provide only a limited snapshot of the current global landscape.

Chapter 3 of this report summarizes the complex set of forces driving the global proliferation of advancing technologies. Also included in this chapter is a brief account of South Africa's former bioweapons program.

Chapter 4 provides a summary of workshop presentations and discussion on emerging technologies, many of which have yet to be applied. These discussions complemented others held by the committee during its previous meetings. The goal of exploring these emerging technologies was to capture a transitory view of some emerging technologies with dual-use potential. Given that advancing technologies have exhibited extraordinarily rapid growth and will likely continue to do so, one workshop participant wondered how different this view might be if the workshop were held just a few years in the future.

Chapter 5 summarizes steps currently being taken in response to the dual-use dilemma and lessons to be learned from other relevant risk experiences, most notably nuclear weaponry. Major topics of discussion were the opportunities and challenges associated with the Biological Weapons Convention (BWC); opportunities and challenges associated with various non-BWC activities, such as those of the Australia Group; and issues pertaining to the role of the individual scientist in managing the dual-use risk of advancing technologies and whether and how a code of conduct might be useful. The chapter concludes with a summary of general approaches for addressing the dual-use risk of advancing technologies.

This summary provides an account of presentations and discussions that took place during the two-day workshop. It bears emphasizing again that the material presented in this and the following chapters represents the views and opinions of individual workshop participants only and are not to be construed as reflective of the deliberations of a formally constituted study committee. It is not intended to be an exhaustive exploration of the subject matter and has contributed to the larger information-gathering efforts of the committee.

2

The International Perspective on the Biotechnology Landscape

The global technology landscape is shifting dramatically and rapidly, both in terms of the types of technological advances being made and the geographical spread and distribution of these advances. Some of the most prominent technological features of today's landscape are derived from recent advances in genomic sequencing, computing, and bioinformatic technologies. As highlighted during the workshop, these include the establishment of national genomic medicine platforms; high throughput microbial sequencing; the research and development of plant-based manufacturing of vaccines, antibodies, and other pharmaceuticals; and advances in transgenic crop bioengineering. This chapter provides a summary of workshop presentations and discussion on these topics.

One of the most prominent features of today's global advancing technology landscape is the range of biomedical possibilities afforded by the 2001 completion of the draft human genome—from the discovery of molecular mechanisms of disease to the development of a new generation of diagnostic tools.[1] The biomedical applications of genomic knowledge are expected to culminate ultimately in the personalized practice of medicine. Although many analysts do not expect personalized—or genomic—medicine to become an affordable, widespread reality for another 10 to 20 years, steps are being taken now and plans are being made to accommo-

[1]The International Human Genome Mapping Consortium. 2001. "A physical map of the human genome." *Nature* 409:934-941, February 15; Venter J. C. et al. 2001. "The sequence of the human genome." *Science* 291:1304-1351.

date the new medicine when it does arrive. Both Singapore and Mexico are aggressively developing national genomic medicine platforms.

Importantly, the human genome is not the only genome that has been sequenced nor the only one from which society can benefit. Beginning with the first complete genetic map of a free-living organism, the bacterium *Haemophilus influenzae*, in 1995,[2] scientists have sequenced more than 200 complete microbial genomes. Although The Institute for Genomic Research (TIGR), Maryland, and The Sanger Institute, Cambridge, UK, lead the world in genomic sequencing, more than 75 centers worldwide have sequenced at least one microbial genome. Included in this chapter is a summary of TIGR's high-throughput sequencing capabilities.

Another large section of this chapter is devoted to plant-based technology platforms, for example plant-based vaccines and transgenic crop technology. Plant-based pharmaceutical manufacturing and transgenic crop technology promise untold economic and societal benefits, particularly for the developing world. Transgenic crop technology, by requiring little initial capital investment, may provide a low-cost means of vaccine production. Experimental data have established proof-of-concept that plant-based vaccines induce immunity, but technical and regulatory obstacles are preventing the field from moving forward more quickly. By contrast, many of the limiting technical challenges of the transgenic crop industry have been overcome, yet the use of the technology is still limited to only a few countries, crops, plant species, and traits.

GENOMIC TECHNOLOGY[3]

Genomic Medicine in Mexico[4]

Mexico is in the process of developing one of the first genomic medicine platform in Latin America, one that is expected to serve as a regional model for other countries in their efforts to ease health and financial burdens (see Figure 2-1). Not only does Mexico view its effort as a strategic tool for the development of the country as a whole (i.e., with respect to public health, biomedical sciences, biotechnology, and the economy), but also with respect to strengthening national security and preserving Mexican sovereignty. The present time presents a window of opportunity for investment in this emerging medical technological trend, so as to mini-

[2]Fleischmann, R. D. et al. 1995. "Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd." *Science* 269:496-512.

[3]This section is based on the workshop presentations of Gerardo Jimenez-Sanchez, Patrick Tan Boon Ooi, and Jacques Ravel.

[4]This subsection based on the workshop presentation of Gerardo Jimenez-Sanchez.

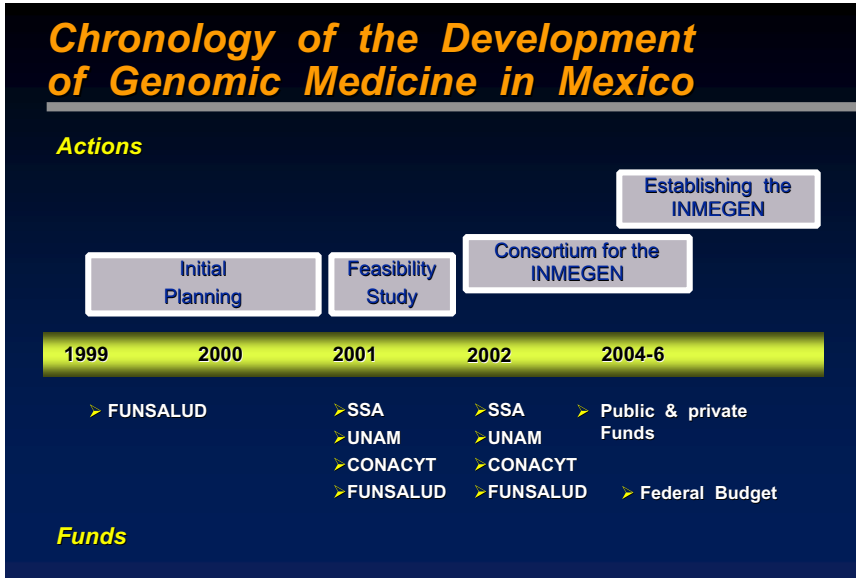

FIGURE 2-1 Chronology of the development of genomic medicine in Mexico. Mexico is in the process of developing one of the first genomic medicine platforms in Latin America. NOTE: Adapted from Gerardo Jimenez-Sanchez's PowerPoint presentation, September 21, 2004.

mize the likelihood of needing to depend on foreign aid and sources in the future and to improve economic growth and social welfare now.

The platform will be concentrated at The National Institute of Genomic Medicine (Instituto de Medicina Genómica, or INMEGEN). INMEGEN, which was created in July 2004 by the Mexican Congress was promoted by the National Autonomous University of Mexico (UNAM), the Secretary of Health (SSA), the National Council of Science and Technology (CONACYT), and the Mexican Health Foundation (FUNSALUD). It is now the eleventh National Institute of Health of Mexico in the realm of the Ministry of Health. Primary goals of the Mexico City and Cuernavaca-based institution are to incorporate genomics into the prevention, diagnosis, and treatment of disease; enhance genomics training and research (e.g., 150 Mexican scientists are ready to be incorporated into the Institution; and a Ph.D. program in genomic medicine has been initiated); develop biotechnology and intellectual property; and educate the public (e.g., through lectures, publications, a Web portal,[5] and extra-

[5]See *http://www.inmegen.gob.mx*.

mural pursuits). Research areas include characterizing the genetic variation of and developing pharmacogenomic strategies for the Mexican people; and studying the ethical, legal, and social implications of genomic medicine in the Mexican cultural framework.

With over 100 million inhabitants (Mexico is the eleventh most populated country in the world) and 65 different ethnic groups, the modern Mexican population has a unique characteristic genetic structure (i.e., as evident by polymorphisms in blood group proteins, serum proteins, major histocompatibility complex genes, and microsatellites) that may preclude importing genome-specific pharmaceuticals. Mexico also has a unique epidemiology that includes emerging infectious diseases, malnutrition, and a wide range of chronic health problems (e.g., cardiovascular disease, obesity, diabetes, and certain cancers). One might question the cost of developing a genomic medicine platform in a country still challenged with basic needs like clean water, maternal health, and nutrition. Importantly, many of the diseases that genomic medicine would target bear a significant economic and public health cost to Mexico. Direct costs of diabetes, for example, account for 4 to 6 percent of the total annual health budget. [6]

As also recognized by the Mexican government, ethnic- and population-based variation raises questions about the dual-use risk of technologies that exploit such variation. For example, although sarin is considered a chemical weapon, not a bioweapon, the human body's ability to defend itself against sarin is ethnic-specific. The active ingredient in sarin is an organophosphate that binds to cholinesterase. When bound, cholinesterase cannot metabolize acetylcholine, which then accumulates in synapses and causes symptoms associated with sarin poisoning. In order to get rid of the sarin, the body uses an enzyme called PON1. There are two allelic variants of PON1 in the human population: the R allele, which is associated with slow inactivation of sarin, and the Q allele, which causes rapid inactivation. As it turns out, the former occurs at a much higher frequency among Asians, suggesting that Asians might be more susceptible to a sarin attack.

A Mexican genomic platform is considered key to discouraging non-Mexican research and development of Mexican-specific products and services. Anecdotal reports indicate that U.S. field workers have, in the past, collected blood samples from Mexican indigenous populations and taken the samples back to the United States. Presumably, polymorphisms could be identified and genomic-specific medicines made and sold at U.S. prices. If this were to happen, Mexicans would likely not be able to afford the

[6]Jimenez-Sanchez, G. 2003. "Developing a platform for genomic medicine in Mexico." *Science* 300:295-296.

drugs, thereby worsening economic and inequity problems that already exist. Moreover, it has been realized that the same knowledge and technology could be used to make Mexican-specific bioweapons. While the dual-use risk is for the most part considered only hypothetical, it has raised a security issue and prompted action.

At the national level, the country is also very aware of how biotechnology developments can and should proceed within the Mexican social context, as the country has an ancient tradition of laws, religion, and traditions that make it difficult to introduce new knowledge and technology.

In addition to its work on genomic medicine, the newly established INMEGEN will also be focusing on several other research areas, including metabolism, cardiovascular disease, infectious diseases, and cancer. The Institute is developing several support units, including scientific and ethic committees, high throughput genotyping facilities, gene expression facilities, bioinformatics units, intellectual property units, and a business "incubator." The business incubator is designed to maximize bench-to-bedside applications, for example by working on intellectual property issues, identifying new markets, developing the commercialization process, scaling up technology, etc.

INMEGEN is concentrating its efforts both internally and externally, with a goal of building national networks in academic research, bench-to-bedside applications, and industrial production. As of September 2004, collaboration agreements had been signed with several U.S. institutions, including the National Institutes of Health, Johns Hopkins University, and the Translational Genomic Research Institute in Phoenix. Recently, in collaboration with the University of Toronto Joint Centre for Bioethics, the Institute held a joint meeting on Latin American genomic medicine. The meeting was held in Venezuela and attracted attendees from throughout Latin America and the Caribbean.

The Mexican Society of Genomic Medicine (SOMEGEN) comprises another component of the effort to build this new national biotechnology platform in personalized health care. The rapidly growing SOMEGEN, which was founded in June 2003, by 35 members of the academic community from various scientific and educational institutions, currently has five chapters. As of September 2004, its Spanish-based Web site[7] had received over 700,000 hits in the previous ten months, and more than 30,000 documents had been downloaded over the same time period. More than 80 percent of the downloads were from Latin America, and more than 52 percent from industrial affiliates.

[7]*http://www.somegen.org.mx.* Accessed on November 1, 2004.

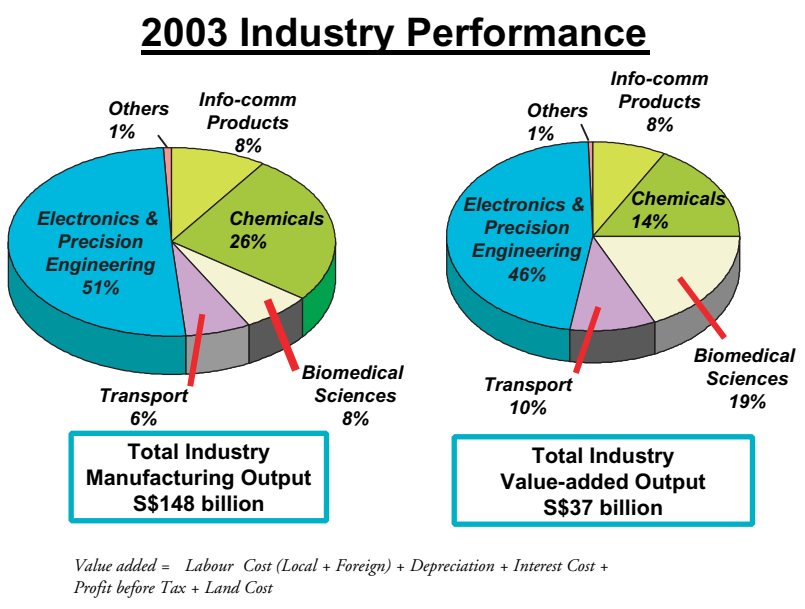

FIGURE 2-2A Singapore's current focus on biotechnology is a natural outgrowth of its already high-tech manufacturing and financial service-based economy. NOTE: Adapted from Patrick Tan Boon Ooi's PowerPoint presentation, September 21, 2004.

Biotechnology Growth in Singapore[8]

Recent biotechnology growth in Singapore promises to push that country to the fore as a regional and global biotechnology hub. At least that is the vision: to create infrastructure and industry pipelines that will serve both upstream basic research and the health delivery system. With a focus on genomic medicine, this will include the development of pharmaceuticals, the manufacture and marketing of pharmaceuticals, and the development of regional headquarters for pharmaceutical companies. Singapore's primary interest in genomic medicine is economic. Already, high tech manufacturing and financial services serve as the fulcrum of the Singaporean economy (see Figure 2-2A and B). Strengthening biotechnology capacity is expected to slow or stop the outsourcing of high tech jobs to India and China.

In addition to the economic potential of genomic medicine, Singapore recognizes the need to understand and address ethnic-specific differences

[8]This subsection based on the presentation by Patrick Tan Boon Ooi.

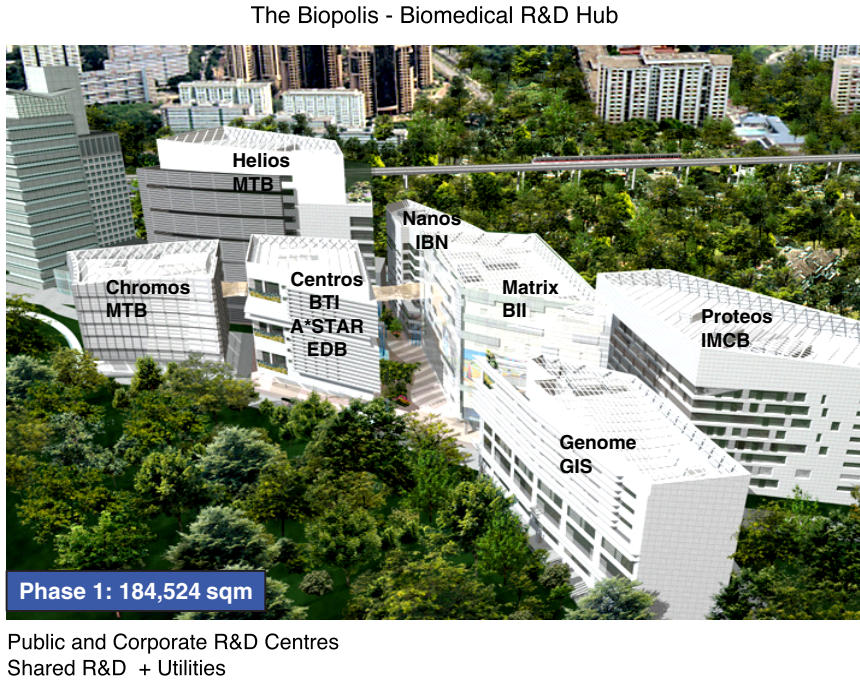

FIGURE 2-2B Singapore invests in high tech. Singapore's current focus on biotechnology is a natural outgrowth of its already high-tech manufacturing and financial service-based economy.
NOTE: Adapted from Patrick Tan Boon Ooi's PowerPoint presentation, September 21, 2004.

in disease. This is particularly true given the ethnic diversity of Singapore[9] (i.e., 98 percent of Singapore's 4 million people are Chinese, Malay, or Indian), despite its small country size (i.e., roughly the size of Washington, DC). Accumulating evidence indicates patients respond to drugs in ethnic- and population-specific ways (see Table 2-1A and B). For example, only certain polymorphisms in the gene that encodes acetylcholinesterase (ACE) are associated with the renal-protective effects of various ACE inhibitors.

In its efforts to become a global genomic hub with strong ties to the international community, the Singapore government took a major step forward when it established Biopolis, which is already considered a

[9]The majority of Singapore's population is ethnic Chinese.

TABLE 2-1A Ethnic Differences in Drug Effects?

Drug	Year	ADR	Common in	Rare in
Chlorpromazine	1950s	Generality	White Caucasiana in West Africa	Nigerians and Ghanaians
Ibufenac	1968	Hepatotoxicity	UK	Japan
Clioquinol	1970s	Neuropathy	Japan	Western world
Perhexiline	1980s	Neuropathy	UK	India
Terodiline	1990-1991	Cardiotoxocity	UK	Japan

NOTE: Adapted from Patrick Tan Boon Ooi's PowerPoint presentation, September 21, 2004..

TABLE 2-1B Genetics Influences Drug Effects

Gene	Medications	Drug Effects Linked to Polymorphism
Ace	Enalapril, lisinopril, captopril	Renoprotective effects, cardiac indices, blood pressure, immunoglobulin A nephropathy
Potassium channels HERG	Quinidine Cisapride	Drug-induced long QT syndrome Drug-induced torsade de pointes
KvLQT1	Terfenadine, disopyramide, mefloquine	Drug-induced long QT syndrome
hKCNE2	Clarithromycin	Drug-induced arrhythmia

NOTE: Adapted from Patrick Tan Boon Ooi's PowerPoint presentation, September 21, 2004..

world-class biomedical research and development hub. Comprised of five different research institutes, Biopolis serves as a site for both public and corporate R&D (e.g., including Novartis and soon GlaxoSmithKline). Remarkably, the facilities went from initial groundbreaking to official opening within a single year. In November 2004, Biopolis hosted the 5th Human Genome Organization (HUGO) Pacific Meeting and the 6th Asia-Pacific Conference on Human Genetics.

Additionally, in partnership with the U.S. Centers for Disease Control and Prevention, the Singapore government recently opened the Regional Emerging Diseases Intervention Center (REDI) to conduct research on new viruses and bioterrorist threats and to establish public health policies for emerging infectious diseases. REDI is already beginning to serve as a regional reference center for molecular diagnostics. For example, in one instance, when the U.S. Embassy in Thailand received a white powder-filled envelope, rather than send it to the CDC, the Embassy sent it to Singapore for analysis.

In response to a question about whether Singapore is engaged in regional training, it was pointed out that the country's top priority is to train persons from Singapore, often through collaborations with the United States. For example, Johns Hopkins University has recently opened a campus in Singapore, from which students are awarded Johns Hopkins degrees upon graduation. A Duke-affiliated medical school is being established, from which students will receive joint degrees. Eventually, training for persons from the rest of the region may become possible, although obviously there is a strong economic incentive not to create regional competition. Again, economics is the major driver in Singapore's pursuit to become a global hub. Much of the funding for these efforts comes from the Ministry of Trade and Industry, not the Ministry of Health.

Challenges to Genomic Medicine[10]

Integrating personalized, or genomic, medicine into routine health care—whether in Singapore, Mexico, the United States, or elsewhere—will require overcoming two major challenges. First, it will be necessary to make the "$1000 genome" a reality (see Figure 2-3A-C). The $1000 genome refers to the cost of determining an individual's entire genomic sequence and, although somewhat arbitrary, has come to represent the point at which the technology is finally affordable enough for widespread use. It is not clear how the $1000 genome hurdle will be met, although major biotech companies are trying. Some experts believe it will require a new technology.

The second and arguably more significant challenge will be making the philosophical jump from the highly interventional, British-style school of medicine to a preventative, predictive health care paradigm. Genomic medicine is expected to revolutionize human medicine by altering the nature of diagnosis, treatment, and prevention. In traditional medicine, diagnosis is based on clinical criteria; treatment is population-based; and intervention is based on the late-stage identification of disease. In genomic medicine, diagnosis is based on molecular criteria (e.g., the use of microarrays in cancer diagnosis); treatment is highly individualized (i.e., genomic-based); and prevention is based on early-stage identification of who is at risk.

Microbial Genomics[11]

If The Institute for Genomic Research (TIGR), Maryland, is any indication, genomic sequencing, per se, is no longer a science—it's an industry.

[10]This subsection is based on comments by Patrick Tan Boon Ooi and Jacques Ravel.
[11]This subsection is based on the presentation by J. Ravel.

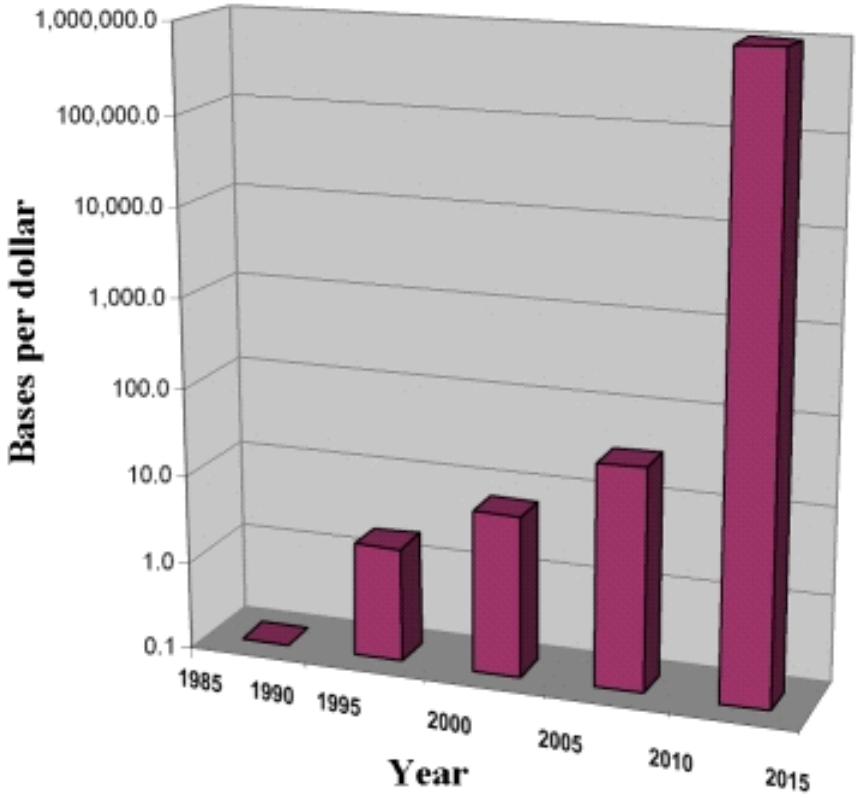

FIGURE 2-3A The $1000 genome. As sequencing technology has improved, production has increased and cost has gone down, but not enough to meet the $1000 mark. The $1000 genome represents a somewhat arbitrary "industry standard" when personalized genome sequencing, and personalized medicine, will be an affordable, widespread reality.
NOTE: Adapted from Patrick Tan Boon Ooi's PowerPoint presentation, September 21, 2004.

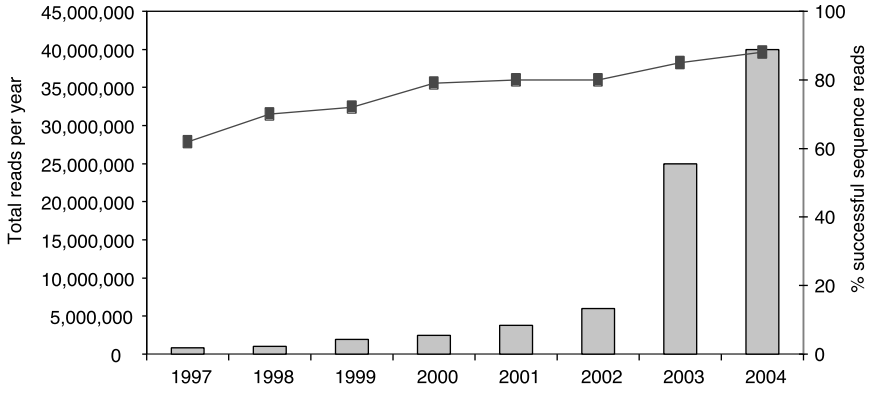

FIGURE 2-3B Sequencing efficiency 1997–2004
NOTE: Adapted from Jacques Ravel's PowerPoint presentation, September 21, 2004.

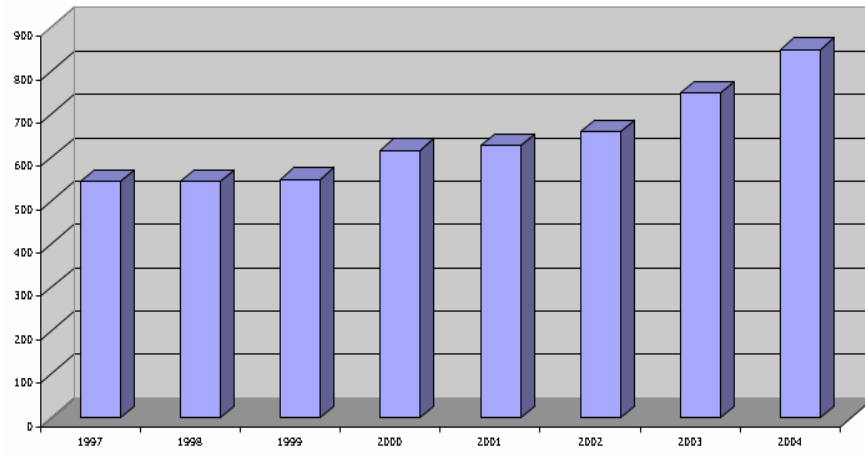

FIGURE 2-3C Number of base pairs read 1997–2004
NOTE: Adapted from Jacques Ravel's PowerPoint presentation, September 21, 2004.

Driven by its people, bioinformatics capacity, and high production, TIGR has turned sequencing into an affordable enterprise. The Institute has not yet reached the industry-standard make-or-break $1000 price tag for a complete human genome sequence, but it does sequence more genomes on a daily basis than anywhere else in the world.

That said, however, genomic sequencing, at least among microbes, is nonetheless a truly global pursuit. TIGR and the Sanger Institute, Cambridge, UK, are the dominant players in this field. However, more than 76 genome sequencing centers worldwide have been involved with sequencing at least one of the more than 200 completed microbial genomes listed in the GenBank database (see Figure 2-4 and Table 2-2) (and see *http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi)*. The question is, although sequencing technology is readily available to the rest of the world, to what extent can it be made as cost-effective and efficient as it is at TIGR? The fact that most institutions who have sequenced a microbial genome have only sequenced one complete genome suggests that most institutions have not achieved this degree of efficiency. This is particularly true given the likely reality that fairly soon all of the current sequencing technology will be outdated.

The financial obstacles to complete sequencing raise an important question, which has been hotly debated: should money be spent to complete the sequencing of an entire genome, or should efforts stop at the draft level? A draft sequence is one sequenced to high redundancy but with still a lot of gaps—you have access to only about 80 to 90 percent of the genes. The gaps can take years to close. In addition to the 183 published complete microbial genome sequences, there are another 150 or so that exist only in draft form.

It was reported that TIGR's success relies on the capacity to sequence genomes at very affordable prices. As sequencing technology has improved, production has increased and cost has gone down. Currently, with 125 high throughput Applied Biosystem sequencers (with capacity to expand to up to 250), the facility can sequence about 40 million reads per year (see Figure 2-3B). In 1996, one sequence read cost U.S. $8, compared to less than $1.00 today (i.e., between 70 and 90 cents). Moreover, the amount of information extracted per read has grown. In the mid-1990s, average base pairs (bp)/read were about 500-600. Now, with better technology, that figure is about 900 bp/read (see Figure 2-3C).

About 40 percent of TIGR's sequencing work is in collaboration with outside institutions and groups, including the U.S. government, law enforcement agencies, and international collaborators. For example, its affordable, high throughput capacity gives the Institute a biodefense readiness that proved extremely helpful during the 2001 anthrax investi-

gation. Without sacrificing other ongoing work, TIGR was able to accommodate government needs by sequencing the genomes of nine *Bacillus anthracis* strains, including two complete and seven draft sequences.[12] With the aid of NIH funding, the Institution is currently developing an extensive strain identification database, which currently contains more than 1500 different pathogenic isolates. [13]

TIGR retains an open-door policy with regards to its genomic data and bioinformatics software. As TIGR president Claire Fraser was recently quoted: "Individuals, terrorist groups or countries interested in doing harm could certainly do that with existing strains or isolates that are available without the need to use genomic information to develop new germs." In the same spirit, a recent National Research Council report concluded that genomics data should be available to everyone.[14] The report states, "The value of sharing data on dangerous germs so vaccines and treatments can be developed outweighs the danger that bioterrorists may use the information to do harm." The committee chair of the NRC report, Stan Falkow, was quoted as saying "open access is essential if we are to maintain the progress needed to stay ahead of those who would attempt to do us harm."

PLANTS AS A MANUFACTURING PLATFORM[15]

Workshop presentations and discussion on the use of plant crops as a manufacturing platform are summarized here. Two main themes emerged from this dialogue. First, the use of plants to produce heat-stable, oral vaccines presents a new major opportunity to deal with some of the problems associated with global vaccine manufacture and delivery. Second, transgenic crops are increasingly being used worldwide to reduce the cost of agricultural production, improve production, and produce better quality products.

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[12]Rasko, D. et al. 2004. "The genome sequence of *Bacillus cereus* ATCC 10987 reveals metabolic adaptations and a large plasmid related to *Bacillus anthracis* pXO1." *Nucleic Acids Research* (32):977-988; Hoffmaster, A. et al. 2004. "Identification of anthrax toxin genes in a *Bacillus cereus* associated with an illness resembling inhalation anthrax." *Proceedings of the National Academy of Sciences* 101(22):8449-8454.

[13]See *http://www.tigr.org/pathema.*

[14]National Research Council. 2004. *Seeking Security: Pathogens, Open Access, and Genomic Databases*, The National Academies Press, Washington, DC.

[15]This section is based largely on the workshop presentations of Charles Arntzen and Miguel Gomez Lim.

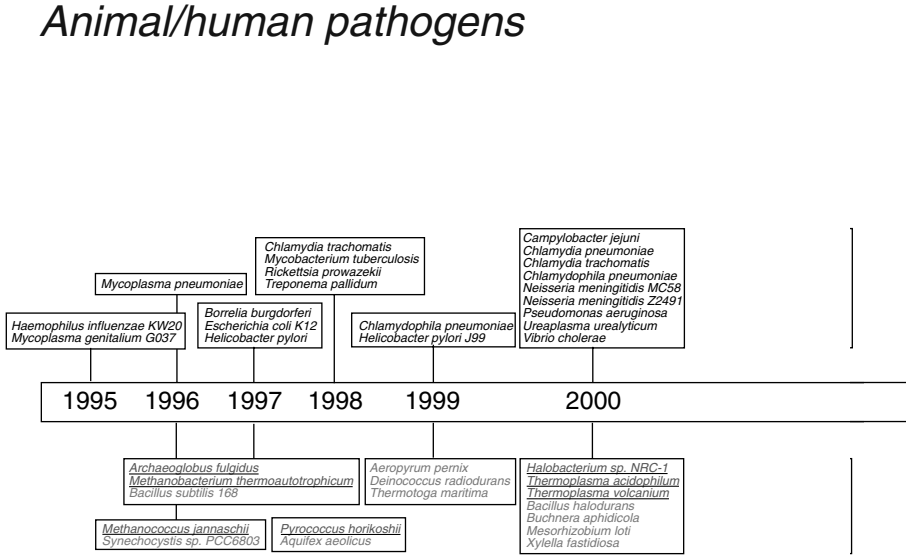
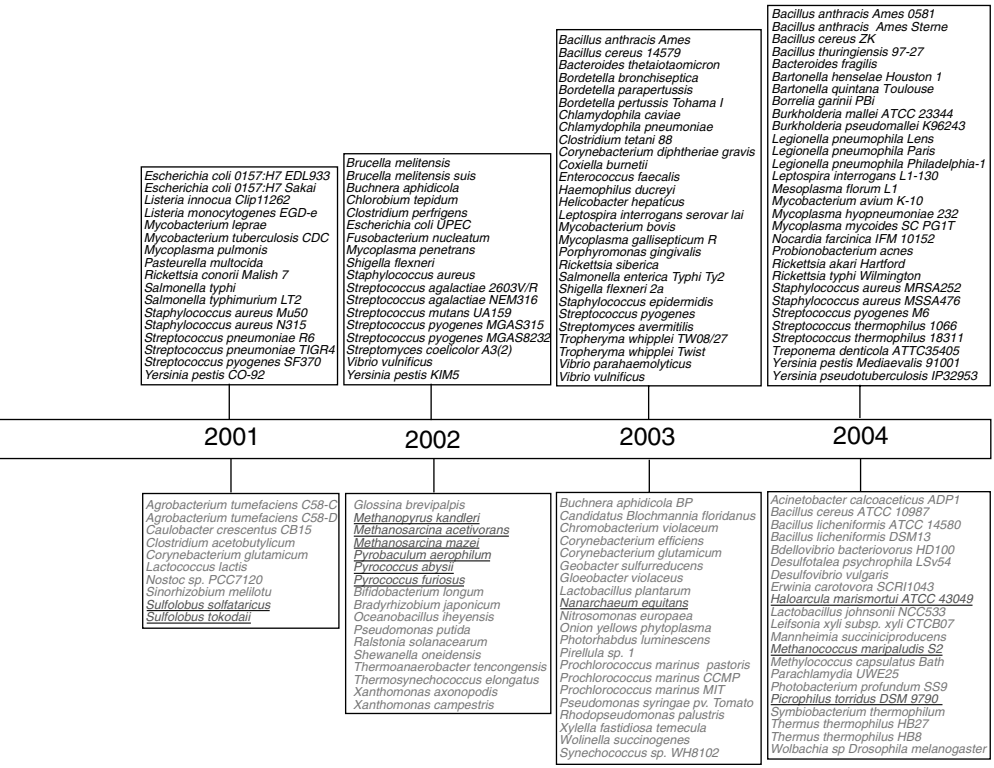


FIGURE 2-4 Global microbial sequencing. More than 76 genome sequencing centers worldwide have been involved with sequencing at least one of the more than 180 completed microbial genomes listed in the GenBank database. NOTE: Adapted from Jacques Ravel's PowerPoint presentation, September 21, 2004.

Plant-Derived Vaccines[16]

Despite the very high social value of vaccines, very few "high-tech" pharmaceutical companies focus on vaccine R&D or production. And most of those that do so currently are departing the infectious disease arena and redirecting their efforts toward higher-value therapeutic products, like anti-cancer and anti-neurological degradation vaccines. It was suggested that developing world countries are attempting to fill the resultant manufacturing gap by creating what may effectively become a

[16]This subsection based on presentations by Charles Arntzen and Miguel Gomez Lim.



new vaccine industry. But the question remains, how would companies turn a profit?

Plant-derived vaccines may be a viable alternative to "traditional" vaccine production. The technology is cheap and scalable and dramatically reduces needed initial capital investment (i.e., compared to protein-based pharmaceuticals). The concept for a plant-based vaccine is an outgrowth of what one workshop participant cited as one of the major advancements in biotechnology over the past two decades: yeast-derived HBsAg (hepatitis B surface antigen) manufacturing. HBV (the hepatitis B virus) was one of the first viral genomes completely sequenced, back in the 1980s, after which the gene for the surface antigen was identified and

TABLE 2-2 Global Microbial Sequencing[a]

Genome Sequencing Centers
35 TIGR
16 Sanger Institute
8 DOE Joint Genome Institute
7 NITE
6 Kazusa
6 Sao Paulo state (Brazil) Consortium
6 Univ. Wisconsin
5 Genoscope
4 Institut Pasteur
4 Uppsala Univ.
4 Max-Plank-Institute
3 Goettingen Genomics Laboratory
3 Lab of Human Bacterial Pathogenesis
2 Broad Institute Genome Sequencing and Analysis
2 CNRS
2 ChGP
2 Chinese National HGC, Shanghai
2 DIVERSA
2 Genome Therapeutics Corporation
2 INRA
2 Integrated Genomics
2 Japan MSTC
2 Juntendo Univ.
2 Nestle Research Center, Switzerland
2 Osaka Univ.
2 Univ. Minnesota
2 Univ. Oklahoma
2 Univ. Valencia
1 ASTRA
1 Academy of Military Medical Sciences, China
1 BSNR
1 Beijing Center.HGP
1 Cereon
1 Chonnam Univ.
1 Eli Lilly and Company
1 European Consortium
1 European/Canadian Consortium
1 Fidelity Systems

continued

TABLE 2-2 Continued

Genome Sequencing Centers
1 GIRC
1 Gottingen Genom. Lab.
1 Heidelberg Univ.
1 Human Genome Sequencing Center, Baylor College of Medicine
1 Institut of Microbiology and Genetics, University of Goettingen
1 Institute for Molecular Biotechnology, Germany
1 Kitasato Institute for Life Sciences, Japan
1 Kitasato Univ.
1 LNCC, Brazil
1 MELILO
1 Microbial Genome Center of ChMPH
1 NHRI, Taiwan
1 NIBHT-JP
1 NIID Japan
1 Novozymes Biotech
1 PathoGenesis Corporation
1 Rikken GSC
1 Royal Institute of Technology, Stockholm, Sweden
1 The University of Tokyo, Japan
1 U. Washington
1 UCAL/CalTech
1 Univ. Connecticut
1 Univ. Kyushu
1 Univ. Ohio
1 Univ. Wuerzburg
1 Univ.AL-Birmingham
1 University of Massachusetts-Amherst, University of Washington
1 University of Vienna, Austria
1 University of Washington
1 Utah Genome Center
1 Valencia Univ.
1 Wageningen Centre for Food Sciences
1 Wash.U-GSC
1 Washington University Department of Molecular Biology and Pharmacology
1 Whitehead Institute
1 Yale Univ.
1 Yamaguchi/Kyushu U.
1 e.gene Biotechnologie GmbH

NOTE: Adapted from Jacques Ravel's PowerPoint presentation, September 21, 2004.
[a]More than 76 genome sequencing centers worldwide have been involved with sequencing at least one of the more than 180 completed microbial genomes listed in the GenBank database: 183 Completed Microbial Genomes (19 Archea and 164 Bacteria).

isolated. Yeast-derived manufacturing involves inserting the isolated gene into yeast cells such that they produce the protein, growing the yeast cells, lysing them, and then purifying the antigen through a multi-step process.[17]

Social vs. economic value of vaccines

Infectious diseases cause 25 percent of all deaths, 45 percent of deaths in low-income countries, and 63 percent of deaths in children worldwide. However, very few companies focus on vaccines against infectious disease; greater returns on investment are likely from vaccines to prevent cancer and other chronic diseases.[18]

HBsAg is now a mandatory component of childhood immunization in the United States. But several countries, including the United Kingdom, do not required hepatitis B vaccination, primarily because it is not cost-effective. For this and other reasons, the vaccine is only being administered throughout about 60 percent of the world.

Several years ago, researchers at Arizona State University, Tempe, AZ, questioned whether plant-derived HBsAg and other antigens, rather than yeast-derived antigen, might confer certain advantages that would make the hepatitis B and other vaccines more affordable and accessible. In places like Mexico, for example, where over 40 million vaccine doses are purchased every year (mostly by the government) at a cost of about U.S. $30 per person, a more cost-effective vaccine production system would be a boon. Expenditure for vaccines comprises approximately 1 percent of Mexico's GNP.

The advantages of plant-based manufacturing stem from the totipotency of plant cells, which allows for the ready regeneration of plant tissue for harvesting; the fact that plant-based vaccines do not require a multi-step antigen purification process; and the oral administration of plant-derived vaccines (as opposed to intramuscularly).

However, the use of plant-derived vaccines will require overcoming several technical, regulatory, and other challenges. One of the main perceived challenges is the degradation of purified product and loss of activity that occur as antigens pass through the stomach and into the intestine. The gut and liver are designed in many ways to prevent a systemic immune response to food allergens and proteins, yet protection against hepatitis B probably requires a systemic response. Because of this,

[17]Sitrin et al. 1993. "Survey of licensed hepatitis B vaccines and their production processes." In: *Hepatitis B Vaccines in Clinical Practice*, R. W. Ellis, ed., Marcel Dekker Inc., NY.

[18]Adapted from Charles Arntzen's PowerPoint presentation, September 21, 2004.

there is concern that plant-derived vaccines either would not work (at least not for all infectious diseases) or would require administering multiple doses. However, researchers have shown that in murine model studies, plant-derived HBsAg vaccines do elicit an immune response; and potato-based products currently in human clinical trial show significant positive results for average mean IgG following the administration of three doses of vaccine (at baseline, week 2, and week 4), serving as proof of principle for plant-derived immunization.

Significant results depend on much higher dosages—about 100 times greater—than intramuscular injections do. They also rely on antigens being in the form of virus-like particles recognizable by the immune system. It has been suggested that one delivery strategy worth exploring is the anchoring of domains onto mucosa-targeting protein subunits, which has resulted in very good mucosal immunization with HIV.[19] Another option is an oral adjuvant, such as *Quillaja saponeria* extract, which is used in the food industry (and is what gives root beer its suds); *Q. saponeria* has been tested as an adjuvant with freeze-dried plant vaccines.

In addition to the technical challenge of bypassing GI tolerance, the eventual widespread use of plant-derived vaccines faces an uphill battle with respect to similar societal issues that GM (genetically modified) foods face. It will be very important that there is not even a single instance of accidental genetic transfer from a plant vaccine crop to a food crop. If this were to happen, not only might it have unpredictable crop-related and human health consequences, it could kill the entire industry.

To avoid such a catastrophe, crop stewardship is a critically important in the development of a plant-based manufacturing system. Neither the USDA nor the FDA have established rules for the production of plant-derived vaccines, but necessary restrictions will likely include growing all materials in physically isolated greenhouses (i.e., separated, sealed buildings that prevent bees and pollen from entering and exiting); and using non-food crops, like tobacco and alfalfa. With regards to the latter, because raw potatoes would not likely be well received in immunization programs in the developing world, ASU researchers have also been experimenting with other modes of delivery, including freeze-drying of tomato and leaf tissue using readily available technology from the food processing industry. The dried, ground-up tissue is put into capsules for easy consumption. Importantly, these tomato-based experimental vaccines come from a

[19]Matoba, N. et al. 2004. "A mucosally targeted subunit vaccine candidate eliciting HIV-1 transcytosis-blocking Abs." *Proceedings of the National Academy of Sciences* 101(37):13584-13589.

tasteless, seedless tomato variety that stands no chance of becoming a food crop and would not likely ever be transported to a grocery store.

Given these difficult delivery and regulatory challenges, one might question the rationale for moving from yeast-based to plant-based vaccine manufacturing. The single most obvious answer is economics. Compared to producing protein pharmaceuticals (which are mostly fermentation-based recombinant proteins, such as monoclonal antibodies), plant-based manufacturing requires considerably less initial capital investment. In the case of protein pharmaceuticals, of which there are currently 99 in late clinical trials, companies must decide fairly early on whether to spend the U.S. $200-500 million to build a production facility. Plant-based production does not require that very tough economic decision. Greenhouses cost a mere U.S. $20 per square foot, which is practically nothing compared to the cost of building a fermentation facility. The materials for the technology can be purchased from a food industry technology catalogue. Not only is it cheap, it is scalable. It is easy to build another greenhouse or another freeze-drier as the market expands.

Other advantages of plant-derived vaccines include the fact that they are needle-free; they are heat-stable and do not require refrigeration; and, since they are oral, they are easier to dispense and do not cause the same contamination problems that needles do.

Why use crops?

- Prepare a strategic reserve of plague vaccine
- Prepare a strategic reserve of post-Ebola exposure therapeutic antibodies[20]

Academic researchers have been investigating plant-based vaccines for about a decade and, despite the apparent promise of the technology, very little venture capital interest has been expressed. The technology still lies within the relatively early assembly phase of the technological development process (i.e., discovery is complete, but now all the various components of the technology platform need to be assembled before the plant-based vaccine manufacturing can be transferred and production begun). Work still needs to be done in the areas of molecular technique development, antigen design, down-stream processing under GMP (good manufacturing process), product formulation, and perhaps most importantly, regulatory clarification.

[20]Adapted from Charles Arntzen's PowerPoint presentation, September 21, 2004.

It is interesting to note that when the hepatitis B injectable vaccine was announced in 1986, it was not quickly embraced either. A WHO-affiliated global task force spent several years convincing various governments, organizations, etc., to adopt the vaccine.[21] Plant-based vaccines will require a similar public education effort.

Plant-Derived Proteins[22]

Not only does plant-based manufacturing have the potential to increase global immunization coverage for hepatitis B and other diseases, the development of the platform serves as a component of U.S. biodefense research efforts. Funded by the U.S. Army and in collaboration with scientists at USAMRIID, Ft. Detrick, the ASU group conducting the plant-based hepatitis B vaccine work described herein is also conducting research on plant-derived antibodies for use against potential biowarfare agents. The scientists are running animal clinical trials with plant-derived antigen protection against *Yersinia pestis*; and they are researching the capacity to use plant-derived antibodies for protection against Ebola virus. In both cases, the goal is to build a strategic reserve of what might be post-event prophylactic agents or post-exposure therapeutic agents in the event of a bioterrorist attack. Because of the high initial investments associated with traditional monoclonal antibody manufacturing, coupled with the large list of potential bioterrorist agents, the relatively inexpensive and scalable plant harvesting is considered a cost-effective approach.

In contrast to plant-derived vaccines, several companies have expressed interest in plant-derived proteins. These include both large companies, such as Syngenta and Dow Chemical Company, as well as small biotech companies. Monsanto reportedly spent several years and hundreds of millions of dollars demonstrating the ease of purifying monoclonal antibodies from corn but then withdrew its efforts, presumably because of the costs in investing in a downstream processing facility. The company was also keenly aware of crop stewardship and gene transfer issues. Four Latin American countries have invested in plant-based protein manufacture: Mexico, Cuba, Brazil, and Argentina.

A question was raised about the technical limitations of so-called biopharming. A major technical problem facing the development of such products is low protein expression levels. As with plant-based vaccines, a second major problem is delivering the product to the right tissue at the

[21]Mahoney, R. in Muraksin, W. 1995. *The War Against Hepatitis B: A History of the International Task-Force on Hepatitis B Immunization.* University of Pennsylvania Press.

[22]This subsection based on the presentations of Charles Arntzen and Miguel Gomez Lim.

right time and in the right amount. A third set of technical/scientific problems relates to the immunological challenge that food-derived products pose (i.e., as with vaccines, in terms of being recognized as foreign and eliciting an immune response). And fourth, as of September 2004, there had been only one human clinical trial of plant-derived monoclonal antibodies and thus practically no precedence with regards to the extent to which products will need to be purified. That first trial was for use against *Streptococcus mutans* (a causal agent of dental caries). The material used was not highly purified—antibiotics were used to cleanse the mouth, and then the material was simply swabbed on.

Limited research funding was cited as one of the challenges to addressing these various technical problems, which may reflect a general public perception that this type of technology is not beneficial or worthwhile.

TRANSGENIC CROPS[23]

Bio-pharming for vaccines, antibodies, and other protein pharmaceuticals may be only an emerging technology, wrought with technical and crop stewardship challenges. Transgenic food crops, on the other hand, have already entered and flourished in the global marketplace. The main producers of transgenic crops are the United States (63 percent of the market), Argentina (21 percent), Canada (6 percent), China and Brazil (4 percent each), and South Africa (1 percent).

China is expected to become the largest market in the world over the next 10 to 20 years. With one-quarter of the world's population and only 7 percent of the world's arable land, the country has made a strong commitment to using transgenic technology and has spent U.S. $120 million in the last three years on transgenic rice technology alone. Between 2001 and 2005, China's investment in transgenic technology was 400 percent greater than between 1996 and 2000. But the country faces several challenges, most notably a strong cultural and historical tradition (which may slow acceptance of the technology) and export complications. With regards to the latter, although China was the first country to produce commercially and export a transgenic plant, tobacco, the transgenic backlash in the European Union forced China to discontinue the program.

Brazil and India are expected to become larger sectors of the production market in the near future. Other developed countries involved in transgenic crop production include Australia, Spain, Rumania, and Bulgaria; other developing countries with small but growing shares of the

[23]This section is based on the workshop presentation of Luis Herrera-Estrella.

market include Indonesia, Mexico, Uruguay, Colombia, Honduras, and the Philippines.

The potential agricultural and societal benefits of transgenic biotechnology include:

- disease resistance (particularly with respect to viruses; about 50 different transgenic plant species, with resistance to some 80 different viruses, have been produced although not made available commercially);
- reduced pesticide use (because of effective insect resistance);
- enhanced nutritive composition of foods;
- herbicide tolerance;
- longer shelf life of fruits;
- more rapid growth of crops; and
- improvements in taste and quality.

Together, these benefits reduce production costs and lead to the production of more and better quality products and ultimately to fewer human health problems (e.g., associated with chemical use, etc.). Currently, approximately 45 percent of the world's crops are lost to disease, insects, drought, etc. In the United States alone, $20 billion worth of crops are lost annually (i.e., one-tenth of production), which represents a large margin that could potentially be impacted by this technology. The situation per hectare is worse in other parts of the world. For example, while the United States produces about 6 tons of rice per hectare, Europe produces about 5 tons per hectare, Africa only 1.7 tons, and Latin America only 2.3 tons per hectare. Likewise with corn (maize), of which the United States produces 7 tons per hectare, Europe produces about 6 tons per hectare, Latin America 2.1, and Africa only 1.7.

Main areas of research on transgenic technology include:

- mechanisms of disease resistance, including how plants recognize pathogens and trigger defense mechanisms;
- drought and salinity tolerance, both of which are major global problems (i.e., about 40 percent of the world's arable land is affected by drought);
- photosynthesis efficiency;
- apomixis (i.e., the ability to reproduce asexually through seeds, so that hybrid performance can be inherited);
- nutrient uptake and utilization efficiency (i.e., to reduce fertilizer use; fertilizer use is considered a major problem not only because of environmental contamination but because of the limited supply of fertilizer);
- yield components;

- development of metabolic profiling (i.e., with the goal of modifying plants to produce desirable metabolites); and
- functional genomics for gene discovery (including proteomic analysis).

The research and development of transgenic crops are associated with a wide range of technological tools:

- Routine gene transfer protocols, which exist for most major crops (e.g., *Agrobacterium*-mediated and particle bombardment)
- Technology for producing transgenic plants without antibiotic-resistant genes
- Technology for suppressing the expression of undesirable genes (or activating the expression of desirable genes)
- Genomic information, which is available for many crops (e.g., the complete genome sequences are available for *Arabidopsis thaliana*, a widespread model plant system, as well as rice)
- Technology for using transgenic plants as bioreactors
- Gene knock-outs (e.g., in *A. thaliana*, knock-outs are available for every single gene, so any one gene can be chosen for study)
- Activation of random genes (i.e., using mobile elements that activate transcription)
- Microarrays and gene expression analysis
- Metabolic profiling
- Genome-wide, high density single nucleotide polymorphism (SNP) maps available for QTL (quantitative trait loci, such as those associated with yield and other major traits) isolation

Despite the potential benefits of transgenic crop technology and the many tools available to build upon and improve the technology, the use of the technology is still limited to a few countries (as mentioned above), a few crops, a few plant species, and a few traits (see Figure 2-5). Major transgenic crops include soja (i.e., *Glycine soja*, wild soybean; 61 percent of global market), maize (23 percent), cotton (11 percent), and colza (i.e., rapeseed oil; 5 percent). Major traits include glyphosate resistance (73 percent of global market), Bt (*Bacillus thuringiensis*, the bacterium from which most biopesticides are derived; 18 percent), or both (9 percent).

A question was raised about whether the "growing" use of transgenic plants might make crops more vulnerable to either natural or intentional disease outbreaks, by virtue of reducing the genetic diversity in a fixed land space. In resposnse, it was pointed out that, in fact, the opposite would likely occur. The problems of reduced genetic variation and increased vulnerability to disease are not a transgenic problem per se.

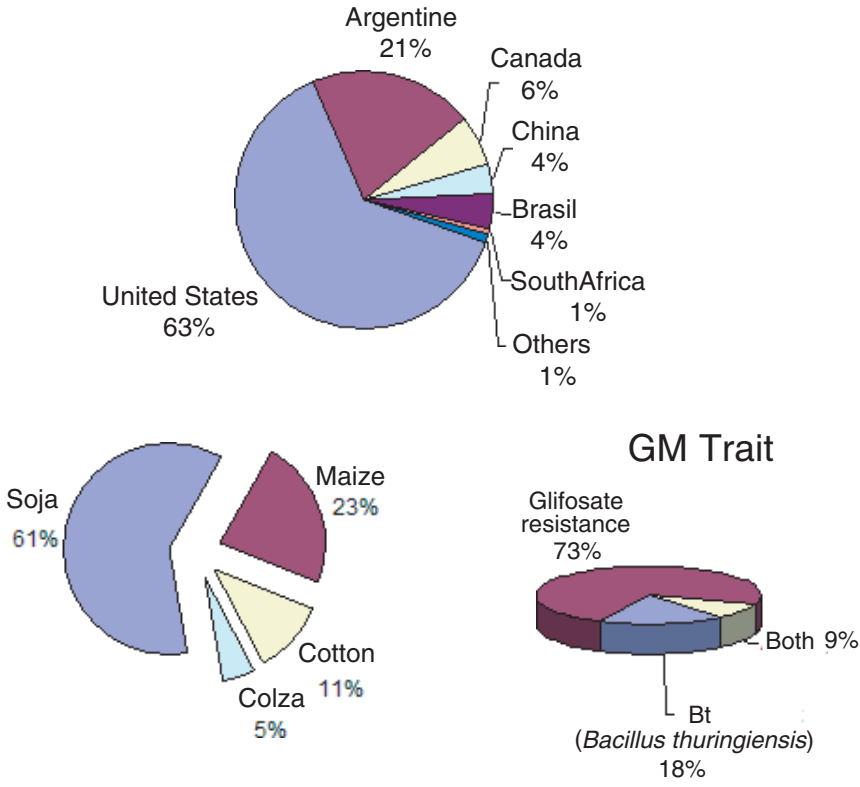


FIGURE 2-5 The limited use of GM agricultural crops. Despite the potential benefits of transgenic crop technology and the many tools available to build upon and improve the technology, the use of the technology is still limited to a few countries (as mentioned above), a few crops, a few plant species, and a few traits.
NOTE: Adapted from Luis Herrera-Estrella's PowerPoint presentation, September 21, 2004.

They became problems in monoculture situations long before transgenic technology emerged, and farmers started sacrificing natural biodiversity for higher productivity varieties decades ago. The use of transgenic technology could, in theory, encourage the preservation of genetic diversity (and thus the reduced risk of disease wiping out an entire crop) by engineering local varieties that are as productive as, if not more productive than, commercial varieties.

Public Opinion and Other Obstacles to Transgenic Technology[24]

The primary obstacle to the broader dissemination of transgenic technology is public opinion, coupled with a lack of trust in government agencies. This stems in large part from controversy in the European Union regarding genetically modified (GM) foods.

As an example of how turbulent public opinion about technology can be, two very different, opinionated articles appeared on the same date in the same issue of the Mexican newspaper *La Jornada*.[25] In one, "Biosafety Law a Threat to Food Sovereignty," a number of non-governmental organizations (NGOs) declared to the newspaper that biosafety laws, which the Mexican government is considering as a way to regulate the use of transgenic crops, were a threat to food sovereignty. In the second article, "Farmers Demand Access to Transgenic Plants," the Mexican corn farmers union demanded access to transgenic plants.

It will be interesting to see how public opinion in Mexico—and throughout Latin America—is swayed by recent decisions in the European Union to grow GM maize. On September 8, 2004, the European Commission approved 17 different transgenic varieties of Monsanto-engineered maize for growth throughout Europe. The approval is the first inscription of GM varieties in the EU Seed Catalogue.[26] Opinion in Latin America with regards to this issue typically reflects European, not U.S. opinion, because of a lack of trust in the U.S. government.

It is believed that the origins of the unfavorable public opinion largely reflect a lack of awareness of the potential benefits of transgenic technology which, in turn, is due partly to the fact that the first generation GM crops were introduced using traits with improved agronomical characteristics rather than features that directly benefited consumers The next generation GM crops will have consumer value-added traits, for example fruits with more nutrients or with neutraceuticals, which presumably will increase public awareness of the potential benefits of GM crops.

However, the nature of these second generation transgenic products, particularly foods enhanced with nutraceuticals, raises yet another consumer-benefit issue. Nutraceuticals are components of food that are not directly nutrient-related but can prevent disease or minimize other

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[24]This subsection based on the presentation of Luis Herrera-Estrella.

[25]Perez, M. 2004. "Biosafety law as a threat to food sovereignty." *La Jornada,* Society and Justice section, September 13:43. Gomez Mena, Carolina. 2004. "Farmers demand access to transgenic plants." *La Jornada,* Society and Justice section, September 13:45.

[26]Inscription of MON 810 GM Maize Varieties in the Common EU Catalogue of Varieties, *http://europa.eu.int/comm/dgs/health_consumer/library/press/i04_1083.en.pdf.* Accessed on November 16, 2004.

health problems. If efforts are directed to these presumably higher market value traits, will this lead to a lower investment in input and productivity traits? If a company were, for example, to invest in tomatoes with anti-carcinogenic properties, will this compromise the much more urgent need to increase food production?

In addition to public perception, another obstacle to the global proliferation of transgenic technology is the lack of technology transfer to small farmers throughout the developing world. Most products currently being commercialized, whether for nutraceuticals or not, are aimed at the U.S. market—not as a solution to any sort of food-security problems but because the U.S. market is the largest in the world. Transferring the technology to smaller farmers with domestic agendas will require the political and economic will of governments and a strong exchange between the public and private sectors. There are signs that this is happening. For example, Monsanto and Mexico are collaborating to produce virus-resistant potatoes. Since Mexico neither imports nor exports potatoes and relies mostly on a single domestic variety, presumably this technology transfer does not pose any sort of market threat to Monsanto. Likewise with avocado, another important Mexican food; 80 percent of the Mexican market for avocado relies on a single variety, and modifying that variety would benefit Mexico without incurring competition for Monsanto.

Other obstacles include restrictive or unclear legislation; lack of infrastructure for biosafety evaluation; patent issues; and a general lack of consensus on ethical aspects of transgenic technology. For example, in Mexico, although transgenic plants were first field-tested some 20 years ago, the country still does not have clear legislation for the commercial use of such plants. The problem is confounded by a widespread lack of infrastructure for biosafety evaluation (i.e., to monitor the environmental and public health impacts of the commercial use of transgenic crops).

Patent restrictions limit opportunities for transgenic technological growth. For example, Monsanto controls 80 percent of the transgenic seed market. Most of the remainder is controlled by four other large companies. This domination of intellectual property is a significant deterrent for smaller, local companies to become involved. If a developing world company wanted to use the technology to produce viral- and insect-resistant local crops but had to pay royalties, its product would have little market value, despite the potential positive impact of such products. This situation does not appear to be improving. In 2001, the United States filed about 9000 patents for the use of various plant genes. That same year, Japan filed about 11,000. Mexico filed only three.

3

Drivers of International Biotechnology Development

The rapid growth, global proliferation, and application of advancing technologies are driven by a range of economic, social, and political factors. This chapter summarizes the several workshop presentations and discussions that revolved around the multitude and complex nature of these drivers, how future marketplace trends will likely drive technological advances, and obstacles that slow growth. As will be evident from the information presented, the driving forces behind the global proliferation of technology are complex and interacting.

Although market-driven profits, particularly within the pharmaceutical industry, have and will likely continue to serve as major drivers of advancing technologies, goals to improve global public health and efforts to strengthen human security and national security play vitally important roles as well. Indeed, many would agree that reducing the enormous inequities in global health is among the most important ethical challenges facing humankind today—a challenge that could be addressed through innovative technological applications.

An important theme that emerged from the presentations and discussions summarized here is that dual-use applications created by the global dissemination of advancing technologies and the know-how to use such technology do not necessarily derive from the growth of the industry per se. Rather, the alarm sounds from the characteristics of this growth. For example, the number of small biotech companies is growing much more rapidly than are the numbers of chemical or nuclear companies. Plus, the number of agents created by the life sciences revolution (e.g., via recombi-

nant and transgenic technology and even synthetic biology) is increasing practically exponentially. So while there are only half a dozen fissile nuclear materials and dozens of "dual-use" chemicals that could be diverted for malevolent purposes, the number of potentially harmful biological agents is virtually limitless. In 15 to 20 years, dual-use technologies that have direct or indirect applications to the life sciences enterprise will continue their global expansion and local adaptations. China, for example, is expected to overtake the United States as the biggest producer of transgenic crops over the next 10 to 15 years.

ECONOMIC DRIVERS[1]

This section summarizes information presented during the workshop on how future market trends are expected to drive the growth and global dissemination of extant and emerging technologies. The focus of this discussion was the life sciences industry; and for the purposes of this discussion, the industry was divided into six sectors: pharma, medicine, agriculture, biomaterials, computing, and military.

All of the market trends described below and the advancing technologies that enable them, and are thus driven by them, are summarized in Table 3-1. Although certain technology trends are more relevant to particular commercial goals (e.g., aerosol technology obviously plays a much greater role in efforts to develop new means of drug delivery than it does for most of the other industrial pursuits), some are common to many or all. Of note, advances in bioinformatic technology will play an important role in all areas of application.

The Pharmaceutical Industry

Worth approximately U.S. $400 billion, the global pharmaceutical market dominates the life sciences industry and, as such, arguably determines the trajectory of life sciences-related technological development and global spread. North America and the European Union together account for three-quarters of the financial activity within the pharmaceutical industry (see Table 3-2). North America comprises 51 percent of the global market (U.S. $204 billion) and enjoys an annual growth rate of 12 percent. At U.S. $102 billion, the European Union comprises 25 percent of the global market and has an annual growth rate of 8 percent.

[1]This section is based on the workshop presentation of Terence Taylor, September 21, 2004.

TABLE 3-1 Future Technological Trends

Sectors	Trend	Goal	Enabling Technologies
Pharmaceuticals	Designer drugs	Patient- and genome-specific drugs	Gene chips, biomedical databases, computing
	Gene profiling	Optimum therapy	Gene chips, databases
	Drug delivery	Alternative routes for drug administration	Nanotechnology, aerosol technology
Medicine	Diagnosis	Automatic analysis of genomic tests	Databases, gene chips
	Infectious disease	Better treatments	Biomedical and genome databases, nanotechnology
	Gene therapy	Identify and treat defective genes	Databases, gene chips, high performance computing
	Life extension	Identify and control the molecular basis for ageing	Gene chips, sequence databases, embryonic stem cells
	Xenotrans-plantation	Develop rejection-free tissues and organs for transplantation	Databases, animal models, recombinant methods
Agriculture	Transgenic foods	Develop higher nutrition foods, vehicles for drug delivery	Genome sequencing methods, databases
Biomaterials	Artificial organs	Develop tissue and associated engineering methods	Databases, transgenic crops/animals, nanotechnology
	Biopolymers	New materials for biological and industrial applications	Databases, computing, transgenic crops/animals, nanotechnology
Biotech Computing	Performance	Faster computing for intensive analysis and filtering	Grid computing and super computers
	Applications	Develop biotech-specific software tools	Advanced software and search algorithms
Military	Defense capabilities	Vaccines and prophylactics, detectors and forensics	Gene chips, databases, nanotechnology, detector hardware
	Weapons	Development of effective biological weapons	Databases, gene chips, molecular synthesis methods, high performance computing

NOTE: Adapted from Terence Taylor's PowerPoint presentation, September 21, 2004.

TABLE 3-2 The Global Pharmaceutical Market

Region	Annual Worth	Market Share	Annual Growth
North America	$204Bn	51%	12%
Europe	$102Bn	25%	8%
Japan	$47Bn	12%	1%
Asia, Africa, Australia	$32Bn	8%	11%
Latin America	$17Bn	4%	–10%

NOTE: Adapted from Terence Taylor's PowerPoint presentation, September 21, 2004.

For comparison, it was noted that the North American and European Union (EU) biotech sector—that is, nonpharmaceutical companies involved with living organisms (as opposed to chemical synthesis)—are together worth about U.S. $33 billion. As of 2002 (i.e., prior to the entrance of new countries into the EU this past year), the EU biotech sector involved some 1700 companies and was worth approximately U.S. $8 billion. Also as of 2002, the United States had about 1400 biotech companies, together worth about U.S. $25 billion.

Worth about U.S. $47 billion, the Japan pharmaceutical sector represents about 12 percent of the global market but with a very small annual growth rate (i.e., only 1 percent). Its limited growth is due to domestic drug price caps, although Japanese companies have become more aggressive and are seeking growth opportunities in international markets.

Again for comparison, based on information from the Japanese Biotechnology Association, the Japanese biotech sector is rapidly and remarkably growing. The number of Japanese biotech companies doubled between 2001 and 2003. In terms of number of companies, if this growth rate continues, Japan, by 2010, will have a biotech sector comparable to that of the United States and the United Kingdom combined.

Asia, Africa, and Australia together comprise the next largest sector of the pharmaceutical industry. Key areas include Singapore (see discussion in Chapter 2), South Korea, China, Taiwan, and Australia. Worth about U.S. $32 billion, this regional market constitutes 8 percent of the global market and enjoys an annual growth rate of 11 percent.

With an annual growth rate of –10 percent, the pharmaceutical industry in Latin America has recently contracted as a result of economic recession. Worth about U.S. $17 billion, it makes up only 4 percent of the global market.

The majority of the global market is targeted toward chronic diseases among the older sector of the population (i.e., persons over the age of 65).

The best-selling pharmaceuticals (and their annual market value in parentheses) are:

- anti-ulcerants ($22 billion),
- cholesterol reducers ($22 billion),
- anti-depressants ($27 billion),
- anti-rheumatics ($12 billion),
- calcium antagonists ($10 billion),
- anti-psychotics ($10 billion), and
- oral anti-diabetics ($8 billion).

The figures above represent worldwide trends and include purchases in developing countries where the older population is rapidly growing. Based on a report by the U.S. Census Bureau, the population in Northwest Europe 60 years of age and older, for example, is expected to increase between 50 and 60 percent over the next 20 years or so.[2] But in the developing world, the aging population[3] is expected to increase 200 percent over the same time period. From the point of view of a pharmaceutical company, the developing world is and will be producing a larger market for these same drugs in the years to come, despite the critically serious global public health threat of emerging infectious diseases.

Three likely major future trends in the global pharmaceutical industry were identified. First will be the development of patient- and genome-specific "designer drugs." (See Chapter 2 for a discussion on genomic medicine initiatives in Mexico and Singapore.) Technical developments that will enable (and already enable) this trend include advances in gene chip technology, improvements in biomedical database technology, and increased computing power.

One participant questioned whether the individualization of pharmaceuticals (i.e., genome-specific drugs) might not limit, rather than expand, the market for such drugs. It is unclear how the economics of this specificity will play out in the future, in terms of profitability. It was suggested that perhaps community-level pharmacogenomics might be more profitable than individual-level genomic medicine (i.e., by targeting larger markets). On the other hand, the chief industry advantage of genomic medicine will be the tremendous cost savings and reduced risk achieved by pre-selecting individuals for phase three clinical trials. Genomic-based pre-selection will save money by reducing the size of the phase three clinical trial and shortening time to market. Presumably, the savings from

[2]Kinsella, K. and Victoria Velkoff. 2001. "An Aging World: 2001." U.S. Departments of Health and Human Services, and Commerce; November (P95/01-1).

[3]This refers to the sector of the population over 60 years of age.

smaller, directed studies would lead to the development (including phase three clinical trials) of multiple additional drugs at a net savings. The pharmaceutical industry may also be interested in the use of gene profiling to develop optimum therapies based on an individual's genetic make-up. As with individualized medicine, these efforts will be enabled by advances in gene chip and database technologies.

A second major trend, and perhaps the most important with respect to dual-use risk of advancing technologies, will be the development of new means of drug delivery, the success of which will be enabled by developments in nanotechnology, aerosol technology, and perhaps other areas. The fact that finding new and alternative ways to deliver drugs is expected to be a major future trend points to the importance of considering technology related to delivery, in addition to the pathogens themselves, when evaluating emerging bioweapon and bioterrorist threats.

A comment was made with respect to how nanotechnology might impact the drug market far in the future. (See Chapter 4 for a more detailed discussion of nanotechnology.) If intelligent nanotech drug delivery systems become a reality (i.e., systems with the capacity to read genomic or other diagnostic markers and then deliver drugs accordingly), presumably the same delivery system would be administered to everybody. It is unclear how the market would adapt to this kind of technology.

There was a question about the role of intellectual property in the global dissemination of these various pharmaceutical-enabling technologies. Over the next five years, a number of blockbuster drugs will be coming off patent, thus providing even greater opportunities for developing countries to participate more actively in the global expansion of the life sciences industry by utilizing their manufacturing capabilities to build a new, cost-competitive market. Yet, at the same time, as developing countries join the World Trade Organization and, by doing so, sign on to a 20-year patent protection obligation, certain drugs may become more expensive and pose yet another dilemma in addressing the health needs of developing countries.

Medicine

The medical sector of the life sciences industry is expected to experience several major changes in the near future:

1. Improved diagnosis, with the goal of automating genomic analyses; enabling technologies will include database and gene chip technology.
2. Better treatments for infectious diseases; enabling technologies will include medical and genomic databases, high-throughput screening of compound libraries, and nanotechnology.

3. Gene therapy for overcoming host defense defects; enabling technologies will include bioinformatics.
4. Xenotransplantation and the drive to find rejection-free tissue and organs for transplantation; enabling technologies will include database and recombinant technologies (i.e. the latter will lead to advances in animal modeling).

Again, these predicted changes derive from expected future trends. Efforts to extend life through modification of aging processes may not be viewed as a major trend today, but there is reason to expect that it will become a market driver in the future.

Biomaterials

Major expected future trends in the biomaterials industry include expansions of the artificial organ and biopolymer markets, the latter with the aim of finding new materials for biological and other industrial applications. Both developments will be enabled by improvements in database and computing technologies, transgenic crop and animal technologies, and nanotechnology.

Agriculture: Transgenic Crops

With regards to agriculture, one of the major future trends will be the expansion of transgenic crops, as described in Chapter 2. Potential benefits of transgenic agriculture range from the development of more disease-resistant crops to the production of better-tasting foods. Societal benefits notwithstanding, ultimately, as with the pharmaceutical industry, economics is the bottom line. Any technology that results in lower production costs, and higher profit margins, will likely progress more rapidly than other, lower-yield ventures.

Computing

In the computing industry, future major trends will likely include performance improvement and application expansion. The former will result in faster overall computing and the convergence of technologies that feed into each other, efforts that will be enabled by advances in grid and super computing. The development of new or improved computing applications, a trend driven in large part by the need to strengthen biotech-specific software, will be enabled by software advances and more advanced search algorithms.

Military

In terms of market value, military needs are not considered a significant driver of technological development and dissemination. However, with respect to the life sciences, an important future military trend will involve strengthening biodefense capabilities. Specific goals will include the improvement and production of a select list of vaccines and prophylactics, rapid diagnostics, pathogen detectors, and forensic tools. Enabling technologies will include database and gene chip advancements, nanotechnology, and improvements in detector hardware.

Another expected and controversial future military trend will be the development of bioweapons by certain governments and non-government (terrorist) groups, despite the illegality of developing such weapons. The development of effective bioweapons will be enabled by advances in database and gene chip engineering, molecular synthesis methods, and high performance computing.

Changing Geographical Trends

Although the United States and the European Union dominate the global life sciences industrial marketplace, they are not by any means the only players. The diffusion of the technologies that enable, or will enable, all of the above listed market trends is and will continue to be truly global. In other words, technological breakthroughs could come from anywhere in the world.

As discussed in the previous chapter, biotechnological growth in Singapore embodies the diverse geo-political efforts directed toward becoming regional or global advancing technology leaders. In January 2003, Novartis opened the Novartis Institute for Tropical Diseases (NITD) in Singapore.[4] In the late 1990s, Eli Lilly and Company opened its only Lilly Clinical Pharmacological unit outside of the United States in Singapore and is recruiting talent from around the globe.[5] More recently, in 2001, Eli Lilly entered into an agreement with the Singapore Economic Development Board to establish an R&D center in Singapore to focus on systems biology.[6]

As another example, China leads the world in agricultural technology development, having created some 150 transgenic crops, of which about 50 are patented or marketed for U.S. purchase. The Chinese military is very active in the country's biotechnology efforts. For example, in 1998, a

[4]*http://www.nitd.novartis.com.* Accessed on October 21, 2004.
[5]*http://www.med.nus.edu.sg/lilly/.* Accessed on October 21, 2004.
[6]*http://www.lsb.lilly.com.sg/.* Accessed on October 21, 2004.

tissue engineering research center was set up at the Academy for Military Medicine and Sciences. China also leads the world in the production of protein-enhanced material, mostly for domestic and regional use. Additionally, China produces about 11,000 tons of antibiotics per year, which is about half of the world's total.

Cuba provides another good example of the global diffusion of advancing technologies. It was the first country in the world to have successfully developed a vaccine against meningitis B, which even the United States is now willing to import despite its trade embargo against Cuba.[7]

South Korea has utilized its biotechnological potential as part of its effort to transform itself rapidly from a developing into a developed country, attracting worldwide attention when scientists performed the first successful therapeutic cloning experiment. In addition, Brazil, Egypt, India, South Africa, and other countries, are also exploiting various technologies both to address health issues and as mechanisms for economic development.

There were questions about whether and how government involvement impacts sustainable, long-term market growth. In other words, does a proactive government increase the likelihood of advancing technological expansion? It seems that the government plays different roles in different places. In the United States and the European Union, for example, where the life sciences industry is almost exclusively privately financed, the government sector plays a largely consumer role (i.e., it purchases products). But in Singapore, for example, the government plays much more than a consumer role. It also provides a highly regulated environment for conducting life sciences, including stem cell, research; and it offers incentives to encourage companies to do business there. Likewise in Cuba and Brazil, for example, where industrial and commercial expansion appears to be occurring in areas where the government is similarly proactive.

SOCIAL DRIVERS[8]

> . . . there can be no peace, no security, nothing but ultimate disaster, when a few rich countries with a small minority of the world's people alone have access to the brave, and frightening, new world of technol-

[7]The meningitis B vaccine was developed in the 1980s at the Finlay Institute in Cuba, and is considered the world's first effective vaccine against this child-killer disease. The Clinton Administration agreed to authorize the British firm, SmithKline Beecham Pharmaceuticals, to market the Cuban anti-meningitis vaccine in the United States.

[8]This section is based largely on the workshop presentations of Abdallah Daar, David Banta, Rosiceli Barreto Goncalves Baetas, and Decio Ripandelli.

> ogy, science, and of high material living standards, while the large majority live in deprivation and want, shut off from opportunities of full economic development; but with expectations and aspirations aroused far beyond the hope of realizing them.
>
> —Lester B. Pearson[9]

This section summarizes the workshop presentations and discussions that revolved around the societal benefits of advancing technologies' growth and globalization. In particular, how can technological advances be used to address the unique public health needs of the developing world and close the growing development gap between the North and South? The promise of genomics figured prominently in this dialogue, as did the notion of a new vaccine market and efforts by the Italy-based International Center for Genetic Engineering and Biotechnology to engage the developing world in the development and application of advancing technologies. However, even as technology growth may provide at least a partial solution to some of these problems, the steadfast challenges associated with the prevention and control of emerging infectious diseases were highlighted as a reminder of the many obstacles still ahead.

The Promise of Biotechnology[10]

In light of growing recognition that technology can and has benefited human development, there have been several recent pleas by individuals and organizations for the use of technology advances to bridge the growing public health gap between developed and developing nations.[11,12,13]

Importantly, although genomic medicine was highlighted during this workshop, it is not by any means the only technology application with potential to improve health in developing countries. A technology foresight study conducted by the University of Toronto Joint Centre for Bioethics (JCB), in partnership with 29 scientists with expertise in health and

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[9]Lester B. Pearson's Public Address at St. Martin-in-the-Fields, London, June 13, 1972, on the Occasion of the Presentation to Him of the Victor Gollancz Humanity Award. The full address can be found at *http://www.unac.org/en/link_learn/canada/pearson/speechgollancz.asp.*

[10]This subsection based on the presentation by Abdullah Daar.

[11]WHO. 2002. Genomics and World Health. *http://www3.who.int/whosis/genomics/genomics_report.cfm.* Accessed on October 28, 2004.

[12]Singer, P. A. and A. S. Daar. 2001. "Harnessing genomics and biotechnology to improve global health equity." *Science* 294:87-89.

[13]UNDP. 2004. *Making New Technologies Work for Human Development.* Oxford University Press, New York, 2001. *http://hdr.undp.org/reports/global/2001/en/.* Accessed on October 28.

biotechnology and in-depth knowledge about public health problems in developing countries, identified the top ten biotechnologies that are likely to improve human health in developing countries within the next 5 to 10 years:[14]

- Molecular diagnostics
- Recombinant vaccines
- Drug and vaccine delivery systems
- Bioremediation
- Sequencing pathogen genomes
- Female-controlled STI protection
- Bioinformatics
- Enriched GM crops
- Recombinant drugs
- Combinatorial chemistry

In a follow-up report entitled "Genomics and Global Health,"[15] JCB identified how these ten biotechnologies could appropriately be used to address some of the UN Millennium Development Goals.[16] The above list is partly intended to serve as a political advocacy tool. Basic science and basic science training are not included on the list but are considered vital investments in the internalization of knowledge and development of innovation capacities.

The Notion of a New Vaccine Market[17]

The fact that many developing world diseases are not on R&D lists of most industrialized nations is a reminder of how vitally important it is that the biotechnology capacity of the developing world be strengthened. This is perhaps nowhere more evident than with vaccines. Since vaccines have, along with clean water, arguably had the greatest historical impact on human health, from a public health standpoint, vaccine R&D could drive the global proliferation of vaccine R&D-enabling technologies.

However, as mentioned in the previous chapter, the infectious disease vaccine market is a high-risk endeavor in terms of profitability,

[14]Daar, A. S. et al. 2002. "Top 10 biotechnologies for improving health in developing countries." *Nature Genetics* 32:229-232.

[15]Canadian Program on Genomics and Global Health, University of Toronto Joint Centre for Bioethics, 2004, "Genomics and Public Health."

[16]Acharya, T. et al. 2003. "Biotechnology and the UN Millenium Development Goals." *Nature Biotechnology* 21:1434-1436.

[17]This subsection based on the presentation by Rosiceli Baetas.

particularly given the high number of competitors and clients with high bargaining power (e.g., governments, UNICEF, etc.). Navigating the R&D pipeline requires significant investment and time, usually about 10 years, and the situation is getting worse. In the 1980s, production costs for new vaccines were between U.S. $10 million and 15 million; in the 1990s, between $50 million and 200 million. Those figures are expected to rise to $200 million to 250 million over the next 10 years. Moreover, regulatory requirements are becoming more complex.

For these reasons, most major vaccine manufacturers in the industrialized world are transitioning into the production of therapeutic vaccines, such as for cancer, allergies, fertility, and various other non-infectious diseases. By 2006, the therapeutic vaccine industry is expected to be worth $10 billion. This new vaccine arena has very high entry barriers (i.e., higher than the traditional vaccine market), more intellectual property restrictions, and requires a longer development time. But its higher-priced products bring greater profits.

With a 200 year history since the inception of virology, scientists have long sought the "ideal" preventive vaccine: one that is effective with a single dose, immunizes at birth, works against many diseases, is easy to administer, can be stored for long periods of time, is genetically stable, does not cause adverse effects, and is affordable. Still, effective vaccines are lacking for many significant infectious diseases, not the least of which is HIV/AIDS. This is true, despite the fact that the newer (i.e., 21st century) third and even fourth generation genomic and bioinformatics-based vaccines represent a doubling in the number of vaccines available since the 1980s, when there were only about 25 vaccines (i.e., there were 51 different vaccines available in 2000).

The need for infectious disease vaccines is as great as ever but without a market to sustain continued R&D. As major vaccine manufacturers in the industrial world direct their attention elsewhere, it has been suggested that developing countries promote their own vaccine industries to fill the gap, produce vaccines of interest to them, and eventually develop the capacity to engineer novel vaccines. Local and/or state-owned manufacturers, as well as international organizations, will play a vital role in this effort; and the public and private sectors will need to integrate their efforts and adjust policies accordingly.

With this vision in mind, some regional networks have been initiated. For example, the Pan American Health Organization (PAHO) has begun efforts in ten Latin American countries to explore the potential for the development of new vaccines.

In summary, it appears that the shift toward more profitable vaccines may serve as yet another economic driver of the global spread of technology, at least among high-income countries. Meanwhile, in low- and

middle-income countries, public health crises are prompting consideration of a new vaccine industry. (As described in Chapter 2, plant-based vaccine manufacture was proposed as a plausible cost-effective solution to the inaccessibility of vaccine production.)

International Center for Genetic Engineering and Biotechnology (ICGEB): Efforts to Involve the Developing World[18]

The ICGEB, with headquarters in New Delhi, India, and Trieste, Italy, was founded in 1983 as a mechanism for involving developing countries in the emerging biotechnology field. It is an intergovernmental organization with 69 signature States, 52 member States, and a 35-center network. The Center recently issued a mandate to establish a code of conduct for scientists, as described in Chapter 5.

Despite its global reach, most high-income countries, including the United States, are not affiliated for several reasons, including industrial sector concerns that transferring technology to developing countries would increase competition and potentially reduce profits, and a general preference for bilateral collaborations, which allow greater control than multilateral efforts. Even some member States view the ICGEB as a non-political provider of technology, training, and research, and believe that its mandate should not extend to issues of prevention and misuse. In a sense, it is a catch-22 situation, since the highest-income countries will have little reason to join if the Center continues without the added value afforded by such activities.

The ICGEB performs several functions, details of which can be viewed on its Web site:[19]

- Research (i.e., there are approximately 400 affiliated scientists working on a range of basic and applied topics)
- Long-term training for pre- and post-doctoral researchers (i.e., the Center trains about 60-70 people a year)
- Short-term courses, many of which are of particular interest to scientists in the developing world (e.g., an upcoming course is entitled "The Molecular Biology of Leishmania")
- Collaborative research with the affiliated centers, whereby the ICGEB provides funding for affiliate-prioritized research
- Cooperation with the industrial sector
- Scientific services, such as the provision of databases and software

[18]This subsection based on the presentation by Decio Ripandelli.
[19]*http://www.icgeb.trieste.it.* Accessed on November 1, 2004.

- Institutional services
- Policy advice regarding intellectual property
- Risk assessment regarding genetically modified organisms
- Issues related to implementation of article X of the Biological Weapons Convention (Article X of the BWC is aimed at avoiding the hampering of state economic or technological development, particularly in low- and middle-income countries; fostering the exchange of equipment, materials, and scientific and technological information within a collective framework; and enhancing international cooperation aimed at developing and applying scientific discoveries for peaceful purposes. Article X represents the eminent value of joining the BWC for those countries who may not otherwise be interested in joining because they do not perceive any threats.)

Lessons from Emerging Infectious Diseases: Obstacles to Biotechnology Proliferation[20]

By examining the current status of prevention and treatment programs for emerging infectious diseases worldwide, it is quite evident that there still is an enormous discrepancy in technology development among different parts of the world. This is particularly true for non-clinical technologies, such as information and systems technologies. Even if the perfect drug for a particular condition exists, if there is no way to deliver the drug to the people who need it for lack of money, a weak public health system, lack of planning, or poor information, etc., then the pharmaceutical is not useful. The current situation in the developing world with regards to four emerging infectious diseases—HIV/AIDS, tuberculosis (TB), trypanosomiasis, and leishmaniasis—was used to illustrate how, despite the global growth of technology, many countries still encounter significant obstacles to accessing such technology.

HIV/AIDS

Of the estimated 40 million people worldwide infected with HIV/AIDS, fewer than 400,000 in low- and middle-income countries have access to life-sustaining antiretroviral (ARV) therapy. The high AIDS mortality in sub-Saharan Africa, which remains the worst-affected region of the world, contrasts sharply with the decreasing HIV-related death rate in high-income countries where ARVs are widely available and affordable.[21]

[20]This subsection based on the presentation by David Banta.

[21]Institute of Medicine. 2004. *Scaling up treatment for the global AIDS Pandemic: Challenges and Opportunities*. Washington, DC: The National Academies Press.

Clearly, there is an enormous global discrepancy in the application of effective biotechnology.

It was pointed out that since most HIV/AIDS drugs have been researched and developed with NIH funding and then licensed to pharmaceutical companies (i.e., contrary to popular opinion that the R&D was privately funded), it seems that there ought to have been some sort of provision for the development of these same drugs in developing countries. Such is not the case.

However, ARV drug prices have fallen sharply in recent years and donor funding has risen, thus encouraging a number of ARV scale-up programs worldwide and fueling WHO's ambitious "3-by-5" campaign, with the global target of providing ARV therapy to 3 million people with HIV/AIDS in developing countries by the end of 2005.[22]

Still, drugs alone are neither the only problem nor the sole solution. As identified during this workshop, there are two major obstacles to the effective management of the global HIV/AIDS crisis: complications associated with patent restrictions and a range of systems-level problems. With regard to the former, a patent is by definition a grant of monopoly power. Under the present World Trade Organization (WTO) rules, new drugs are under patent for at least 20 years with a number of ways to extend that time period. The expansion of the WTO (e.g., in 2005, India will join the WTO) will call into question the ability to make and export generic ARVs. The 2001 Doha resolution[23] addressed this problem to some extent by allowing compulsory licensing (i.e., countries with the capacity to do so can reproduce patented drugs without permission of the patent holder). However, countries without their own pharmaceutical industry will be in much the same situation that pre-dated the dramatic drop in ARV costs, that is with little recourse.

Despite access to ARVs, many HIV/AIDS treatment programs fail due to so-called "systems technology" problems, particularly at the national level (e.g., due to the lack of a national HIV/AIDS coordinating authority.) It is vitally important that a national policy and single monitoring and evaluation system be in place in every country. In fact, the need for this national-level focus inspired the "three 'ones' principle" for HIV/AIDS: one agreed national HIV/AIDS action framework as the basis for

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[22]Institute of Medicine. 2004. *Scaling Up Treatment for the Global AIDS Pandemic: Challenges and Opportunities*. Washington, DC: The National Academies Press; WHO. 2003. "Treating 3 Million by 2005. Making it Happen. The WHO Strategy." Geneva, WHO. *http://www.who.int/3by5/en/.* Accessed on October 21, 2004.

[23]World Trade Organization. "Declaration on the TRIPS agreement and public health. Adopted November 14, 2001. (known as the Doha Resolution). Available at *http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.*

coordinating work; one national HIV/AIDS coordinating authority; and one agreed country-level monitoring and evaluation system.

Tuberculosis

One-third of the world's population is infected with *Mycobacterium tuberculosis* (TB), and 2 million people die from TB every year. The main pillar of treatment is still isoniazid, and there is an enormous need for new, better drugs. Drugs requiring only a relatively short treatment course could solve problems associated with poor adherence and the consequent rise of multi-drug resistant TB, which is increasing in incidence not only in the developing world but also throughout the United States and the European Union. In fact, middle-income Russia is believed to have one of the fastest growing rates of multi-drug resistant TB, and TB is increasing in the UK at a rate far greater than any other western EU country. Despite these trends and international efforts to encourage anti-TB drug development, there has been very little R&D, either private or public, directed toward new therapies.

In addition to new drugs, there is an urgent need for improved diagnostics and public health monitoring technologies. The ones currently in use were developed more than a century ago by Robert Koch himself. Fortunately, the biotech industry has recently expressed considerable interest in developing new TB diagnostic tools, some of which should be ready for testing and perhaps deployment within the next 5 years or so.

As with HIV/AIDS, irrespective of whether effective drugs exist or not, systems-level problems limit the capacity to manage effectively the global TB crisis. Most notably, inconsistent or poor adherence to the 6-9 month course of drug therapy is a major reason for the rapid emergence of multi-drug resistant TB, even among patients who attend clinics participating in the DOTS (Directly Observed Treatment Short Course) program. In many parts of the world, attending a clinic daily for at least two months is simply not a feasible reality. This is not to imply that DOTS has not been a very important step forward, as it has proven to be a very effective strategy. However, it either needs to be improved in ways that will allow it to reach more people, or alternative strategies need to be sought.

Neglected diseases

Neglected, or so-called tropical diseases, continue to be significant public health problems worldwide. These include drug-resistant malaria, African trypanosomiasis (also known as sleeping sickness), visceral leishmaniasis (also known as kala azar), Chaga's disease, lymphatic filariasis, and schistosomiasis. Even TB is sometimes considered a neglected dis-

ease because of the lack of anti-TB drug R&D. Tropical diseases are considered neglected because, although they account for about 90 percent of the global burden of disease, they draw only about 10 percent of the world's health research expenditure. For example, only 1 percent of the almost 1400 drugs registered between 1979 and 1999 were indicated for use against "neglected" diseases.

The current situation with regard to sleeping sickness highlights the neglect. Sleeping sickness is endemic in 36 African countries, where altogether it infects some 300,000 persons every year. The disease has been controlled in the past almost exclusively by the use of insecticides, fly-trapping, and other vector control strategies. Despite successful past control efforts and largely because of armed conflict in endemic areas, trypanosomiasis has reemerged in many localities. The primary treatment, melarprosol, is an old, arsenic-based drug with many side effects, including encephalopathy, which occurs in 5 to 10 percent of all patients and kills half of those affected. Interestingly, a newer drug, eflornithine, was known to have anti-trypanosomal potential but was not commercially developed until its hair-removing effects were discovered. Now, Aventis, in cooperation with WHO, provides the drug free of charge. Still, drug delivery poses a problem since, although effective, eflornithine requires four daily IV infusions for two weeks. As with DOTS, in an African setting, this is not very practical.

POLITICAL DRIVERS[24]

The lack of interest on the part of governments to fund certain types of scientific research and insufficient scientific policy for directing research were cited as major impediments to the global proliferation of certain technologies. For example, the Mexican government is apparently not particularly interested in funding transgenic crop research, although quite the opposite seems to be the case with genomic medicine. Part of the problem is the transitory nature of governmental administrations: one administration may favor one technology, while the next does not. It was suggested that a more informed public and government (i.e., informed about the beneficial applications of scientific knowledge and technology) would create more sustainable governmental commitment.

Of note is Canada's recent commitment to international R&D. In the February 2, 2004 Speech from the Throne (which officially opens every

[24]This section is based on individual comments by multiple workshop participants, comments on Canada by Daar, comments on Singapore by Patrick Tan Boon Ooi, and the summary of South Africa's Project Coast by Jerome Amir Singh.

new session of Parliament by setting out broad goals and directions of the government), the following declaration was made: "We are a knowledge-rich country. We must apply more of our research and science to help address the most pressing problems of developing countries." The following day, Prime Minister Martin replied by announcing the country's "5 percent commitment": "Our long-term goal as a country should be to devote no less than 5 percent of our R&D investment to a knowledge-based approach to develop assistance for less fortunate countries."

Biodefense[25]

Most experts consider biodefense a relatively minor economic driver of biotechnology. After all, the annual global pharmaceutical market is worth more than 70 times the $6.5 billion that the U.S. government has promised for the purchase of vaccines and drugs over the next 10 years.[26] Nonetheless, several workshop participants questioned whether the United States biodefense efforts might be setting a significant "tone" or "backdrop," which may nonetheless impact the global transfer of technology.

As an example of how terrorism-conscious thinking pervades national dialogue even outside the United States, those who are involved with establishing the new national genomics medicine platform in Mexico are aware that such a platform will serve a dual biodefense role (see Chapter 2 for details). In other words, if genome-specific medicines can be made specifically for use in the ethnically diverse Mexican population, so too can genome-specific bioweapon or bioterrorist agents.

Even though biodefense efforts may not greatly impact the absolute growth and spread of technology, they could pose disproportionately greater dual-use risks. For example, a question was raised about whether a greater investment in biodefense might increase the dual-use risk posed by knowledgeable, skilled insiders.

A question was asked regarding the dual-use potential of agricultural transgenic technology and whether any U.S. biodefense research efforts were being driven by this particular threat. In response, it was mentioned that the USDA recently called for proposals but that only a trivial amount of money was dedicated to the consideration of plant pathogens as bio-threats. A similar concern was expressed about plant-based vaccines: if plants can be used as delivery vehicles for vaccines, might they not also

[25]This section summarized comments made by individual workshop participants throughout the course of the workshop.

[26]Project BioShield. Available at *http://www.whitehouse.gov/bioshield/.*

serve as delivery vehicles for bioweapons? A recent experiment generating considerable attention along these lines involved the engineered expression of insecticidal viruses by plants, in order to kill insect predators that happen upon the plant.[27] This type of work has immediate dual-use implications for plant biotechnology.

Questions were raised about whether and the extent to which future increased investments in biodefense might dissuade international R&D donors from supporting developing countries with capabilities that could conceivably be used by either state bioweapons or non-state bioterrorist programs. Anecdotal reports suggest that some international R&D companies are reluctant to support countries with capabilities that may be directed towards the production of bioweapons. No specific cases were mentioned. Along the same lines, concern was expressed that the limited entry of foreign nationals into U.S. training programs may have an enormous negative effect on the global dispersion of beneficial knowledge and talent in relevant technologies.

There was concern regarding how the current focus on bioterrorism in the United States may be impacting, perhaps worsening, the general public perception of biotechnology. Does the bioterrorist backdrop make it more difficult to convince people that these products are safe to eat or use?

Looking to the bright side, some workshop participants wondered if the investment and attention paid to biodefense might not provide "terrific opportunities" for the continued global proliferation of knowledge and biotechnology. For example, technical breakthroughs in the area of rapid diagnostics not only will strengthen biodefense capabilities but may benefit public health generally (i.e., by improving early diagnostic capabilities with regards to naturally occurring infectious diseases). As one workshop participant noted, "There is almost a seamless boundary between the needs and issues in defense against natural disease and the needs and issues in defense against disease of deliberate or malevolent origin."

It was noted that the information technology industry was initially a non-commercial endeavor started by the military but was then quickly and ultimately driven by commercial demands.

Singapore and Biodefense[28]

A question was raised about whether the degree to which concern about bioterrorism drives biotechnology investment in Singapore in

[27]Ranjekar, P. K., A. Patankar, V. Gupta, R. Bhatnagar, J. Bentur, and P. A. Kumar. 2003 "Genetic engineering of crop plants for resistance." *Current Science* 84(3):321-329.

[28]This section based on the presentation by Patrick Tan Boon Ooi.

biodefense, given its rapidly growing biotechnological capacity and the fact that the country is surrounded by Indonesia, Thailand, and Malaysia, all predominantly Muslim countries with known Al Quaeda terrorist cells. An important theme that emerged from this discussion was the difference in prioritization of specific "select" agents as a function of geographic location around the world. For example, the CDC-identified category B biological agent *Burkholderia pseudomallei* is not viewed as a high priority agent of concern by Singaporean authorities, given the ubiquity of this bacterium in the local natural environment. In general, naturally occurring emerging infectious diseases are generally considered a greater threat to national security than bioterrorism. Investment in public health infrastructure and detection/diagnostic technologies is viewed as an attractive strategy. For example, because of its strong domestic DNA sequencing and other relevant technology capacities, Singapore was able to contribute to the global SARS response by genetically profiling a number of different viral isolates. The same capabilities could be used in the event of a bioterrorist attack.

In addition to the more immediate threat posed by naturally emerging pathogens, there is a general sense that chemical (e.g., something being introduced into the water supply) and physical attacks (e.g., car bomb) are more likely than a biological attack. Singapore has also acknowledged the existence of a black market in the trafficking in these terrorist tools and the difficulty in curtailing the spread of established dual-use agents and advancing technologies.

However, the chance that a bioterrorist attack could happen is definitely on the table. In April 2004, for example, an outbreak of melioidosis that killed 15 people prompted a genotyping effort to determine whether the strains originated from a single source or a variety of sources, the latter an indication of natural emergence. Generally, even outside the context of the changing global climate with respect to terrorism, Singapore security is very tight; everyone is screened, public institutes require card-key access, and the military has very strict entry guidelines.

Bioweapons: South Africa's Past[29]

Although bioweapons programs are illegal in accordance with the 1972 Biological Weapons Convention,[30] some experts nonetheless consider them a driver of the global proliferation of dual-use agents, knowledge, and technology. There is concern that as the means to acquire or engineer

[29]This section based on the presentation by J. A. Singh.
[30]*http://www.opbw.org/.* Accessed on October 28, 2004.

more lethal bioweapons become easier and cheaper, state actors that have not been involved with biological weapons in the past (e.g., because such weapons have not been considered accessible or particularly useful) may start developing new bioweapons programs. Some believe that this may already be occurring under the cover of defensive weapons research.

The now defunct offensive bioweapons program of South Africa—known as "Project Coast"—illustrates how biotechnology has been used for malevolent purposes in the past, in this case at the state level and unbeknownst to the rest of the world.[31]

Apartheid South Africa's chemical and biological warfare program, known as "Project Coast," was commenced in the 1980s, in response to the perceived threat of communist regimes flanking the country. The fact that South African troops had been exposed to biowarfare agents in both World Wars, coupled with being privy to British bioweapons secrets, motivated the country to devote resource towards bioweapons research and training and, ultimately, Project Coast.

In 1993-1994, South Africa dismantled Project Coast, along with its ballistic missile and nuclear weapons programs.[32] Indeed, it was the first country in the world to dismantle all weapons of mass destruction (WMD) programs. But the extent of Project Coast was not publicly known until 1998-1999, when the Truth and Reconciliation Commission hearings coerced many scientists to disclose their involvement with the Project in order to gain immunity. The now transparent history serves as a horrific example of how science can be subverted to undermine entire communities and how scientists can be persuaded to participate in the proclaimed national interest. At the time of the Project, research conducted for the sake of the national interest was considered the most important research in the country.

At the workshop, three dual-use technologies allegedly produced under the auspices of Project Coast were described:

- Up to as many as 45 *Bacillus anthracis* strains, including a penicillin-resistant strain, were bio-engineered. There are disputed claims that South Africa may have played a role in the 1979-1980 anthrax epidemic in Zimbabwe (formerly Rhodesia), which killed more than 80 people and injured thousands (although this occurred before the formal creation of Project Coast).

[31]Burgess, S. and H. Purkitt. 2001. "The Rollback of South Africa's Chemical and Biological Warfare Program," USAF Counterproliferation Center, Air War College, Air University, Maxwell Air Force Base, Alabama; April.

[32]Ibid.

- There is no proof that race-targeting bacterial bioweapons were actually produced, but significant sums of money were spent on the effort and the intent existed.
- Acquisition of a peptide synthesizer was ostensibly for the purposes of AIDS research, but court testimony indicated that the synthesizer was in fact being used for research on behavior-changing peptides absorbed through the nasal mucus membranes (e.g., they could make a person either more aggressive or more passive). Again, although it's not clear whether this approach was ever tested or used on humans, the malicious intent existed.

Although South Africa has dismantled Project Coast and its other weapons programs, and post-apartheid legislative initiatives address the need to regulate dual-use technologies with WMD potential, it is interesting to note that the Non-Proliferation Council does not fall under the Ministry of Defense, presumably because of the realization that such technologies have commercial use.

It is also interesting to note and of concern that apartheid bioweapons expertise still exists and may be "at large," that is for sale to the highest bidder. As recommended by the international community, the South African government has attempted to keep many of these experts employed under its watch rather than have them take their expertise elsewhere.

4

Emerging and Converging Technologies[1]

> During the century just begun, as our ability to modify fundamental life processes continues its rapid advance, we will be able not only to devise additional ways to destroy life but will also be able to manipulate it—including the processes of cognition, development, reproduction, and inheritance.
>
> —Matthew Meselson[2]

It is difficult to predict what the global technology landscape will look like in 20, 10, or even 5 years into the future. But it is not difficult to predict that as advances are made, so too will the opportunities for misuse. This chapter summarizes information on emerging technologies that are expected to have significant economic, societal, and dual-use risk impact in the near future. As highlighted during the workshop, prominent among these are advances in knowledge and delivery technology that have increased the dual-use potential and risk of non-lethal bioregulators; and the convergence of nanotechnology and biotechnology in the form of DNA nanotechnology.

[1]This section is based on the workshop presentations of Kathryn Nixdorff and Elliott Kagan.

[2]Meselson, M. 1999. "The problem of biological weapons." Presentation given to the 1818th Slated Meeting of the American Academy of Arts and Science, Cambridge, MA, January 13. *http://www.pugwash.org/reports/cbw/cbw5.htm.* Accessed on October 30, 2004.

A major theme that emerged from these discussions is the notion that pathogens are not the only potential bioterrorist agents. Some experts argue that bioregulators, which are non-pathogenic organic compounds, may pose a more serious dual-use risk than had been previously perceived, particularly as improved targeted delivery technologies have made the potential dissemination of these compounds much more feasible than in the past. This shift in focus highlights the reality that the materials, equipment, and technology necessary for disseminating and delivering the agents to their intended recipient(s) are equally, if not more, important than the agents themselves in terms of their dual-use risk.

The immune and neuroendocrine systems are particularly vulnerable to bioregulator modification. In fact, the capacity to develop bioweapons that can be aimed at the interaction of the immune and neuroendocrine systems again points to a shift in focus from the agents to, in this case, how a range of agents can be exploited (or created) to affect the human body in targeted, insidious ways.

A controversial issue that arose from these discussions is how all research on immune system evasion could be considered potentially dangerous, thus highlighting the very important need to uphold the norms of the Biological Weapons Convention. The unlikely possibility that reaffirming these norms will have any immediate effects further complicates the problem. Discussion of these issues is reserved for Chapter 5.

Another important theme that emerged from discussions of the material presented here is the notion of time and how the advancing technology landscape has an uncertain future and unpredictable dual-use risk implications. This unpredictability poses a significant challenge for developing and implementing a strategy to manage these risks.

Added to the temporal challenge are difficulties associated with adapting or developing prevention strategies that are effective against the wide range of risks posed by the various types of dual-use agents, materials, and technologies. Comments were made about how the CDC Select Agent Program does not accurately reflect the variable nature of these risks.[3]

Importantly, the growth and proliferation of dual-use agents, materials, equipment, and technology summarized here does not necessarily imply that the acquisition, creation, or effective use of a biological agent is easy. The Japanese cult Aum Shinrikyo's nine failed attempts between 1990 and 1994 to disperse biological weapons in Tokyo and nearby areas are a reminder of the difficulty of carrying out an attack, even with category A agents (*Bacillus anthracis* or botulinum toxin), despite the expenditure of

[3]The interim final rule on the possession, use, and transfer of select agents and toxins can be viewed online at *http://www.cdc.gov/od/sap/docs/42cfr73.pdf.*

considerable time, effort, money, and talent. Not only did Aum Shinrikyo obtain a non-lethal vaccine strain of anthrax, it had not mastered the aerosolization technology required to disseminate it.[4]

BIOREGULATORS AND INNATE IMMUNITY[5]

Bioregulators are naturally occurring organic compounds that regulate diverse cellular processes in multiple organ systems and are essential for normal homeostatic function. They are structurally diverse and play key roles in many critically important bodily functions, such as maintaining bronchial smooth muscle tone, blood pressure, heart rate, body temperature, mood and consciousness, and innate and adaptive immune responses. Most bioregulators operate by targeting specific cell receptors and signal transduction pathways, ultimately impacting mRNA synthesis (see Figure 4-1 A and B). Several different types of bioregulators are considered potential threat agents: cytokines (pro-inflammatory agents, such as IL-1; chemokines; and growth factors); hormones (catecholamines, insulin); neurotransmitters (neuropeptides, biogenic amines, amino acids); eicosanoids (e.g., prostaglandins, leukotrienes); enyzmes (e.g., kallikreins, tissue factor); and nucleic acids (i.e., DNA, RNA).

In the past, the dual-use risk of bioregulators was considered minimal because of their lack of suitability for aerosolization unless microencapsulated; their limited shelf life after atmospheric release; the fact that proteins denature at very high temperatures and lose activity at low temperatures; and high purchase costs. However, new knowledge and advancing technologies, particularly delivery technologies, have raised concerns about the dual-use risk of bioregulators. Potential delivery platforms include the use of bacterial plasmids or viral vectors for cloning the genes that encode bioregulators; the use of transgenic insects (i.e., to secrete and inoculate the bioregulators); nano-scale delivery systems (e.g., engineered proteins either within or bound to nanotubes); and microencapsulated delivery systems (i.e., incorporating vectors or the proteins themselves into biodegradable microspheres or liposomes for controlled release).[6]

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[4]Leitenberg, M. 2000. "An assessment of the biological weapons threat to the United States." A White Paper prepared for the Conference on Emerging Threats Assessment: Biological Terrorism, at the Institute for Security Technology Studies, Dartmouth College, July 7-9, *Journal of Homeland Security*, *http://www.homelandsecurity.org/journal/Articles/Leitenberg.htm.* Accessed on October 30, 2004.

[5]This section is based on the workshop presentations of Kathryn Nixdorff and Elliott Kagan.

[6]Wang, D. et al. 1999. "Encapsulation of plasmid DNA in biodegradable poly(D,L-lactic-co-glycolic acid) microspheres as a novel approach for immunogene delivery." *Journal of Controlled Release* 57:9-18.

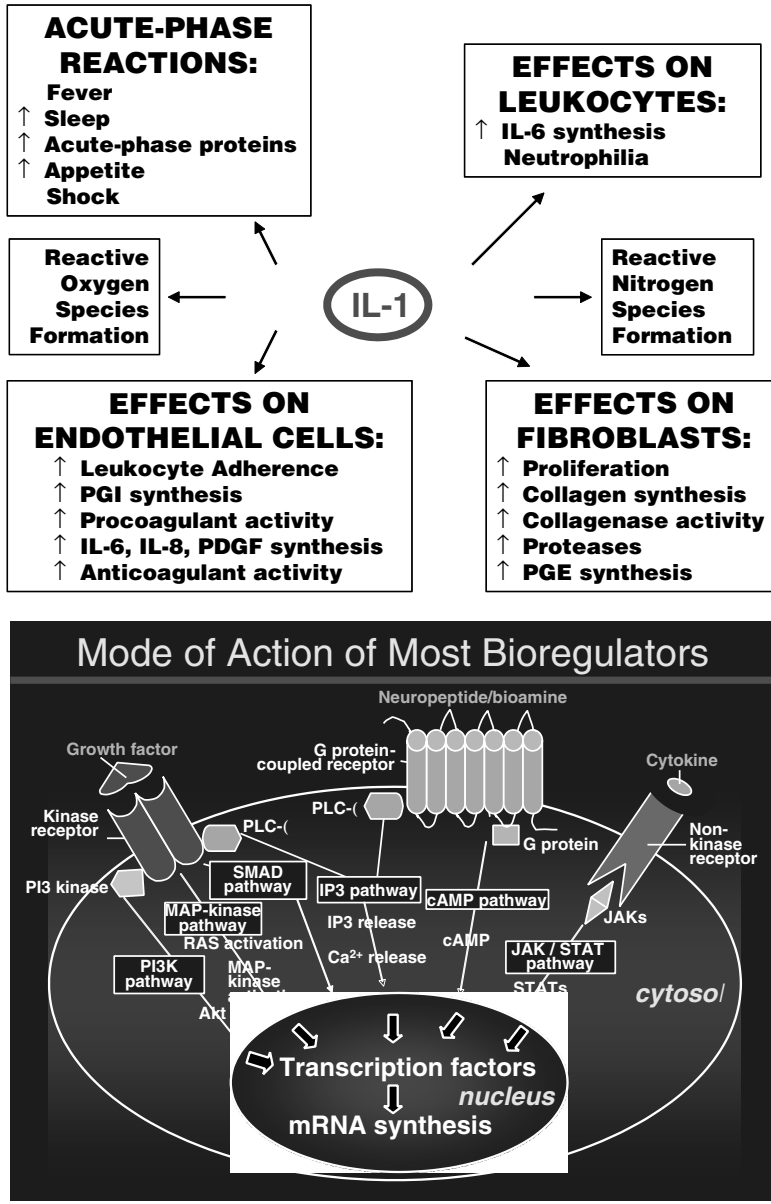

FIGURE 4-1 A and B The multiple ways that bioregulators impact mRNA synthesis. Because of the key role that bioregulators play in so many cellular and physiological processes, their dual-use risk increases as delivery technologies advance. NOTE: Adapted from Elliott Kagan's PowerPoint presentation, September 22, 2004.

Given that anything less than 3 microns in diameter is respirable across what amounts to a 75 square meter absorptive surface, the miniaturization of respiratory delivery systems comes with considerable dual-use risk. Moreover, transgenic plants could be put to dual-use as bioregulator-production factories.

In many ways, bioregulators pose serious dual-use risks:

- Their onset of action is rapid, occurring within minutes to hours.
- They can potentially cause injury or death with no obvious evidence of attack (i.e., stealth factor).
- Their clinical effects are non-specific (i.e., very low index of clinical suspicion).
- Casualties may manifest as multiple occurrences of unexplained symptoms.
- They target critical human biochemical pathways.
- They may target multiple organ systems (e.g., central nervous system, lungs, immune system, gastrointestinal system, cardiovascular system, etc.).
- Potential long-term consequences include pulmonary fibrosis, cancer, sterility, autoimmunity, etc.
- There are no vaccines available.
- Most bioregulators are not on standard military threat lists, meaning there is no provision for appropriate antidote stockpiling.
- The effects of bioregulators may synergize with those of traditional BT/BW agents.
- They can be engineered to target specific human biological systems at the molecular level.
- Future potential as threat agents will parallel advances in biotechnology.

Bioregulators have been used in prior state-sponsored bioweapons programs, including South Africa's Project Coast, which included a peptide synthesis program aimed at enhancing the effects of certain bioregulators (see Chapter 3). Also, according to congressional testimony by Soviet defectors, the former Soviet Union reportedly synthesized recombinant bioweapon peptides that could induce autoimmunity.[7]

[7]Alibek, K. 1999. Congressional Testimony before the House Armed Services Committee; October 20.

The Vulnerability of the Immune System[8]

The immune system plays a crucial role in protection against infectious disease. The immune system is particularly vulnerable to the numerous evasion strategies that microorganisms utilize; as the development of a lethal form of the mousepox virus by Australian scientists in 2001 demonstrated, the manipulation of microorganisms can lead to the creation of mechanisms to evade the immune system in devastating ways.[9] The immune system is also vulnerable to modulation by bioregulators.

There are two components of immunity, innate and adaptive. The innate immune system has a relatively low specificity for microorganisms; the immune cells recognize what are known as pathogen associated molecular patterns (PAMPs). In contrast, the adaptive immune system has a very high specificity and recognizes specific antigens on single microorganisms. Innate immune system actors are ready to work immediately, sometimes within minutes, and do not require much induction or activation. Adaptive immune cells must be activated by interaction with specific antigens; in fact, adaptive immune cells must go through three phases—activation, proliferation, and differentiation—before they can exert their effector functions, a process that takes days and sometimes weeks. Another key difference is that the innate system has no memory, whereas adaptive immunity does. Although adaptive immunity may not afford much initial protection, its long-term protective power is better. On the other hand, if the innate immune system, which represents the first line of defense, is destroyed, the battle is lost from the start.

In light of the vulnerability of both components of the immune system to immune evasion strategies, it was suggested that any research that would enhance the ability of an organism to evade the immune system should be considered potentially very dangerous and that there should be a closer interaction and information exchange between security professionals and funding agencies. For example, NIH has issued grants to compile an encyclopedia of the innate immune system; one could imagine using such an encyclopedia as a blueprint for ways to maliciously manipulate the innate immune system. It was also pointed out that a number of pharmaceutical companies are examining the use of toll-like receptors (TLRs) to induce the innate immune response.[10] In fact, drugs that target

[8]This subsection based on the presentations of Kathryn Nixdorff and Elliott Kagan.

[9]Jackson, R. J. et al. 2001. "Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox." *Journal of Virology* 75(3):1205-1210.

[10]O'Neill, L. A. 2004. "A battle cry to decipher immunity." *The Scientist* 21:20.

TLRs are already commercially available. For example, imiquimod is an immune response modifier typically prescribed for genital warts and some skin cancers; it stimulates TLR7, a key antiviral TLR. Other participants expressed concern that such a restrictive stance on immune system research would hinder valid and beneficial scientific and technological progress.

The immune system is doubly vulnerable to either natural or deliberate attack by virtue of its interaction with the neuroendocrine system. The dual-use risk of bioregulators is particularly relevant within this context. Both the immune and the neuroendocrine systems produce cytokines, peptide hormones, and neurotransmitters and regularly communicate with each other via shared receptor circuitry.[11]

For example, when an immune system cell is activated, the signal is transduced and a cascade of reactions initiated, ultimately ending in activation of genes encoding various protein products. These cells include the pro-inflammatory cytokines, particularly macrophages, T-lymphocytes, and interleukin-4 (IL-4). (Considerable research efforts are being directed toward manipulating these cellular reactions to either increase or suppress the production of these various bioregulators. Increased bioregulator production, particularly of the pro-inflammatory cytokines, can cause misguided auto-immune reactions, and suppression runs the danger of compromising protection against infection.) These pro-inflammatory cytokines have a profound effect on the neuroendocrine system by inducing the over-production of hormones in the hypothalamus, thereby damaging neurons and producing sickness behavior (i.e., a lethargic, sleepy, sick feeling). They can also induce the hypothalamus to make corticotropin-releasing hormone (CRH) which, if produced in large enough quantity, can cause neuronal damage; experiments have shown that inhibition of CRH production can lessen neuronal damage after a stroke. By inducing the pituitary production of adrenocorticotropic hormone which activates the adrenal glands to produce cortisol, excessive cytokine production can have a profound effect on immune suppression.[12]

Normally, these various interactive reactions are kept in balance, but modulating one system could have profound effects on the other. The greater, systemic damage that could be done by targeting single components of these interacting physiological systems leave both systems doubly open to assault and represent a necessary shift in focus (in terms of what

[11]Blalock, J. E. 1994. "The syntax of immune-neuroendocrine communication." *Immunology Today* 15:504-511.

[12]Straub, R. S. et al. 1998. "Dialogue between the CNS and the immune system in lymphoid organs." *Immunology Today* 19:409-413.

constitutes the greatest dual-use risk) from the bioagents themselves to interacting physiological systems as the targets of malign intent.

In light of the increasing bioterrorist threat posed by bioregulators, due to greater knowledge about their systemic damage and advances in delivery technology, it was emphasized that it will be critically important to uphold the BWC norm against the hostile use of science and technology generally (and specifically with regards to bioregulators); and to strengthen future biodefense surveillance by developing next-generation biosensors for the detection of human bioregulators.

DNA NANOTECHNOLOGY[13]

In just five years, nanotechnology has catapulted from being a specialty of a relative handful of physicists and chemists to a worldwide scientific and industrial enterprise.[14] The U.S. government estimates that the nanotech economy will be worth $1 trillion by 2012. Compare that to the current $4 billion pharmaceutical market (see Chapter 3).

In the popular literature, definitions of nanotechnology range from "the science involving matter that is smaller than 100 nanometers"[15] to anything dealing with "human-built structures measuring 100 nanometers or less."[16] At the workshop, three definitions were provided: "arranging molecules (atoms) as precisely as possible so as to perform a designated function," "doing with real molecules what computer graphics does with molecular models," and "putting what you want where you want it and having it do what you want it to do."

Semantics aside, an intriguing feature of the nanoscale is that it is the scale upon which biological systems build their structural components, like microtubules, microfilaments, and chromatin.[17] In other words, biochemistry is a nanoscale phenomenon. Even more intriguingly, a key property of these biological structural components is self-assembly. The most successful biological self-assembler is, of course, the DNA double helix. In their quest to emulate these biological phenomena, scientists have

[13]This section is based on the workshop presentation of Nadrian Seeman.

[14]Service, R. F. 2004. "Nanotechnology grows up." *Science* 304:1732-1734, 18 June.

[15]Blumenstyk, G. 2004. "Big Bucks for Tiny Technology." *The Chronicle of Higher Education* 51:A26. *http://chronicle.com/weekly/v51/i03/03a02601.htm.*

[16]Monastersky, R. 2004. "The dark side of small." *The Chronicle of Higher Education* 51(3): A12. *http://chronicle.com/free/v51/i03/03a01201.htm.*

[17]Seeman, N. C. and A. M. Belcher. 2002. "Emulating biology: building nanostructures from the bottom up." *PNAS* 99:6451-6455.

created the field of DNA nanotechnology,[18] as well as the closely related field of DNA-based computation by algorithmic self-assembly.[19]

DNA nanotechnology is the design and development of objects, lattices, and devices made of synthetic DNA. Since the DNA helix is naturally linear (i.e., unbranched), the assembly of structures or devices built with synthetic DNA requires constructing branched molecules that can then be connected to form structural networks or motifs. The DNA motifs are combined by means of sticky-end cohesion, a high specificity DNA reaction.

There are two types of DNA nanotechnology: high structural resolution DNA nanotech, which involves using DNA as both brick and mortar in the construction of various kinds of nano-objects; and compositional DNA nanotech, which involves using a DNA mortar to join non-DNA particles. The latter, which was not discussed in detail at the workshop, can be used in many ways to organize large complexes; multiple labs worldwide are involved in this technology. The focus of the workshop presentation was on high structural resolution DNA nanotech, which only about a dozen labs worldwide are researching.

The potential applications of high structural resolution DNA nanotechnology are many and varied:

- Architectural control and scaffolding
    - Improving macromolecular crystallization protocol (which is how the field began)
    - Nanoelectronics organization
    - DNA-based computation
    - Constructing and controlling polymers
- Nanomechanical devices
    - Nanorobotics
    - Nanofabrication
    - Sensors and detectors
    - Computational devices
- Self-replicating nano-systems

[18]Seeman, N. C. 1982. "Nucleic acid junctions and lattices." *Journal Theor. Biol*., 99:237-247; Seeman, N. C. 1999. "DNA engineering and its application to nanotechnology." *Trends Biotech*. 17:437-443.

[19]Winfree, E. 1996. "DNA Based Computers." R. J. Lipton and E. B. Baumvol, Eds., vol. 27 of *DIMACS Series in Discrete Mathematics and Theoretical Computer Science* (American Mathematical Society, Providence, RI, 1996): 199-215; Lipton, R. and Baum, E. Eds. 1995. *Proceedings of DIMACS Workshop on DNA Computing*. Am. Math. Soc. Providence; and Adleman, L. 1994. "Molecular computation of solutions to combinatorial problem." *Science* 266:1021-1024.

The primary difference between nanomechanical devices and self-replicating systems is that the former are "clocked" devices, meaning that someone (a person or robot, as the case may be) has to do something in order for the nano-device to operate. Self-replicating systems, on the other hand, are autonomous devices that do not need direction intervention in order to work. Purdue University researcher Chengde Mao is credited with having made one of the first autonomous nano-devices, in this case a DNAzyme, which can bind and cleave RNA molecules one by one.[20] The creation of this device exemplifies the extraordinary progress that the DNA nanotech field has achieved just over the course of the past two years. Autonomous devices were unimaginable two years ago.

The future trajectory of the technology is unclear, although it will almost certainly have multiple medical applications, including therapeutic delivery by nanoparticles. One could imagine, for example, synthetic, enzyme-carrying DNA devices interfering with amyloid fibrils by binding to them and unloading a load of peptidase or protease. It is also conceivable that devices could be engineered to conduct nano-searches of what is present or what is needed (e.g., in terms of pharmaceutical intervention or even environmental detection). Another possibility might be the development of implants made of new, bio-compatible materials that are stronger and better than ever before.

Similar technology may someday enable people to inject or attach removable devices for the monitoring of metabolic parameters and controlled release of drugs, insulin, or other compounds. In October 2004, scientists from the Institute of Bioengineering and Nanotechnology, Singapore, invented a contact lens capable of releasing precise amounts of medication to treat glaucoma and other eye diseases.[21]

While nanotechnology (and all other emerging, converging technologies) promise radical changes in science and society, future progress in the field will require overcoming many scientific challenges.

As far as the nature of the dual-risk posed by this field, since the technology is expected to make for relatively inexpensive, small scale science, the dual-use risks will be similar to those of more conventional biotechnology in terms of ease of access and difficulty of detection. On the other hand, one participant noted that the "intellectual footprint" left by bringing two or more technologies together to create a bioweapon (e.g., nanotechnology and synthetic biology) might make bioweapons activity more noticeable and easier to detect.

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[20]Chen, Y. and C. Mao. 2004. "Putting a break on an autonomous DNA nanometer." *Journal of Am. Chem. Soc*. 126 (28):8626-8627.

[21]*http://www.ibn.a-star.edu.sg/news_interface_article.php?articleid=54.* Accessed on October 30, 2004.

CONVERGING TECHNOLOGIES[22]

Some experts consider the convergence of bio-, nano-, and information technologies, along with the neuro- and cognitive sciences, will enable humans to do things never dreamt of until now (see Figure 4-2). Some experts consider the convergence of these so-called enabling technologies a transformation that will prove as powerful as the industrial revolution.

Enabling technologies are those that interact with each other to create novel products that would otherwise be impossible to achieve. Nanotechnology enables by providing a common hardware for molecular engineering and allowing for the realization of desirable architectures. Nanotechnology enables biotechnology by developing new imaging techniques, probes and sensors; and it contributes to the miniaturization demands of information technology. Biotechnology enables other technologies by identifying chemical and physical processes and algorithmic structures in living systems that have a genetically-based material organization. It enables nanotechnology by providing a paradigm that nanotechnologists use in developing systems; much of the work in nanotechnology involves mimicking biotechnological processes while simultaneously redesigning them to fit particular purposes. Biotechnology enables information technology by providing new systems of computing, some of which may be based on DNA. Information technology enables through its ability to represent physical states as information and model processes. It provides the computing power that is essential to all research; it enables nanotechnology through precision control of patterning and intervention; and it enables biotechnology by providing the means to model complex processes and thereby solve difficult research problems.

The transformative potential of the convergence of these enabling technologies is attributed to four shared features:

- *Embeddedness:* Converging technologies (CTs) will form an invisible technical infrastructure for human action. CTs will produce incredibly intrusive devices, like devices in a refrigerator that not only "decide" when certain items need to be restocked but send a message to the supermarket. Marks and Spencers, a clothing retail store in England, is reportedly collaborating with a Japanese manufacturer to create microchips that will be embedded in every single item of clothing; the microchips will transmit information back to the store headquarters, such as when the item was purchased, if and when it was returned, how much it cost, how it's selling generally, and whether it needs to be restocked.

[22]This section is based on the workshop presentation of Michael Morgan and ensuing discussion.

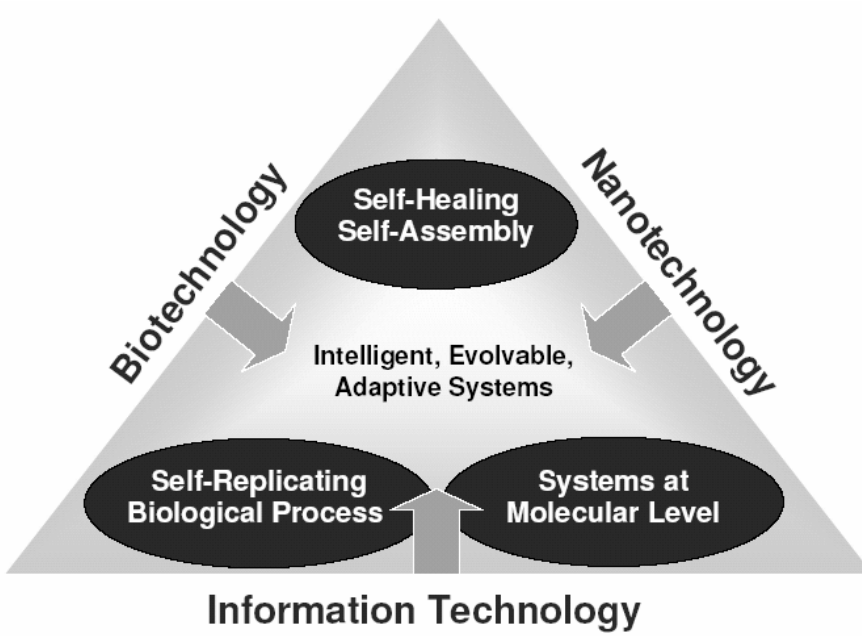

FIGURE 4-2 Converging Technologies (CTs). Biotechnology, nanotechnology, and information technology are converging in ways that will enable humans to do things never dreamt of until now.
NOTE: Adapted from Michael Morgan's PowerPoint presentation, September 22, 2004.

- *Unlimited reach:* As the convergence continues to draw in new technologies and technology-enabling sciences, it would appear that nothing can escape the reach of CTs and that the mind, social interactions, communication, and emotional states can all be engineered.
- *Engineering the mind and body:* The reality of CTs has led to the notion that it may be possible to "improve" humankind with greater molecular or physical powers, for example by using electronic implants.
- *Specificity:* The convergence of enabling technologies and knowledge systems can be geared to address very specific tasks, such as the targeted delivery of designer pharmaceuticals tailored to an individual's genome to effect a cure without side effects.

Most applications of CTs are perceived as positive opportunities for economic growth. However, there are potential negative consequences. It is not difficult to imagine the problems that might occur if brain implants,

for example, were finally commercially available. The implants might give the user access to encyclopedias and dictionaries, maps, etc., or they could be customized to include databases of expert knowledge. But after the first two years of marketing, troubling statistics might emerge. In, say, 5 percent of the cases, the implants might not appear to work at all (i.e., the user somehow never learns to access them), and another 5 percent of the users might lose access to the implant with the first few months of use. Among the remaining 90 percent, although some people might be able to access the implant on the fly while performing other mental operations, others might only be able to access them with their eyes closed or while otherwise taking time out from other activities to concentrate. Finally, a small percentage of users might suffer irreversible brain damage. Consequently, the implants would fail as a consumer product.

The economic risk associated with this type of technological application is only one of many challenges that CTs face. More importantly, there are serious ethical issues associated with invasions of privacy and enhancing human capabilities and possibly changing the very notion of humanity. Moreover, CTs may have a socially destabilizing effect. In stark contrast to the potential benefits of biotechnology with respect to addressing human security concerns and closing the health, economic, and development gap between the North and South, the specificity afforded by CTs threatens to do the opposite. CTs may produce greater unemployment (e.g., as robots replace humans), and they may exacerbate the divide between the rich and poor and between technologically advanced and traditional countries. Other potential problems include adverse health effects associated with the use of novel materials and devices.

Particularly troubling and potentially internationally destabilizing are CTs exploited for "domination on the battlefield." Proposed military applications exploit the most dangerous potential of CTs. These applications include surveillance, the physical enhancement of soldiers' bodies, remote manipulation of soldiers' minds, and the creation of autonomous killing machines. Founded by a $50 million contract from the U.S. Army, MIT's Institute for Soldier Nanotechnologies (ISN) is designing "the soldier system of the future," one that will make soldiers less vulnerable to enemy and environmental threats.[23] Some experts question the feasibility of such endeavors. Nonetheless, the intent exists.

The very uncertainty about these capabilities may lead to a new, highly unstructured and non-negotiable arms race. This raises issues about transparency, as secrecy would likely accelerate the race. A question was raised about whether nanotechnology, like blinding laser weaponry,

[23]*http://web.mit.edu/isn/.* Accessed on October 28, 2004.

might ever reach a point where it would simply be unacceptable as a form of warfare. It was suggested that issues of arms regulation associated with emerging and converging technologies be addressed in an international forum, with an insistence on unambiguous adherence to international agreements.

However, looking to the bright side, some experts expect that, like current biotechnologies, CTs will be market-driven and/or driven by health or human security needs. If so, military applications may not be as worrisome as futuristic scenarios anticipate. In fact, the more important question may be, to what extent will health-related CTs be sustainable by governments? Will society be able to afford CTs, or will the price of CT medical devices drive the cost of health care up even further? Several groups are grappling with these sorts of issues. As it is difficult to imagine any third-party payer covering the costs of health-related CTs, a comment was made that the entire system of third-party payers will likely need to be completely overhauled in order to benefit health-wise from these technologies.

In order to manage the risks created by converging technologies—not just the dual-use risks created by potential military applications but the tremendous risk to human security by civilian CT use—the European High Level Expert Group (HLEG) on "Foresighting the New Technology Wave," as called upon by the European Commission and Member States, suggested the development of a "societal observatory" with the following goals:[24]

- to monitor in real-time and assess international CT research;
- to study social drivers, economic and social opportunities and effects, and ethics and human right dimensions;
- to serve as a clearing-house and platform for public debate;
- to deal with questions regarding the applicability of patents, the definition of the commons, and the allocation of intellectual property in multidisciplinary collaborations; and
- to monitor roadmaps, benchmarks, and public response.

It is unclear to what extent the working groups of this observatory would be comprised of scientists, as opposed to philosophers, historians, social scientists, and other experts. This touches upon the more general issue of the role of the individual scientist in managing the dual-use risk

[24]Nordmann, A. 2004. "Converging Technologies—Shaping the Future of European Societies, European Communities." Report of the expert group "Foresighting the New Technology Wave."

of advancing technologies (see Chapter 5 for summary of workshop discussion on this topic).

It was suggested that the idea of a societal observatory could arguably be a piece of the "web of prevention" that some workshop participants said will be necessary for managing the dual-use risk of advancing technologies, as described in Chapter 5. Unfortunately, at the time the above-mentioned EU workshop was held, the notion of an observatory was more visionary than planned, and there had not yet been any discussion regarding its detailed development and implementation. The report in which this suggestion was made (along with 15 other recommendations) was only the first of what are expected to be many more steps in exploring the breadth, potential, and risks of CTs, particularly within the European Union and in relation to the Lisbon Declaration.

A question was raised about the reality of implementing potential CT applications. Some CTs, like brain implant technology, will not likely become a reality until far into the future, although there are devices currently being built that interact directly with the brain.

5

Models for Managing Change

In a special feature on the 2004 U.S. presidential election, the journal *Nature* published statements by both candidates regarding the gradual dissemination of knowledge about bioweapons (and other "weapons of mass destruction"). In his response, President Bush correctly and very importantly acknowledged that "stopping the gradual dissemination of knowledge is impractical if not impossible." But then he claimed that the "the key to stopping the proliferation of weapons of mass destruction is preventing those seeking these weapons from gaining access to their most significant and technically challenging components."[1] The notion that limiting access would be an effective strategy for controlling widely disseminated "dual-use" technologies may not appreciate fully the complexity of the "problem." If it were possible to gain such tight control, emerging infectious diseases (i.e., naturally occurring outbreaks and epidemics) would not be on the global public health agenda.

But if limiting access is not the solution, what is? What can and should be done? How can scientific knowledge, dual-use biological agents, equipment, and technology be managed such that invoked strategies do not hamper the growth of scientific knowledge and the global spread of beneficial advancing technologies?

This chapter provides a summary of the workshop presentations and discussions that revolved around control strategies currently being used

[1]Macilwain, C. 2004. "Head to head." *Nature* 431:239-243.

or pursued worldwide with respect to the dual-use risk posed by extant, emerging, and converging technologies. These strategies can be roughly categorized as one of three types: formal (e.g., state-level arms control agreements, including the Biological and Toxin Weapons Convention, or BWC); limited-membership consensus (e.g., the non-binding Australia Group export control program); and informal (e.g., codes of conduct for scientists).

Two important themes emerged from the lengthy dialogue on these various strategic approaches. First, several workshop speakers commented that no single approach will likely be effective by itself. For example, during the discussion on challenges faced by the BWC follow-up process (i.e., annual meetings being conducted as a lead-up to the 2006 Review Conference), it was emphasized that there is a danger in being too restrictive with regards to believing in the omnipotence of any single tool. The workshop participants also suggested that there is a natural tendency to overemphasize the potential contribution of formal arms control. However, the BWC is not the only tool available for managing the dual-use risk of advancing technologies.

Second, some workshop speakers emphasized that proposed solutions were dependent upon how one defined the dual-use problem and identified risks. This point is illustrated by the difference in perceptions between Singapore and the United States as to whether the bacterium *Burkholderia pseudomallei* constitutes a risk. As discussed in previous chapters, *B. pseudomallei* is on the U.S. select agent list because of its dual-use potential. However, in Singapore, where the bacterium is an endemic soil microorganism, it is viewed as a source of naturally occurring disease.

The controversy surrounding the lack of a compliance and verification protocol to the BWC was mentioned several times during the workshop. An important theme to emerge from these discussions is that there are many non-verification related components of the BWC, as well a broad range of non-BWC efforts and accomplishments, that might play important roles in building and strengthening a global effort to minimize the dual-use risks posed by the rapid progress and proliferation of technological knowledge, technology, and materials. A comment was made that even if the BWC compliance and verification protocol had been adopted several years ago, it would not have been sufficient. Given the nature of the threat, particularly the constantly changing and unpredictable future of the global biotechnology landscape, a successful biological weapons control regime will undoubtedly involve a multi-dimensional approach comprising multiple components.

ARMS CONTROL[2]

For the past century, the United States has historically been one of the world's leaders in establishing and promoting norms and regimes to limit the proliferation of nuclear, chemical, and biological weapons and missiles. A "regime" comprises the multitude of cooperative and coercive measures—including international agreements, multilateral organizations, national laws, regulations, and policies—intended to prevent the spread of dangerous weapons and technologies. The fundamental purpose of developing and strengthening any weapons regime is to establish a clear sense of legitimate behavior by virtue of implicit and explicit rules, regulations, and norms. This section summarizes the workshop presentations and discussions that focused on the role of formal arms control measures in managing the dual-use risk of advancing technologies and lessons to be learned from the nuclear and chemical regimes.

The Biological Regime[3]

The biological weapons regime dates back to the 1925 Geneva Protocol, which entered into force in 1928. The Protocol, which was supported by one of the most outspoken and ferocious public appeals the International Committee of the Red Cross has ever made, was drafted in response to the horrific consequences of the extensive use of gas in World War I. It prohibits the wartime use of "asphyxiating, poisonous, or other gases, and of all analogous liquids, materials, or devices" and of "bacteriological methods of warfare."

The most important international step taken to strengthen the biological weapons regime occurred decades later, with the 1972 Biological and Toxin Weapons Convention (BWC), which entered into force in 1975. The BWC prohibits the development, production, stockpiling, or acquisition of biological agents or toxins of any type or quantity that do not have protective, medical, or other peaceful purposes, or any weapons or means of delivery for such agents or toxins. According to the treaty, all such material must be destroyed within nine months of entry into force. As of 2002, there were 164 signatories and 146 ratifying and acceding countries.[4]

Although much of the workshop dialogue surrounding problems and gaps in the BWC tended to revolve around its lack of a compliance and verification protocol (which is discussed in detail below), some speakers

[2]This section is based on the workshop presentations of Tibor Toth, Robert Mathewa, and Amy Sands and lengthy discussion among workshop participants.

[3]Based on presentations by Tibor Toth and Amy Sands and comments by many individuals.

[4]*http://www.stimson.org/cbw/?sn=CB2001121271.* Accessed on November 16, 2004.

and discussants argued that resolving the verification controversy is not necessary for moving forward in other areas and should not be used as an excuse not to take steps that can thwart or minimize the threat of biological terrorism.

Challenges to the Biological Regime[5]

Despite its relatively long history, beginning with the Geneva Protocol, the biological weapons regime and the BWC in particular are fraught with challenge. This section summarizes the nature of some of these challenges, as discussed during the workshop.

Recent history of the BWC

Several events in the 1990s created an incentive to strengthen the biological weapons prohibition regime. These included the acknowledgment of past bioweapons programs by the former Soviet Union and South Africa; growing suspicions of ongoing bioweapons programs in Iraq and a number of other states; a wave of non-biological terrorist attacks in the mid-1990s, including the Oklahoma bombing and Tokyo sarin attack; and widespread concern that rapidly advancing technological developments were paving the way for the easy means to create and produce novel bioweapons.

Although the dangerous reality of non-state bioterrorism has thus far resulted in only limited casualties, it has had a terrible psychological impact. In the one and half months following the 2001 anthrax mailings, which led to 5 deaths and 17 other cases of disease in the United States, there were 10,000 hoaxes, each of which stirred public concern, cost money, and diverted resources and attention away from equally compelling, competing problems. More than U.S. $100 million was spent on the emergency during those first one and a half months, and the complete clean-up and modification of the U.S. postal system is expected to cost more than $5 billion. The anthrax attack demonstrated the blatant breaking of deliberate use rules which had been in place for more than seven decades.

That same year, the BWC and all that it entailed, including its annual review conferences and confidence-building measures and negotiations, came under attack. Compliance and verification negotiations, which had been underway since 1995, were suspended, the Fifth Review Conference was postponed (after the United States proposed to terminate the Ad Hoc Group in charge of negotiating a verification protocol to the Convention), and general widespread doubts about BWC compliance were articulated.

[5]Based on comments by T. Toth and A. Sands, and comments by many individuals.

Not only did the BWC fail to adopt a verification protocol, but states parties were also unable to agree on a routine reaffirmation of the objectives, principles, and norms as they had done in every other review conference. Between December 2001 and September 2002, there was a danger of completely shutting down the entire review process until 2006. But in November 2002, a Fifth Review Conference was successfully completed and a follow-up process of activities established as a lead-up to the Sixth Review Conference in 2006.

Opportunities and challenges of the BWC follow-up process

The BWC follow-up process involves three weeks of meetings per year (i.e., two weeks with experts, one week with States parties) and does not (or will not) produce any legally binding documents. The focus is on five discrete sets of BWC issues, all of which play a direct role in the "health" of the prohibition regime and, importantly, none of which are directly related to treaty compliance: national implementation, biosecurity, disease control, the investigation of deliberate disease, and codes of conduct (see Box 5-1).

Thus far, the follow-up process has accomplished several major achievements:

- There has been a wide exchange of information about activities undertaken by intergovernmental organizations, states parties, and non-State actors. In the past, review conferences have not generally been a useful forum for undertaking such exchange, since they usually focused on drafting provisions about general implementation aspects of the Convention. Moreover, past provisions have been quite generic with respect to the future direction of the activities of states parties.
- This new widespread exchange of information has led to a greater sharing of best practices with regards to national implementation of disease control and deliberate disease investigation. In 2004, there were about 200 presentations on this topic.
- The follow-up process provides a forum where countries can identify mutual interests in undertaking corporation-level biomolecular projects, while simultaneously offering a forum for consolidating perspectives.
- The large number of proposals in 2003 (200 discrete proposals, clustered into 55 groups) and in 2004 (more than 400 proposals, which have yet to be clustered) demonstrate a strong interest by States parties in promoting cooperation in relevant areas. The proposals represent ideas that could readily be converted into executable projects with the necessary budget and infrastructural support.

BOX 5-1 Areas of BWC Follow-up Process

- 2003: the adoption of necessary national measures to implement the prohibitions set forth in the Convention, including the enactment of penal legislation
- 2003: national mechanisms to establish and maintain the security and oversight of pathogenic microorganisms and toxins
- 2004: enhancing international capabilities for responding to, investigating, and mitigating the effects of cases of alleged use of biological or toxin weapons or suspicious outbreaks of disease
- 2004: strengthening and broadening national and international institutional efforts and existing mechanisms for the surveillance, detection, diagnosis, and combating of infectious diseases affecting humans, animals, and plants
- 2005: the content, promulgation, and adoption of codes of conduct for scientists

NOTE: Adapted from Tibor Toth's PowerPoint presentation, September 22, 2004.

- The 2004 forum was the largest multidisciplinary meeting of the topic under discussion, with about 5000 persons participating and 90 States parties represented. These numbers exceed the attendance numbers at review conferences, including the number of decision-making delegates.

However, the follow-up process and, ultimately, the 2006 Sixth Review Conference and BWC still face many important challenges (i.e., verification issues aside). Perhaps most importantly, there is a certain danger in being selective.

This selectivity dilemma exists on several levels. First, there may be a danger in selecting one tool—in this case, the BWC—among the many in the toolbox against deliberate disease. For example, within the disarmament constituency, there is a natural tendency to overemphasize the potential contribution of arms control in addressing this threat. In fact, historically, over the past 30 to 40 years, every few years the "flavor" of the period changes, believing in the omnipotence of one or another tool, whether it be the BWC or something else, and ignoring the synergy that results when multiple tools are combined and used appropriately (see Figure 5-1). The question then becomes, under what conditions should certain tools be used?

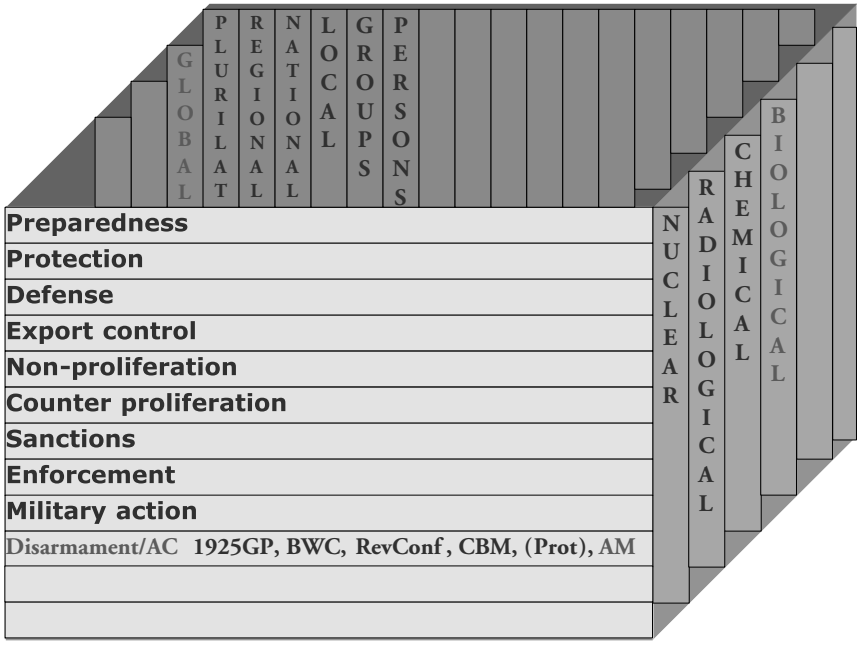

FIGURE 5-1 Weapons of mass destruction toolbox. Within the disarmament constituency, there is a natural tendency to overemphasize the potential contribution of arms control in addressing the dual-use risk of advancing technologies. This chart represents the reality that, for all weapons regimes, disarmament is only one of many tools available.
NOTE: Adapted from Tibor Toth's PowerPoint presentation, September 22, 2004.

Second, just as "solving" the dual-use risk of advancing technologies of biotechnology will require developing and relying on a multitude of tools (the BWC being one of them), strengthening the BWC itself will require developing and ultimately relying on several components. Many countries may be suffering from "verification fatigue," not just because of the BWC controversy but also because of past experience with the intrusive verification protocol of the CWC. But it would be dangerous to put all of one's eggs into the follow-up process and ignore verification. Likewise, it would be dangerous to ignore the potential of the follow-up process and attempt to put all of one's eggs into verification (or another basket). There are lessons to be learned about the verification protocol process and how, to some extent, there was a sense of complacency while

the negotiations were occurring and a sense that the arms control experts in Geneva would solve the problem. Meanwhile, the problem became more complicated and is still complicated, with no protocol in hand. Extreme thinking on either end would pose a significant challenge to the 2006 Review Conference.

A third selectivity dilemma arises from the multiple participatory levels in the BWC (i.e, global, multilateral, national, regional, local, etc.) and questions that arise over who should implement what. There is often a tendency to underestimate or deny the positive contributions that global interstate cooperation could make. On the other hand, there might be a tendency to ignore the extremely important efforts that regional, local, or multilateral parties make.

Fourth, by considering biological weapons as weapons of mass destruction, comparable to nuclear, chemical, and radiological weapons, there is a danger in ignoring bioweapons—the "Cinderella" of weapons of mass destruction—and their true threat in both absolute and relative terms.

A second major challenge to the BWC, despite early achievements of the follow-up process, is the dilemma between what is necessary and what is feasible. As President Kennedy once said, "Whatever is logical is not realistic and whatever is realistic is not logical." Although the BWC follow-up process was deemed feasible, in light of the difficulties and controversy surrounding verification at the 2001 Fifth Review Conference and as a lead-up to the 2006 Review Conference, urgent action will be needed beyond 2006. This dilemma will only be solved when the absolute and relative dangers of biological weapons (i.e., relative with respect to nuclear, chemical, and radiological weapons) are realized. Table 5-1 summarizes the differences among these classes of weapons, with respect to weapons characteristics, requirements for weapons production, and sources of diversion.

Not only are biological weapons different than other weapons of mass destruction, they are more destructive than they have generally been perceived to be in the past.

Steps that will *need* to be taken beyond 2006, in order to strengthen the BWC once the follow-up process is complete:

- making the BWC process more sustainable than the 5 to 10 year length of most political cycles (e.g., by identifying sustainable activities);
- building upon the achievements of the follow-up process by moving from what is feasible to what is needed;
- acting, as opposed to producing provisions;
- assisting in the five areas (of the follow-up process) beyond the bilateral framework (as disease and biosecurity will not respect this limited level of cooperation);

- deepening and widening cooperation between IGOs without endangering their core mission; and
- consolidating the mechanism of interaction between States Parties.

Feasible steps that could be taken *now* include:

- consolidate what has been achieved in the new BWC follow-up process so far;
- assist in further national implementation efforts;
- promote implementation-related assistance between interested countries; and
- raise awareness about on-going activities and further needs outside the BWC framework.

Non-state actors

There is serious concern about whether and how the BWC thwarts or (if strengthened) could thwart or minimize the growing threat of *non-state terrorist use* of dual-use agents and technology. As one participant said, "arms control really has to be relabeled as 'counter-terrorism' because that, in effect, is what's happening, whether we like it or not." In light of this, although the BWC accommodates counter-terrorism activities to some extent, one of the major challenges it faces is translating the internationally agreed prohibitions into effective domestic enforcement.

In response, it was argued that all five areas of focus for the BWC follow-up process offer possible spin-offs that address non-state terrorist scenarios. In fact, in most BWC discussions over the past 10 years or so, this issue has figured prominently, in terms of both conceptualizing the threats and addressing the problems. It is widely realized that, with regards to national implementation of the BWC, the stronger the national mechanisms (e.g., legal, bureaucratic, etc.), the lesser the potential for misuse of the technology. With regards to disease control and investigation, the need to create a system with the shortest lead time possible and one with the capacity to differentiate natural from deliberate occurrences will strengthen biodefense against state and non-state actors alike.

Moreover, articles III and IV of the BWC clearly refer to non-state terrorist groups as well as state actors. Article III creates a very clear obligation not to transfer to any recipient whatsoever any sort of material, equipment, or know-how for making biological weapons:

> Each State Party to this Convention undertakes not to transfer to any recipient whatsoever, directly or indirectly, and not in any way assist, encourage, or induce any State, group of States or international organizations to manufacture or otherwise acquire any of the agents, toxins,

TABLE 5-1 Biological Weapons

Weapons Characteristics	NW	CW	BW	RW (Dirty Bomb/NF Release)
Destruction	= 100,000 p	=10,000 p	=100,000 p	=1,000 p or =10,000 p
Time	seconds	=sec/hours	=hours/weeks	=months/years
Area	=10 km^2	=1 km^2	=10 km^2	=1 km^2 or =1,000 km^2
Quantity/Size	=1,000 kg (12.5 kt)	=1,000 kg (sarin)	=100 kg (anthrax)	=1,000 kg
Manifestation	Clear	No manifestation during delivery	No manifestation during delivery	Clear (prior radioactivity)
Delivery	Bomb	Aerosol, liquid, or solid	Aerosol, liquid, solid, other	Bomb release from facility
Diversion Requirements	**NW**	**CW**	**BW**	**RW**
Lead Time	=10 years	=1 year	=1 month	=1 year or more
Size of Effort	= 10 km^2 (multiple facilities)	= 1 km^2	=100 m^2	= 100 m^2
Manpower	=100 p	=10 p	=1 p	=1 p or more
Financing	=$1,000,000,000	=$1,000,000	=$10,000	=$10,000 or more
Know-how	= Ph.D.	=Ph.D.	=Ph.D.	=Ph.D.

Diversion Sources (present)	NW	CW	BW	RW
Weapons	=10 states = 10,000 warheads =1,000 storage sites	=10 states =10 locations =100,000 t = 10,000,000 munitions	= 10 states =10,000 t	= 1,000 t
Facilities	=1,000	=10,000	= 100 biodefense =10,000 industry	=1,000 to 100,000
Agents/Materials	=1	=10	=100	=10
Experts	=1,000,000	=10,000 CWC =10,000 industrial	=10,000 BWC =10,000 industrial	=1,000

Diversion Sources (2015)	NW	CW	BW	RW
Weapons	=10 states =10,000 warhead	= 10 states = 1,000 t	= 10 states =10,000 t	
Facilities	= 1,000	= 10,000	= 10,000 (=10% increase)	=100,000 =1,000
Agents/Materials	=1	=10	=1,000	=10
Experts	=1,000	=10,000 CWC = 10,000 industrial (=1% increase)	= 10,000 BWC = 100,000 industrial (=10% increase)	= 1,000

NOTE: Adapted from Tibor Toth's PowerPoint presentation , September 22, 2004.

> weapons, equipment, or means of delivery specified in Article I of this Convention.

Article IV obliges all States parties to take national measures to fully implement these obligations and responsibilities, which means that all States parties must enact national legislation containing the prohibitions of the BWC and penalties for noncompliance:

> Each State Party to this Convention shall, in accordance with its constitutional practices, take any necessary measures to prohibit and prevent development, production, stockpiling, acquisition or retention of the agents, toxins, weapons, equipment and means of delivery specified in Article I of the Convention, within the territory of such State, under its jurisdiction or under its control anywhere.

A question was raised about the fact that these articles and the counter-terrorist spin-offs of the follow-up process apply only to the 151 States parties to the Convention. What about the other 40 states that have not signed or joined the BWC? These 40 states are under no obligation to the BWC, are not obliged to have national laws in place regarding BWC prohibitions, and are not obliged not to assist other states or terrorist groups in acquiring the equipment, know-how, or materials to make biological weapons. This creates a major international gap in terms of preventing bioterrorists from obtaining the materials they need to construct a biological weapon or device. Moreover, although the BWC has been operational for almost 30 years, less than half of the States parties have national laws in place as required by the Convention and it is unlikely to have any influence on non-State sponsored activities.

Cooperative commitment

The difficulties that BWC states parties have experienced with regards to adopting a verification protocol and implementation norms highlight the reality that, in order to be effective, a non-proliferation regime must contain a clear cooperative commitment on the part of all those involved. Otherwise, the ensuing lack of trust makes it very difficult to meet the regime's needs for things like data exchange; a peaceful conflict resolution mechanism; a feedback loop in order to discuss problems constructively while also allowing discussions to move forward; agreement on a sufficient level of transparency with regards to particular types of activities, such as on-site inspections; and information on capabilities and facilities. This last issue is particularly difficult for the biological regime, since the science and capabilities have already been established and it is not clear what "baseline" is.

Several factors probably contribute to the lack of cooperative commitment to the BWC. Perhaps most importantly, partly because of the unpredictable and variable nature of the threat, there is a lack of common ground and no specific goal or weapons system. Traditionally, states voluntarily join non-proliferation regimes because it is in their best interest to cooperate, and cooperation tends to be specific, for example with regards to a specific goal or specific weapons system (i.e., one that they want to dismantle, control, or eliminate).

Voluntary commitment of states parties also reflects a shared sense of norms and standards and the willingness to create short-term sacrifices, for example by giving up some sovereignty or permitting more intrusiveness, for the sake of longer-term stability and security. As one participant noted, "It may be that, with biological weapons, countries and individuals just aren't quite there yet."

However, it was argued that the ultimately central role of a shared sense of norms does not mean that the BWC and biological regime cannot move forward until such norms are formally in place. After all, the international initiative to control nuclear non-proliferation occurred before shared international norms were established. In particular, the International Atomic Energy Agency (IAEA) was formed in 1957, more than a decade before the Treaty on the Non-Proliferation of Nuclear Weapons (NPT) opened for signature. Rather than because of any shared sense of what the norms should be regarding prohibiting weapons from proliferating, the IAEA was formed because of a general sense that there was a need for some sort of control. Later, the activities of IAEA were integrated with implementation of the NPT. So the IAEA created the context for the eventual establishment of a set of shared international norms.

Upholding norms

When the United States decided to withdraw from the BWC compliance and verification negotiations in 2001, there was neither enough knowledge nor broadly based political will to react strongly by either finishing the job or revising the process in a dynamic way. In September 2002, the International Committee of the Red Cross (ICRC)—seeing the implications of many recent developments in the life sciences coupled with the inability of the international community to agree on a compliance and verification protocol for the BWC—launched a very public appeal to put the dual-use dilemma and BWC issues on the political agenda. The purpose of the appeal was to raise the awareness of decision makers, and call on all actors—including industry, science, government, and the military—to recognize the risks, be aware of the existing norms, and assume their own responsibilities. Details of this public appeal are

included in an ICRC document entitled "Biotechnology, Weapons, and Humanity."[6]

The biological prohibition regime encompasses more than law. It is also based on unspoken norms and ancient taboos stemming from the public abhorrence to poison and the deliberate spread of disease. Millennia ago, the Hindu, Greeks, Romans, and Muslim all prohibited the use of poisons, declaring their use below the dignity of any warrior. In fact, these norms are so engrained in society that one workshop participant expressed disbelief that they would ever be overwhelmed by technological advancements.

But others argue that reaffirming and upholding BWC norms will be critically important to minimizing the threats of the dual-use risk of advancing technologies, particularly since the nature of these threats changes. However, given that reaffirmation is a slow process that may not have immediate effects, it was suggested that one of the most important measure to be taken may be educational efforts to heighten awareness about the BWC and scientists' responsibilities under the convention.

Bioregulators

Neither the BWC nor the Chemical Weapons Convention (CWC) are clear about the use of bioregulators in armed conflict. Although the BWC is very clear about not using biological agents, including bioregulators, for hostile purposes, there is some question as to exactly what a hostile purpose entails. The CWC allows bioregulators for riot control purposes but does not address their use on the battlefield. Given this vagueness and the dual-use threat posed by bioregulators, there were comments regarding the importance of clarifying these conventions.

The point was raised that many military research institutes are conducting research on bioregulators for the enhancement of soldier performance, for example by using adrenaline capsules to keep soldiers awake for several days. In fact, research on bioregulators is an accepted component of military physiological research.

Verification

The BWC has no verification protocol, an issue that has stirred up considerable controversy. There are a range of opinions about whether and how such a protocol would truly strengthen the BWC and biological

[6]International Committee of the Red Cross. Biotechnology, Weapons, and Humanity Initiative, Geneva, 2002.

regime; and whether and how biological verification can be modeled after either nuclear or chemical verification. This section summarizes discussion on this issue.

As one participant illustrated, arms control can be viewed as a spectrum, with nuclear at one end and cyber weapons at the other. The nuclear regime is a nearly-global verification regime, carried out in large part by the International Atomic Energy Agency (IAEA) and with the Nuclear Non-Proliferation Treaty (NPT) as its pivot point. The goal of this regime is to prevent the diversion of fissile material from civilian use to weapons programs. It has enjoyed considerable success because the 1100 or so nuclear weapons facilities and installations worldwide are large and easy to find and inspect. On the other, cyber extreme, however, a comparable non-proliferation regime would be impossible since verification would require the monitoring or unannounced inspections of hundreds of millions (perhaps eventually billions) of residences and businesses.

Biological weapons (and chemical weapons) fall between these two extremes. The international verification regime for chemical weapons is more challenging than that for nuclear weapons because of the larger number of facilities and dual-use materials (there are over 5000 facilities and an entire industrial sector). Biological weapons pose an even greater challenge (although not as great as cyberweapons), since many of the relevant materials, technologies, and knowledge are far more widespread and are rapidly becoming even more so. Biological agents can be acquired from naturally occurring disease outbreaks and the course of legitimate scientific research; and producing biological agents in large quantities makes use of fermenters that are widespread in the pharmaceutical, biotechnology, and beer and wine industries.

Largely because of this challenge, the BWC lacks an inspection and monitoring regime and an agency analogous to IAEA or OPCW (the Organization for the Prohibition of Chemical Weapons; it is responsible for verification). The lack of a formal means of monitoring country compliance with BWC makes it very difficult to determine what level of defensive efforts are legitimate and which serve as camouflage for illicit weapons programs. There is concern that verification problems will become even more overwhelming in the future, as new technologies create more complicated verification needs.

It was suggested that there may be lessons to be learned from the nuclear regime, despite the very different proliferation potentials of nuclear versus biological weapons. Specifically, verification measures were integrated into the nuclear regime as a means of protection against cheating. By implementing activities ranging from data exchange to expensive, intrusive on-site inspections, verification is a way to deal with the gaps in a "worse-case-scenario" system. The rationale is that, although

100 percent verification may not be possible, it is possible to detect and deter cheaters as much as is necessary to avoid significant military action. During the Cold War, the United States primarily focused on its bilateral nuclear agreements and since then has focused its nuclear non-proliferation activities on keeping developing countries from developing a nuclear weapons capability. The nuclear regime has always required very detailed verifiability and accountability. The nuclear non-proliferation regime is now moving entirely away from verification and is adopting an approach that looks to how states are implementing their treaty obligations.

It was noted that one of stumbling blocks to the BWC adoption of a verification protocol appears to be that each state needs to first determine what its own standard of evidence would be and what sort of system it needs in place to collect this evidence (e.g., some states want to adopt a multilateral approach, whereas others just want a multilateral system to fill their gaps).

One workshop participant raised the possibility of a bio-safety clearinghouse (either in lieu of verification or as a way to facilitate verification), whereby information is shared and stored on a voluntary basis by states parties. Some pessimism was expressed, however, with regards to whether this type of endeavor would be possible in the near future and thus whether energy should be focused toward it now.

Importantly, verification is only one of many aspects of arms control. In the nuclear regimen, it represents only about one-third of IAEA activities. Given the absolute and relative dangers of biological weapons, coupled with the fact that the same trends that alerted people in the 1990s still exist today (although the specific nature of the threats may be different), a comment was made along the lines of how difficult it is to comprehend why the nuclear and biological regime efforts have been so drastically different in terms of volume of activity. An interesting exercise for bioscientists would be to take all of the IAEA documents on nuclear safety, nuclear security, and nuclear terrorism and see to what extent those documents would be applicable to the biological arena if the word "nuclear" was deleted. In one expert's opinion, a high proportion of those documents would be applicable, as the similarities between the two regimes in terms of soft, non-binding measures are striking.

Lessons to be Learned from the Nuclear Regime[7]

Many analysts are quick to look for strategic clues from the younger but more developed nuclear arms regime. With a 40 to 50 year history,

[7]Based on presentations by Amy Sands and Tibor Toth and comments by many individuals.

beginning with the Atoms for Peace proposal in 1953, the cornerstone of the nuclear non-proliferation efforts is the Treaty on Non-Proliferation of Nuclear Weapons (NPT), which opened for signature in 1968. The UN-affiliated International Atomic Energy Agency (IAEA) was established in 1957 to reduce the risk of nuclear war and the spread of nuclear weapons to non-weapon states, as well as assisting in the use of nuclear materials for peaceful purposes. In addition to the NPT and other relevant treaties, the nuclear regime has relied on the strength of a range of other activities, including unilateral actions, supplier control, cooperative threat reduction and, most recently, the proliferation security initiative.

An important topic of workshop discussion was whether and how biological arms control can be compared to the nuclear regime and what, if any, lessons can be learned from the latter. On the one hand, some experts claim that there is a fundamental disconnect between the nuclear and biological regimes, which makes it difficult to compare them. Moreover, as the technological trajectories for nuclear and biological weapons potential diverge in the future, it will become even more difficult to compare the two. But other workshop participants argued that the parallels between the two regimes are more important than the differences and that there is a great deal to be learned from the "nuclear paradigm."

The most important lessons to be learned from the nuclear regime may be those derived from the manner in which the regime developed through a slow, step-wise arms control process, involving various treaties and efforts. Two lessons in particular were highlighted during the workshop discussion. First, its incremental history gave rise to what has become a very flexible regime with the capacity to readily adapt to new and changing circumstances. This, despite slow improvements in the effectiveness of verification efforts (i.e., weapons inspections) and in efforts to secure universal adherence to this protocol. The same flexibility will be even more critically important for the biological prohibition regime, as the advancing technology landscape continues to change in unpredictable ways.

As a second lesson to be learned, most of the treaties and activities associated with the nuclear regime were meant to facilitate discussion in recognition of the fact that it was very difficult to otherwise constructively assemble all the relevant groups of people, including military and national security representatives. Only through such discussion could previously destabilizing, crises-driven approaches make way for peaceful, conflict-resolution approaches, while also recognizing that actions taken to reduce or eliminate threats would impact military capabilities. The early accomplishments of the BWC follow-up process seem to similarly demonstrate the value of engaging in activities that facilitate this vitally important type of discussion.

One workshop participant pointed out that the flurry of activity in the nuclear non-proliferation regime has only been in the past five to six years, after the United States starting providing leadership and money. Given this, is U.S. leadership the missing component in the biological prohibition regime? The response was that, yes, in the wake of 2001, a new era of nuclear terrorism began, but the regime has a longer history than just these past few years. Work in the areas of nuclear safety, nuclear security, nuclear terrorism, and other areas is historically very strong, especially over the course of the last couple of decades (i.e., after the Chernobyl disaster in 1986).

Along the same lines, a question was raised about the extent to which the use of nuclear weapons on Hiroshima and Nagasaki demonstrated to the world what nuclear weapons "really mean" and catalyzed the development of a strong nuclear non-proliferation regime. Given this, again, is this what might be missing in the biological prohibition regime: an encounter with the horrific damage that a biological attack could do?

In response, it was argued that, yes, these events did play a historical role in how the scientific community thinks about the dangers of nuclear technology and why differences exist between those thoughts and perceptions of the biological dual-use threat. However, very importantly, the differences between the nuclear and biological regimes are much more complicated than by virtue of their historic past and will become increasingly complicated in the future. So the one hand, yes, perhaps these events have led to a certain expectation with regards to nuclear technology and thus a much greater level of bureaucratic involvement. On the other hand, there is really no need to demonstrate the potentially devastating consequences of biological weapons, because naturally occurring diseases clearly illustrate what could happen. Indeed, if we do not take seriously the World Health Organization's projection that 6 million to 7 million people could potentially become victims of a flu pandemic, then we will have dozens of demonstrations of what a bioweapon could do.

The nature of biological weapons proliferation

This section summarizes discussion on how differences in the nature of nuclear versus biological threats bear on lessons to be learned from the nuclear regime. It was argued that using the term "biological arms race" connotes a meaningless analogy to the Cold War nuclear arms race, since the natures of the races are so different. Although there is legitimate concern that defensive research undertaken in one country's program could be misperceived as offensive and could drive other nations to pursue offensive research in response, the biological arms race is not a competition between states. More accurately, it is a race against the global

proliferation of technology and the increasing opportunity for non-state actor access and misuse of such technology. Biological agents and technology are much less expensive and much more dispersed than nuclear weaponry and effect a much lower entry barrier.

Another way to interpret the biological arms race (to the extent that it is occurring) is as an offensive-defensive race. Again, because of the proliferative nature of biological agents and technology, the defensive challenges are great. Unlike with the nuclear regime, retaliation is not necessarily an effective defensive measure against a bioweapon attack, since a prolonged incubation time may create difficulties in tracing an attack back to its perpetrators; and non-state terrorists may not be concerned with retaliation or may not even be identifiable. The situation is further complicated by the fact that multiple offensive-defensive races are occurring. Over the last 10 years, the United States has increased defense funding more than two orders of magnitude. Other countries have similarly increased defense spending although on a lesser scale. But there's no single, unified global mindset with respect to which agents or technologies pose the greatest risk. If one country or set of countries or set of terrorist groups is moving in one particular direction, then defensive measures and deterrent actions will be based on that regional or sub-regional mindset.

Lessons to Be Learned from the Chemical Regime[8]

The Chemical Weapons Convention (CWC) entered into force in April 1997.[9] It is the only multilateral treaty that seeks to eliminate an entire category of weapons of mass destruction within an established time frame (by 2007, with possible extensions to 2012) and verify their destruction through inspections and monitoring by the Organization for the Prohibition of Chemical Weapons (OPCW). Although the CWC has helped reduce chemical weapons risks, CWC member states are experiencing delays in meeting CWC requirements. For example, neither Russia nor the United States is expected to have completed destruction of its stockpiles until after 2012, and less than 40 percent of member states have adopted national legislation to criminalize CWC-prohibited activities. Moreover,

[8]Based on comments by workshop participants.

[9]The treaty was the product of 23 years of negotiation and drew heavily (perhaps too much) on the IAEA experience for its routine inspection system. Its most significant advance on the nuclear inspection system was having a single verification protocol instead of the complex series of bi-lateral agreements between the inspection agency and individual governments. In this regard the CWC arrangements represents a step forward that was impossible to achieve in the period of the Cold War.

although as of March 2004, the OPCW had conducted nearly 1600 inspections in 58 member states over the previous seven years, the organization does not have enough resources to conduct as many inspections as are needed.[10]

During the workshop, it was suggested that, despite apparently greater similarities between biological and chemical weapons than between the former and nuclear weapons (e.g., with respect to verification), the slower, step-wise approach to building and strengthening the nuclear regime may be the only practical option—in lieu of a "legally binding instrument" to strengthen the BWC—for managing the dual-use risk of advancing technologies.

NON-BWC TOOLS[11]

The lack of universality of the BWC and weak national implementation of the BWC among states parties have created "safe haven" states for terrorists. The Australia Group (AG) and the UN Security Council Resolution 1540 represent non-BWC efforts to close this "safe haven" gap. This section summarizes workshop presentations and discussions revolving around these efforts, as well as other non-BWC tools that could help inform general efforts to strengthen the biological weapons regime.

The Australia Group and Export Control[12]

The "Australia Group" (AG) is an informal consultative group of nations (38 countries plus the European Commission) that meet annually with the objective "to ensure, through licensing measures on the export of certain chemicals, biological agents, and dual-use chemical and biological manufacturing facilities and equipment, that exports of these items from their countries do not contribute to the spread of CBW."[13] The group formed in 1985, in response to evidence that Iraq had used chemical weapons in the Iran-Iraq war and that Iraq had obtained many of the materials for its CW program from the international chemical industry. In 1990, the AG group expanded its efforts to address the increasing spread of bioweapons materials and technology.

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[10]"Delays in Implementing the Chemical Weapons Convention Raise Concerns about Proliferation," Report to the Chairman, Committee on Armed Services, House of Representatives, *http://www.gao.gov/new.items/d04361.pdf.* Accessed on November 16, 2004.

[11]This section is based on the workshop presentation of Robert Mathews and comments made by individual workshop participants.

[12]Based on the presentation of Robert Mathews.

[13]Available at *http://www.australiagroup.net.*

The AG's primary activities revolve around national export licensing procedures based on the Group's common control lists of pathogens, toxins, and equipment. All countries participating in the AG are States parties to the BWC (and CWC). The AG considers export control measures an essential means to ensure that participating countries are fully meeting their non-proliferation agreements under Article III of the BWC. The lists were first agreed upon in 1993 and have been reviewed and adjusted since then. Although the lists are not (cannot be) comprehensive, given the impossibility of controlling every pathogen, toxin, or dual-use item that can potentially be misused, a "catch-all" category is designed to serve as a safety net.

Since the early 1990s, there has been considerable debate about whether the export licensing system of the AG is a legitimate means of assisting BWC States parties in fulfilling their non-proliferation agreements (in accordance with Article III) and whether the AG system hinders free trade. However, following September 11 and the anthrax attack, a number of these previously critical countries have recognized that the AG national licensing measures are an effective means to implement non-proliferation obligations and that they do raise the barrier to biological terrorism. In fact, AG measures now serve as an international benchmark in relation to export controls, and a number of non-AG countries are adopting their own similar national licensing export systems and/or have implemented domestic monitoring procedures based on the AG dual-use lists.

A question was raised regarding whether export control, AG-implemented or otherwise, limits the capacity to rapidly response to a global infectious disease emergency. In the event of a naturally occurring emerging infectious disease outbreak, an effective response would require the rapid exchange of pathogenic strains, information, and sometimes scientists themselves. In response, it was pointed out that export controls, at least those implemented by AG states, do not ban the export of any particular materials unless there is a particular concern about possible diversion for bioweapons purposes. Listed commodities merely require an export license (because of their potential for misuse); the AG export control measures in and of themselves should not cause undue delays in terms of getting approval to export a particular strain, particularly if there is an urgent medical reason to do so.

Another question was raised about the actual extent to which export controls and other national boundary control measures are effective with respect to countering terrorism, particularly given that dual-use biological agents, knowledge, and technology are already well dispersed throughout the world. A story was told about a South African scientist who injected himself with a nonpathogenic strain of his study organism so that

he could "download" it and continue his vaccine research when he arrived in the United States, demonstrating the ease of circumventing the national boundary security system. In response, it was argued that export controls were not originally developed to prevent non-state terrorists from importing materials, since terrorists historically have obtained most of their materials on the domestic market. Rather, they were designed to prevent rogue states from developing weapons programs, whether nuclear, chemical, or biological.

It was then suggested that because of the limitations of export control, perhaps strengthening domestic monitoring would be a more effective counter-terrorist defense. It was also suggested that the role of a people-oriented legal framework be considered. After all, regulation is about people as much as it is about agents and materials.

UN Security Council Resolution 1540[14]

UN Security Council Resolution 1540 (2004) represents another, more recently implemented mechanism for dealing with the same "safe haven" gaps that the AG dual-use lists are intended to close. The actual measures in place under Resolution 1540 are effectively identical to the measures to which all BWC states parties are obliged under Articles III and IV of the BWC. But unlike the BWC, Resolution 1540 applies to all UN member states, so it overcomes BWC's problem with universality, at least with respect to counter-terrorism. All UN member states are under the same obligations as BWC states parties: all member states are obliged to have national laws in place to prohibit the proliferation of terrorism with biological materials; all member states must adopt concrete national measures to fulfill these obligations; and all member states must report to a Security Council committee. The first report was due October 2004.

Since Resolution 1540 does not provide a list of pathogens, toxins, or equipment (although it does define "related materials"), many UN member states have indicated informally that they consider the AG dual-use lists as starting points for meeting their Resolution 1540 obligations.

Environmental Treaties[15]

It was suggested that environmental treaties may serve as a model for managing biological dual-use threats. In particular, rather than focusing on violations and compliance and whether to sanction certain countries, environmental treaties deal with how well certain standards are being

[14]Based on the presentation of Robert Mathews.
[15]Based on workshop participant comments.

met and whether those standards should be strengthened or enhanced. Even industry has bought into some of these treaties. For example, in order to purchase maritime insurance and conduct certain types of shipping, for example, a customer must abide by certain environmental regulations. The notion of creating incentives to do the right thing, rather than imposing sanctions for doing the wrong thing, is very different than what traditional arms control regimes have done.

South African 1993 Non-Proliferation of Weapons of Mass Destruction Act[16]

It was suggested that there may be lessons to be learned from South Africa's 1993 Non-Proliferation of Weapons of Mass Destruction Act.[17] The Act is successful in large part because it brings all weapons of mass destruction under one controlling regime. The Act includes a code of conduct (see below for detailed discussion on issues surrounding the need for a code of conduct for scientists). Also of note with regards to verification is how the Act provides for the protection of commercial confidentiality (so that not even the committee itself is privy to certain information that might be gleaned, for example, from an inspector); and the provision for a board of inquiry with the power to subpoena.

INFORMAL STRATEGIES[18]

This section summarizes workshop presentations and discussion that revolved around the many somewhat informal tools being used or considered as useful means of reconciling the dilemma posed by the bright and dark sides of the global spread of dual-use agents, information, materials, and technology. These include a code of conduct for scientists; research oversight; education and awareness-raising efforts; the unclear role of industry; and risk assessment.

Codes of Conduct[19]

A prominent theme of much workshop discussion was the role of the individual scientist in the misuse of biotechnology, the need to develop

[16]Based on workshop participant comments.

[17]Available at *http://www.info.gov.za/gazette/acts/1993/a87-93.pdf.* Accessed on October 30, 2004.

[18]This section is based on lengthy workshop discussion and the presentations of Peter Herby, Terence Taylor, Decio Ripandelli, and Abdallah Daar.

[19]Based on presentations of Peter Herby, Terence Taylor, Decio Ripandelli, and multiple workshop participant comments.

awareness-raising strategies for scientists, and the potential role of a code of conduct for life scientists. The conduct of individual scientists is considered vitally important to successful dual-use management, as the dispersed nature of dual-use agents and materials places more responsibility on individual scientists in knowing what is happening in their sphere of influence.

However, a major challenge to developing a useful code for biological dual-use agents, knowledge, and technology is the lack of exemplary model codes. Most codes of conducts do little but gather dust.

Moreover, there are concerns that a code of conduct is useless if it cannot be implemented. It is one thing to charter a code but quite another to make it operational. This raises several questions. Who will enforce the code? What sanctions should be in place in case of non-enforcement? Can and should employment of research funding be conditional on the evidence of having followed whatever code(s) of conduct is in place? Several workshop participants agreed that, ultimately, both private and public funding organizations will play a central role in assuming ethical responsibility and monitoring research conduct. This is how most funding institutions seem to currently operate, for example with regards to the ethical use of animals.

Another potential problem is that scientists may not be willing to participate if they do not feel a sense of ownership with respect to the process. This raises the question, who would draft the code? Scientist would need to be involved, and a dialogue among scientists, bioethicists, and bureaucrats would need to be moderated and an effective means of communication developed so that scientists are involved as much as possible from the beginning.

Given the religious and cultural nature of many militant terrorist groups, an international code of conduct must reflect worldwide participation and will need to draw upon global values. If it is perceived as Western-driven, it may not be widely accepted. Indeed, this is why the working group responsible for drafting ICGEB's code of conduct (see below) involves scientists from several different countries (the United States, Italy, Nigeria, China, and Cuba).

There are varying opinions about the extent to which a code of conduct can and should address specific needs of different fields of study and different sectors of life sciences research. Some experts suggest that any code adopted should be very specific with respect to addressing the needs of different groups of researchers. Others think that the code should be broad enough to include all fields of study and sectors of research, since the problems are the same across the board: there is a general lack of awareness regarding the law, ethic responsibilities, and how potential work could be misused by terrorists.

A comment was made about whether it might be helpful to think of a code of conduct as an enabling platform for education and other activities. In other words, if it were considered the beginning and as something to build upon, rather than an end in and of itself, the code might stand a better chance of being implemented and proving useful. For example, although an ethics code would not prevent a determined, disgruntled scientist with malicious intent from making a bioweapon, it could create an enabling environment for voluntary reporting by people who notice unusual behavior.

Several international forums are dedicated to this debate and are making efforts to develop a biotechnological dual-use code of conduct for life scientists. For example, in 2002 the UN General Assembly and Security Council endorsed a report by the Policy Work Group on the United Nations and Terrorism recommending the establishment of codes of conduct for scientists related to weapons technologies. The 2005 BWC intersessional meeting will be dedicated partly to debating the design, promulgation, and adoption of an international code. The International Centre for Genetic Engineering and Biotechnology (ICGEB) is in the process of developing a draft code of conduct (see below), and the International Institute for Strategic Studies (IISS) has already drafted a relevant charter.

Lying mid-way between the hard norms of the BWC and the softer norms of a code of conduct, the International Committee of the Red Cross (ICRC) has been investigating the potential for a "principles of practice." In 2002, the ICRC issued its "Public Appeal of the ICRC on Biotechnology, Weapons, and Humanity." Directed toward all political and military authorities, scientific and medical communities, industry, and civil society, the ICRC appeal calls on all actors in the life sciences to recognize the potential risks, be aware of the existing rule and norms, and assume their responsibilities (see Box 5-2). The idea is that these principles could serve as the life sciences equivalent to the Hippocratic Oath. A comment was made that this middle ground position might address some of the challenges that a code of conduct would face but, importantly, reinforcement would still be a problem. Who would enforce these principles, and who would be responsible for taking action in the case of non-compliance?

The ICGEB draft code of conduct

In 2001, the International Centre for Genetic Engineering and Biotechnology (ICGEB; see Chapter 3 for more information on this organization) signed an agreement with the United Nations Secretariat to "cooperate in activities related to the sustainable and safe use of genetic engineering and biotechnology, as well as in the implementation of the international

BOX 5-2
Public Appeal (2002) of the ICRC on Biotechnology, Weapons, and Humanity

- To all political and military authorities
- To scientific and medical communities
- To industry
- To civil society

General support from States Parties to the Geneva Conventionsl 28th International Conference (2003)

In 2002, the ICRC issued its "Public Appeal of the ICRC on Biotechnology, Weapons, and Humanity." Directed toward all political and military authorities, scientific and medical communities, industry, and civil society, the ICRC appeal calls on all actors in the life sciences to recognize the potential risks, be aware of the existing rule and norms, and assume their responsibilities.

NOTE: Adapted from Peter Herby's PowerPoint presentation, September 21, 2004.

cooperation programmes foreseen by the convention on biological diversity and its Cartagena Protocol on Biosafety and to foster international cooperation in the exchange of information in the field of peaceful use of biotechnology, in accordance with the Biological Weapons Convention."

Based on this agreement, in 2003, the ICGEB was called upon to "assist the UN Secretariat in fulfilling the mandate received from the Security Council to reinforce ethical norms and the creation of codes of conduct for scientists through international and national scientific societies and institutions that teach sciences or engineering skills related to weapons technologies."

The ICGEB then received approval to establish an operational committee—composed of members of ICGEB and the National Academies of Sciences of China, Cuba, Italy, Nigeria, and the United States—to draft a code of conduct. The operational group met for the first time on May 11, 2004, in Trieste, and then again on September 27, 2004, in Rome. In April 2005, the draft code of conduct was presented to the Secretary-General of the United Nations and, in August 2005, transmitted as a working document to the BWC.

The draft ICGEB code of conduct will be based on several principles:

- The code will be based on scientific deontology, addressed to the individual conscience of the scientist (i.e., with no juridicial implications).
- Focus will be on the individual responsibility of the scientist and on the principle that ethical values shall overcome hierarchy.
- In contrast to nuclear research programs, which require much larger set-ups, life scientists should have under their control the complete procedure related to the potential misuse of the experiment.
- The code will not provide a definition of permissible or forbidden experiments, rather the concept of acceptable versus unacceptable intents of research.
- The code should not be aimed at establishing the principle of self-censorship but should serve as an example of self-governance by the scientific community.

A question was raised about the third component listed above and whether a researcher can ever really have a complete vision of the scope of an experiment, from beginning to end, given the fact that so many advances in the life sciences result from unpredictable multidisciplinary interactions. But flying a plane into a building is not a highly technological accomplishment and yet is made possible by other incredibly beneficial accomplishments. It is very difficult for scientists to anticipate how their technologies might be used. Thus the question, how can and will this code of conduct encompass these unforeseen trajectories?

One workshop participant questioned whether ICGEB anticipates any sort of international educational program to disseminate the code and integrate it into scientist training programs. In response, it was pointed out that, at least as far as the ICGEB is concerned, the code would likely become a compulsory document for all scientists who even remotely come into contact with ICGEB activities.

There was a question about why industry is not currently represented on the ICGEB code of conduct committee. In response, it was noted that the inclusion of industry was viewed as being too complicated at the very beginning of this process; once a straw-person code of conduct has been developed, then industry might be involved in later stages. There are concerns that not involving the private sector early on could seriously hinder further progress down the line.

IISS/CBACI charter

In contrast to the ICGEB code, the code (or charter) drafted by the International Institute for Strategic Studies (IISS) and the Chemical and

Biological Arms Control Institute (CBACI) has relied on extensive consultation with the private sector as well as academia and government. This charter is one of several building blocks that the IISS and CBACI considers important in promoting what it calls a "culture of responsibility." Other building blocks include an analysis of developments in the life sciences; epidemiological surveillance; and an international leadership forum for young life scientists working in academia, the private sector, and government organizations. A "culture of responsibility" would support an independent International Centre for the Life Sciences (ICLS) and a specific mandate to focus on a safety and security agenda; and it would bring together scientists, technologists, and policy experts in the life sciences and encourage partnerships between private foundations and independent research institutes.

The CBACI and IISS charter covers five categories:

- International and national laws and regulations: "Observe, promote and cooperate to help develop effective national and international laws and regulations in relation to the life sciences."
- Personnel: "Exercise the highest standards in the recruitment, training and management of personnel during and after employment, with special attention to those with access to information, materials and technology that could directly affect public safety and security if misused or not operated safely and appropriately."
- Information: "Ensure the security of information by observing the relevant international and national laws and regulations in the handling of information that could have a negative impact on public safety and security; and also to contribute to developing, in cooperation with governments, the academic community and commercial sector as appropriate, effective and responsible procedures for the release of such information into the public domain."
- Safe and secure operation of facilities: "Observe the highest possible standards for the safe and secure operation of all facilities in the interest of public and environmental safety; and to contribute to the development of more effective international and national laws, regulations, guidelines, and standards in this regard."
- Governance of research and development activities: "Take full account of security, safety and ethical concerns when planning and conducting research and development activities and to support and contribute to effective and responsible international and national entities engaged in developing and promoting codes of conduct in this regard."

IISS's vision for an International Centre for the Life Sciences (ICLS) is of a center that operates independently; has a supervisory board of inter-

nationally recognized and highly regarded experts; operates with a small number of highly qualified staff; supports a range of activities, such as annual forums, projects, workshops, and information exchange; and serves as the hub of an international network of organizations, institutions, and individuals. It is believed that an ICLS could be a vital contribution to biological safety and security.

Awareness-Raising and Education of Scientists[20]

As mentioned previously, given the widespread preconceptions about the BWC, its history, the controversy over verification, and indeed its very existence, there seems to be a need for some sort of BWC education program for life scientists. In fact, it was argued that awareness-raising and education may be more valuable than an established code of conduct, particularly if it encompasses not just ethical but also legal norms with regards to dual-use agents, information, and technology. Many scientists are not aware that the BWC applies to both states and individuals and that any individual who engages in the development, production, and stockpiling of biological weapons is subject to criminal legislation.

Awareness-raising could occur formally or informally. It would seem relatively straightforward to incorporate the concept of dual-use into the formal training in research ethics that National Institutes of Health (NIH) postdoctoral trainees, for example, are required to undergo. Most bioethics courses focus on human and animal experimental use and other non dual-use issues. Dual-use educational efforts could also be integrated into continuing education courses, licensure courses, or other regular sets of activities such that anybody in the field would be expected to be updated with respect to dual-use risks. It would be important not to normalize the requirement to the extent where it involves simply checking a box.

Awareness-raising could also be integrated into other, less formal activities, such as mentoring and role-modeling by leaders in the field. This points to the need for more scientists to become involved in the dual-use challenge by speaking out and assuming leadership roles, rather than waiting or relying on government or industry to take charge.

Research Oversight[21]

The notion of dangerous research, whether it be immune system evasion research or molecular biology research in general, does not neces-

[20]Based on multiple workshop participant comments.
[21]Based on multiple workshop participant comments.

sarily imply that prohibitive actions be taken, as it would be counter-productive to do so. Rather, it points to the need for some sort of oversight, perhaps something along the lines of what has been suggested in the recent National Research Council report *Biotechnology Research in an Age of Terrorism*.[22] One of the recommended measures is the recognition by the scientific community that they must pay greater attention to the potential misuse of their research.[23] However, even full implementation of this and other recommended measures would leave significant gaps, for example among private laboratories not federally funded and not subject to the federal system of review. At the same time, open-ended or vague definitions for "experiments of concern" will subject vast components of the research enterprise (e.g., in microbial pathogenesis) to unnecessary and counter-productive review.

It was also suggested that lessons might be learned from South Africa, where research applications that involve dual-use technology must pass through a first stage of review by a non-proliferation counsel before they can be authorized; the process has been very effective and has resulted in a number of arrests over the years.

The purpose of oversight is to instill transparency such that flagged research projects (i.e., flagged by a review committee) create an entirely different level of awareness. As an example of how this might play out, if the Australian scientists who accidentally created a lethal mousepox virus had foreseen some of the consequences of their research (i.e., the effect that IL-4 would have in this model system), or if a review committee had foreseen the consequences, the researchers could have taken a different route to seek the answers they sought.

In the United States, just as NIH review committees are obliged to consider work on human subjects and work on animals, they could be obliged to consider dual-use threats. Along the same lines, editors of scientific journals could add an extra layer of oversight during manuscript review. Eventually, some sort of licensing process may be necessary, whereby investigators receive their research license only after meeting certain BWC and ethical decision-making instruction requirements.

One participant questioned whether scientists working with dangerous pathogens or dual-use materials or information should be registered. Even hairdressers in most countries must be licensed, so why not scientists who are dealing with dangerous research? In countries with transparent

[22]National Research Council. 2004. *Biotechnology Research in an Age of Terrorism.* Washington, D.C.: The National Academies Press.

[23]Chyba, C. F. and A. L. Greninger. 2004. "Biotechnology and bioterrorism: an unprecedented world" *Survival* 46:143-162.

registries, this could pose a problem (e.g., UK researchers conducting animal experimentation would not want their names available to the public). In the United States, registration and transparency are not currently linked. A potential problem could arise if registration required of certain sectors (i.e., industry and academia) was not required of others (i.e., governmental biodefense researchers), as exempting the latter would raise suspicions about government activity and intent. Perhaps the greatest challenge would be identifying what qualifies as "dangerous."

Although oversight could be feasible at the national level, a question was raised about how it would be negotiated internationally. Because not all countries, including those of greatest concern, have the capacity to establish comparable oversight systems, one possibility might be a global system of internationally agreed rules for the oversight of high-consequence biological research.[24] Challenges to this approach include global implementation (how would such a system be effectively and widely implemented?); the capability, or lack thereof, to identify and stop groups or persons who are not following the rules (although it is believed that most non-state terrorist groups are unlikely to carry out sophisticated research themselves—rather they will track the scientific literature, in which case high-consequence work can be overseen); and complications associated with identifying "high-consequence research."[25]

The Role of Industry[26]

Questions were raised about the role of the pharmaceutical and biotech industries in mitigating the risk of dual-use biological materials, as there has been a blatant lack of involvement by the life sciences industry in the dual-use debate. The ICRC has made a number of efforts to include industry in discussions of these issues, but it has been very difficult to make any sort of connection. As an example of the current lack of awareness among experts outside of the defense sector, a story was told about a bioterrorism panel discussion at an international toxicology meeting several years ago. The audience was comprised largely of pharmaceutical and biotech industry professionals, whose attitude was along the lines of "why are we talking about this?"

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[24]Steinbruner, J. et al. 2003. "Controlling Dangerous Pathogens: A Prototype Protective Oversight System." September. *http://www.cissm.umd.edu/documents/pathogensmonograph.pdf.* Accessed on October 18, 2004.

[25]Chyba, C. F. and A. L. Greninger, 2004. "Biotechnology and bioterrorism: an unprecedented world." *Survival* 46:143-162.

[26]Based on workshop discussion; multiple comments.

It was noted that many companies seem to paint a rosy picture of the ultimate use of their products and the knowledge generated, without much concern for potential risks and the need to examine those risks in advance of the proliferation of the products and knowledge. Considering that every scientific revolution has been put to hostile use, believing or pretending that hostile consequences will not result in the absence of preventative measures almost constitutes intentional naiveté and practically defies history.

Given that the pharmaceutical industry is the most highly regulated industry in the world with a lengthy production process, it is not surprising that it is difficult to generate interest in these public concerns. Industry, for the most part and rightly so, looks after its own commercial strategic interests. However, would it not be in the pharmaceutical industry's best strategic interest to respond to public anxiety and concerns, whether those concerns be about biodefense, public health safety, or other threats?

This complacency may be changing in response to the changing security climate. The private sector has recently expressed greater interest in engaging on this front. But who will be first? Is it not in each company's best interest to sit back and wait for another company to take the initiative?

It was suggested that, since biotech companies are driven largely by innovation, U.S. biodefense spending (i.e., BioShield[27]) should represent the type of innovation initiative that attracts these companies. It would be interesting to hear from the biotech industry about whether and how it could take advantage of opportunities afforded by the governmental allocation of funds to biodefense in ways that would be useful not just for biodefense but also would serve the companies' own internal needs.

Rather than expecting industry to step forward now, perhaps a more immediate challenge is to mobilize the public and government in order to create a context in which industry can take its cue. It seems that commitment to the idea that industry may have something to gain from being involved needs to be built on a broader front, that is by engaging industry, academia, government, and military sectors in a common interest, with the understanding that industry is as much a part of the solution as anyone else. Approaching the problem from this presumably more feasible and realistic stance represents the building block approach that a global response to the dual-use dilemma is going to require. Rather than waiting for industry to wake up, efforts should be directed toward moving what can be moved in ways that will catalyze others and accelerate the process.

[27]Project BioShield Act of 2004 (S.15, HR 2122). Signed by President Bush on July 21, 2004. PL 108-276.

The World Association of Nuclear Operators was cited as a successful private endeavor to improve nuclear plant operational safety,[28] which is a notable achievement for a private enterprise given the political barriers in the nuclear field. It represents the type of private sector self-regulation that, according to one participant, will likely (or should) play a hugely important role in managing the dual-use risk of advancing technologies.

Risk Assessment[29]

It was emphasized that any proposed strategy must avoid promulgating the notion that "science is dangerous," given the enormous untold benefits of technological progress, while also recognizing the risks associated with the dissemination of scientific knowledge and dual-use biological agents, materials, and technology. This raises the fundamental question, what are those risks?

The question is made more complicated by the fact that, as new sciences and technologies emerge, so too do new risks. It is further complicated by the reality that one's perception of risk changes, depending on how and where in the world one lives and works (e.g., a U.S. defense official would probably perceive certain risks differently than a Singaporean epidemiologist). In order to move forward, common ground must be sought among the diversity of threat perceptions.

There is disagreement about which agents are or should be considered dangerous, and questions have been raised about whether the recent U.S. governmental decisions regarding dual-use risks (i.e., the Select Agent Rules and Regulations) and the allocation of biodefense resources (i.e., Project BioShield, which was signed into law in July 2004[30]) may be misguided. It was noted how the number of media references to smallpox changed leading up to, during, and after the Iraq war, despite the lack of any objective measure of the risk whatsoever.[31]

There was some discussion about whether current efforts run the danger of being too "pathogenocentric" and whether enough focus has been directed toward non-pathogenic agents, let alone dual-use equipment and delivery and dissemination technologies. On the other hand, too many measures may constrain or dissuade beneficial biomedical research and the capacity to respond to a global infectious disease emergency.

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[28]Available at *http://www.wano.org.uk.*

[29]Based on discussion and multiple comments.

[30]Available at *http://www.whitehouse.gov/bioshield.* Accessed on October 23, 2004.

[31]Cohen, H. W. et al. 2004. "The pitfalls of bioterrorism preparedness: the anthrax and smallpox experiences." *American Journal of Public Health* 94:1667-1671.

It was suggested that it would be prudent to have at least some minimal level of objective risk assessment in place before actions are taken, not only to prevent misguided national-level decisions but in order to strengthen the critically important international component of dual-use management. As it currently stands now, varying assessments of risk hamper international cooperation.

One participant emphasized that sorting through the diversity of risk perceptions in order to establish an objective, usable framework for action will require the involvement of the scientific community. Because of their first-hand knowledge and experience, scientists need to publicly articulate what the risks are, what preventative measures can be taken, and what policies should be put in place.

Another participant commented that risk analyses should involve assessing the entire spectrum of risks, from naturally occurring pandemics to deliberate use. If risk analyses and biodefense/public health preparedness measures fail to consider all possible risks, then it will be very difficult to recruit the type of multi-disciplinary participation that effective biotechnology dual-use management will require further down the line.

It was noted that it may be impossible to identify all the risks, given that the plethora of possibilities practically defies definition and that new risks will continually emerge.

The Human Security Lens[32]

It was suggested that it might be helpful to view the dual-use dilemma through a human security lens by asking the question, does the application advance human security? The concept of human security was developed decades ago, in the United Nations Development Programme's 1949 Human Development Report.[33] More recently, in its 2003 report, *Human Security Now*, the Commission on Human Security, an initiative of the Government of Japan, proposed that a human security framework be used for enhancing and redirecting policies and institutions to address 21st century conditions and threats, including terrorism.[34] Most importantly, human security is about people, not states, which makes it very different from the military framework that state and national security operate within. Efforts to strengthen biodefense, clean up the environment, reduce hunger, reduce poverty, and improve human health all lie within the

[32]Based on the presentation by Abdullah Daar.

[33]United Nations Development Programme. 1949. *Human Development Report.*

[34]Available at *http://www.humansecurity-chs.org/finalreport/FinalReport.pdf.* Accessed on January 4, 2005.

"human security" framework. As outlined during the workshop, human security is:

- shielding people from critical and pervasive threats and empowering them to take charge of their lives;
- protecting the vital core of all human lives in ways that enhance human freedoms and human fulfillment;
- protecting fundamental freedoms that are the essence of life;
- protecting people from critical (severe) and pervasive (widespread) threats and situations;
- using processes that build on people's strengths and aspirations; and
- creating political, social, environmental, economic, military, and cultural systems that together give people the building blocks of survival, livelihood, and dignity.

Viewing the dual-use dilemma through a human security lens, for example as the Global Genomics Initiative does, provides what one participant described as a "meta-guiding principle" for balancing the benefits and risks of advancing technologies. It was suggested that only those scientific and technological applications that advance human security be encouraged. On the other hand, it was argued that the very difficult question remains: does the application pose a threat? The most beneficial science could, in principle, also be (or become) the most dangerous.

Possible Approaches to Balancing the Benefits and Risks of Advancing Technologies[35]

Emerging biotechnology trends have the tremendous potential to strengthen the social and economic development of all countries, improve the health and quality of life for billions of people, and alleviate the growing economic and health disparities between industrialized nations and their low- and middle-income neighbors. Technologies once affordable only to the wealthiest nations, including genomics-based applications and pharmaceutical and vaccine manufacturing, have expanded globally. From Mexico to Singapore to South Africa, the world is unabashedly embracing technological growth in the name of national sovereignty, national security, economic growth, and improved health care for all.

However, this extraordinary potential creates a challenge with respect to dual-use threats. The challenge is expected to magnify over time, as the

[35]Based on comments by many participants.

global proliferation and progress of biotechnology continue to accelerate. No amount of national or international legislation, regulation, or control can eliminate the proliferation of dual-use agents, knowledge, and technology. Thus the question, what can be done?

The purpose of this workshop was to gather information on the international nature of the dual-use risks of advancing technologies, not formulate conclusions or recommendations for next steps. However, many participants voiced their opinions with regards to how, on a very general level, challenges might be addressed. Importantly, the suggestions summarized below do not reflect a workshop or committee consensus. They reflect individual thoughts expressed during the workshop.

Several participants opined that there is no magic bullet. For example, as helpful and relevant as it may be, the traditional approach of relying on arms control is not enough, even if the BWC can evolve to overcome the challenges it faces, including more clearly accommodating the widening range of non-state bioterrorism threats. A multi-dimensional, multi-focused approach will prove more effective and timely. Elements of all measures presented during the workshop—from the BWC to the AG to all of the various informal strategic steps being taken or considered—will be critical to recognizing, anticipating, preventing, and mitigating the destructive potential associated with advancing technologies. The International Committee of the Red Cross (ICRC) refers to this approach as building a "web of prevention." Each thread of the web may be weak on its own but together can serve the purpose.

One workshop participant said that there seems to be little question that the BWC, despite the controversy surrounding a proposed verification protocol, has a definite role in preventing the assistance and propagation of bioterrorism. Perhaps most importantly, it provides a statement of universally accepted ethical norms that are considered vitally important in deterring the use of biological weapons and agents. But strengthening the BWC is only of many steps that can and should be taken.

Another participant said that the United States must avoid the trap of the "silver bullet fallacy," the notion that if a particular step does not magically solve a problem in its entirety, it ought not to be pursued. Instead, the focus should be on the broader range of smaller, feasible steps and on prioritizing these steps.

An analogy was made between managing the dual-use risk of advancing technologies and fire prevention. You cannot park fire trucks outside of everyone's house in an effort to prevent catastrophic fires. But you can take what may seem like small, mundane measures that, over the course of months and years, minimize the risk of fire and provide the means for a rapid response if fire should break out. These mundane measures include building codes, fire sprinklers, fire departments, fire insurance,

and the like. Together, they provide a broad-based approach to reducing the risk and consequences of fire. Likewise, a broad-based approach built on an ever-evolving set of measures, or tools, may be the best way to respond to the dual-use risks posed by the global proliferation of advancing technology.

It was suggested that the response must be global and must involve international dialogue. It was argued that even if the United States chose to take unilateral action, it would not be enough to eliminate the threat posed by dual-use technology. Even with controls in place, biological materials and small equipment could be readily transported across international borders. This creates the need for very high levels of international cooperation in comparing notes, adopting measures, and meeting regularly. One of the achievements of the BWC follow-up process has been the creation of a new forum for international dialogue. But even this may not be enough, as challenges will persist well beyond 2006, when the follow-up process ends.

In light of the continuing need for international dialogue beyond the formal BWC process, it was suggested that a broad-based, multi-sectoral forum be developed so that all key actors can convene and work on these issues in a cooperative way. No detailed suggestions were put forth as to how this forum would be established or what it would look like, but various groups have already planned or conceived of assemblages that could serve as models. For example, as described in Chapter 4, the European High Level Expert Group (HLEG) on "Foresighting the New Technology Wave," as called upon by the European Commission and Member States, suggested the development of a "societal observatory." Or, the forum could be modeled after the U.S. National Science Advisory Board for Biosecurity.[36]

It was pointed out that discussions need to occur at the national level as well, since all too often the multi-disciplinary nature of effective biotechnology dual-use management is underestimated at this level. The ICRC reportedly conducted a national roundtable forum in the United Kingdom on the dual-use dilemma and was told by the governing agency that this was the first time that all actors had sat around the same table to discuss their relevant and complementary roles and responsibilities. Interestingly, the United Kingdom has one of the most advanced response capabilities of any country and yet this type of discussion had not occurred before.

It was suggested that the best way to address this practically infinite realm of perspectives is to seek grassroots solutions and build a strategic

[36]Available at *http://www.biosecurityboard.gov.*

response from the bottom up, particularly with respect to behavioral norms.

It was also mentioned that raising the awareness of the temporal dimension of the problem is critical. While technology is on the fast track to a perhaps unimaginable technological landscape by 2020, the response to the dual-use dilemma is at best static. In some cases, we may even be moving backward, for example with respect to problems ensuing from the BWC verification protocol controversy.

Appendixes

Appendix A

Workshop Agenda

Advancing Technologies: Surveying the Global Capacity for Research, Development, and Application

Policy and Global Affairs Division/National Research Council
The Board on Global Health/ Institute of Medicine

The National Academies

September 21-September 22, 2004

Instituto Nacional de Salud Publica
Cuernavaca, Mexico

Committee on Advances in Technology and the Prevention of Their Application to Next Generation Bioterrorism and Biological Warfare Threats

AGENDA

Tuesday, September 21, 2004

8:30	Coffee
9:00	Welcome and Opening Remarks/Goals of the Meeting

Stanley Lemon, M.D., *Committee Co-Chair/The University of Texas Branch at Galveston*
David Relman, M.D., *Committee Co-chair/ Stanford University*
Mauricio Hernandez, M.D., *Instituto Nacional de Salud Publica, Cuernavaca, Mexico*

Session I: Drivers of Global Technological Development

Moderator: David Relman, M.D., *Committee Co-chair/ Stanford University*

9:45 The Economic Opportunities of the Global Workforce and Marketplace (comparative advantage; market capture; select workforce)
Terence Taylor, *IISS-US*

10:05 Q&A/*Discussion*

10:20 Technological Approaches to Overcoming Health and Development Challenges
David Banta, M.D., *WHO and World Bank Consultant*

10:40 *Discussion*

11:00-11:15 BREAK

Session II: The Global Landscape of Technology/Efforts to Mitigate Risks for Misapplication

Moderator: Stanley Lemon, M.D., *Committee Co-Chair/ The University of Texas Branch at Galveston*

11:15-11:35 Global Cooperation in the Development of Biotechnology
Decio Ripandelli, *International Centre for Genetic Engineering and Biotechnology*

11:35-12:00 *Discussion*

12:00 LUNCH

1:00-2:15 AGRICULTURE/ LIVESTOCK BREEDING/BIOPhARMING
1:00-1:45 *Panel Discussion:*

Charles Arntzen, Ph.D., *Arizona State University, and*
Miguel Gomez Lim, Ph.D., *CINVESTAV-Irapuato, Mexico*
Luis Herrera-Estrella, Ph.D., *Center for Research and Advanced Studies, National Polytechnic Institute, Irapuato, Mexico*

1:45-2:15 *Q&A/Discussion*

2:15-3:50 VACCINES, PHARMACEUTICAL DEVELOPMENT AND HUMAN GENOMICS
Panel Discussion:
Rosiceli Barreto Gonçalves Baetas, D.Sc., *Biomanguinhos, Fiocruz, Brazil*
Jacques Ravel, Ph.D., *The Institute for Genomic Research*
Patrick Tan Boon Ooi, Ph.D., *Genome Institute of Singapore*
Abdallah Daar, M.D., *Center for Bioethics, University of Toronto*
Gerardo Jimenez-Sanchez, *National Institute of Genomic Medicine, Mexico*

3:50-4:05 BREAK

4:05-5:05 *Q&A/Discussion*

Session III: Discussion

Moderators: Nancy Connell, Ph.D., *UMDNJ/NJ Medical School*
Christopher Chyba, Ph.D., *Stanford University and SETI Institute*

5:05-6:00 *—Open Discussion—-*

6:00 Adjournment of Day 1

Wednesday, September 22, 2004

8:30 Coffee
9:00 Opening Remarks / Summary of Day 1
Stanley Lemon, M.D.

Session IV: Safeguarding the Benefits of Technology—Addressing the "Dual-Use" Dilemma

Moderator: Christopher Chyba, Ph.D., *Stanford University and SETI Institute*

9:00-9:30 An Update on the BWC Intercessional Meetings, Ambassador Tibor Toth

9:30-10:00 *Q&A/Discussion*

10:00-11:45 Non-proliferation and Other Mitigation Strategies Discussion Panel:
10:00-10:15 Amy Sands, Ph.D., *Monterey Institute of International Studies*
10:15-10:30 Robert Mathews, D.Sc., *Australian Defence Science and Technology Organisation*
10:30-10:45 Jerome Amir Singh, Ph.D., *Nelson R. Mandela School of Medicine, Durban, South Africa*
10:45-11:00 Peter Herby, *International Committee of the Red Cross, Geneva, Switzerland*
11:00-11:15 Terence Taylor, *IISS-US*

11:15 BREAK

11:30-12:30 OPEN DISCUSSION

12:30-1:30 LUNCH

Session V: Emerging and Converging Technologies

Moderator: David Relman, M.D., *Committee Co-chair/ Stanford University*

1:30-3:00 NANOTECHNOLOGY/BIOTECHNOLOGY/CONVERGING TECHNOLOGIES
9:30-10:45 L*ead Discussants:* Nadrian Seeman, Ph.D., *New York University*
Michael Morgan, Ph.D., *The Wellcome Trust*

3:00-3:30 *Q&A/Discussion*

3:30 BREAK

3:45-4:20 POTENTIAL "DUAL-USE" APPLICATIONS of DISCOVERIES IN BIOREGULATORS AND NEUROBIOLOGY:
Kathryn Nixdorff, Ph.D. *University of Darmstadt, Germany*
Elliott Kagan, M.D., *Uniformed Services University of the Health Sciences*

4:20-4:30 *Q&A/Discussion*

4:30-5:00 OPEN DISCUSSION

Session VI: Open Discussion/Q&A

5:00 Moderator: Stanley Lemon, M.D., *Committee Co-Chair/The University of Texas Branch at Galveston*

—Open Discussion/ Q&A—

6:00 CLOSING REMARKS/ADJOURN

Appendix B

Participants List

COMMITTEE ON ADVANCES IN TECHNOLOGY AND THE PREVENTION OF THEIR APPLICATION TO NEXT GENERATION BIOTERRORISM AND BIOLOGICAL WARFARE THREATS

Stanley Lemon, Co-chair, The University of Texas Medical Branch at Galveston
David Relman, Co-chair, Stanford University
Roy Anderson, Imperial College London
Steven Block, Stanford University
Christopher Chyba,* Stanford University and SETI Institute
Nancy Connell, University of Medicine and Dentistry of New Jersey
Freeman Dyson, Princeton University
Joshua Epstein, Brookings Institution
Stanley Falkow, Stanford University
Stephen S. Morse, Columbia University
Randall Murch, Virginia Polytechnic Institute and State University
Paula Olsiewski, Alfred P. Sloan Foundation
Kumar Patel, Pranalytica, Inc.
Clarence Peters, The University of Texas Medical Branch at Galveston
George Poste, Arizona State University
Kameswara Rao, Foundation for Biotechnology Awareness and Education, Bangalore

*Princeton University after July 1, 2005

Julian Perry Robinson, University of Sussex
Peter Singer, University of Toronto
Christopher Waller, Pfizer Global Research and Development

INVITED PARTICIPANTS

Charles Arntzen, Arizona Biodesign Institute, Arizona State University
David Banta, WHO and World Bank Consultant
Rosiceli Barreto Gonçalves Baetas, Biomanguinhos, Fiocru
Abdallah Daar, University of Toronto Joint Centre for Bioethics
Miguel Gomez Lim, CINVESTAV
Peter Herby, International Committee of the Red Cross
Mauricio Hernandez, Instituto Nacional de Salud Publica
Luis Herrera-Estrella, Center for Research and Advanced Studies, National Polytechnic Institute
Gerardo Jimenez-Sanchez, National Institute of Genomic Medicine
Elliott Kagan, Uniformed Services University of the Health Sciences
Robert Mathews, Australian Defence Science and Technology Organisation
Michael Morgan, The Wellcome Trust
Janet Nicholson, National Center for Infectious Diseases, Centers for Disease Control and Prevention
Mikeljon P. Nikolich, Walter Reed Army Institute of Research
Kathryn Nixdorff, Darmstadt University, Germany
Jacques Ravel, The Institute for Genomic Research
Decio Ripandelli, International Centre for Genetic Engineering and Biotechnology
Amy Sands, Monterey Institute of International Studies
Nadrian Seeman, New York University
Jerome Amir Singh, Nelson R. Mandela School of Medicine, South Africa
Patrick Tan Boon Ooi, National Cancer Centre, Singapore
Terence Taylor, International Institute for Strategic Studies
Tibor Toth, Hungarian Embassy

NATIONAL ACADEMIES STAFF

Eileen Choffnes, Senior Program Officer
Stacey Knobler, Senior Program Officer
Kate Giamis, Senior Program Assistant

Appendix C

Committee Member and Participant Biographical Sketches

COMMITTEE ON ADVANCES IN TECHNOLOGY AND THE PREVENTION OF THEIR APPLICATION TO NEXT GENERATION BIOTERRORISM AND BIOLOGICAL WARFARE THREATS

Dr. Stanley M. Lemon, M.D., *Co-Chair,* is the John Sealy Distinguished University Chair and Director of the Institute for Human Infections and Immunity at the University of Texas Medical Branch (UTMB) at Galveston. He received his undergraduate A.B. degree in biochemical sciences from Princeton University *summa cum laude*, and his M.D. with honor from the University of Rochester. He completed postgraduate training in internal medicine and infectious diseases at the University of North Carolina at Chapel Hill, and is board certified in both. From 1977 to 1983, he served with the U.S. Army Medical Research and Development Command, followed by a 14 year period on the faculty of the University of North Carolina School of Medicine. He moved to UTMB In 1997, serving first as Chair of the Department of Microbiology & Immunology, then as dean of the School of Medicine from 1999 to 2004. Dr. Lemon's research interests relate to the molecular virology and pathogenesis of positive-strand RNA viruses responsible for hepatitis. He has had a longstanding interest in anti-viral and vaccine development, and has served previously as chair of the Anti-Infective Drugs Advisory Committee, and the Vaccines and Related Biologics Advisory Committee, of the U.S. Food and Drug Administration. He is past chair of the Steering Committee on Hepatitis and Poliomyelitis of the World Health Organization Programme on Vaccine Development. He presently serves as a member of the U.S. Delegation of

the U.S.-Japan Cooperative Medical Sciences Program, and chairs the Board of Scientific Councilors of the National Center for Infectious Diseases of the Centers for Disease Control and Prevention. He is Chair of the Forum on Microbial Threats of the Institute of Medicine, and recently chaired an Institute of Medicine study committee related to vaccines for the protection of the military against naturally occurring infectious disease threats.

David A. Relman, M.D., *Co-Chair,* is an associate professor of medicine (infectious diseases and geographic medicine) and of microbiology and immunology at Stanford University School of Medicine, Stanford, California, and chief of the Infectious Diseases Section at the Veterans Affairs Palo Alto Health Care System, Palo Alto, California. Dr. Relman received his bachelor of science degree in biology from Massachusetts Institute of Technology, Cambridge, Massachusetts, and his medical degree from Harvard Medical School. He completed his residency in internal medicine and a clinical fellowship in infectious diseases at Massachusetts General Hospital, Boston, after which he moved to Stanford as a research fellow and postdoctoral scholar. He joined the Stanford faculty in 1994. His major focus is laboratory research directed toward characterizing the human endogenous microbial flora, host-microbe interactions, and identifying previously-unrecognized microbial pathogens, using molecular and genomic approaches. He has described a number of new human microbial pathogens. Dr. Relman's lab (*http://relman.stanford.edu*) is currently exploring human oral and intestinal microbial ecology, sources of variation in host genome-wide expression responses to infection and during states of health, and how *Bordetella* species (including the agent of whooping cough) cause disease. He has published over 150 peer-reviewed articles, reviews, editorials, and book chapters on pathogen discovery and bacterial pathogenesis. Dr. Relman has served on scientific program committees for the American Society for Microbiology (ASM) and the Infectious Diseases Society of America (IDSA), and advisory panels for NIH, CDC, the Departments of Energy and Defense, and NASA. He is a member of the Board of Directors of the IDSA, the Board of Scientific Counselors at NIDCR/NIH, and the Forum on Microbial Threats at the Institute of Medicine. He received the Squibb Award from IDSA in 2001, the Senior Scholar Award in Global Infectious Diseases from the Ellison Medical Foundation in 2002, and is a Fellow of the American Academy of Microbiology.

Roy Anderson, Ph.D., FRS, FMedSci, is professor of Infectious Disease Epidemiology and Head of the Department of Infectious Disease Epidemiology at Imperial College Faculty of Medicine, University of London.

Roy Anderson is a Fellow of the Royal Society and a Foreign Member of the Institute of Medicine at the U.S. National Academy of Sciences. He has published over 400 scientific papers on the epidemiology, population biology, evolution and control of a wide range of infectious disease agents, including HIV, BSE, vCJD, parasitic helminths and protozoa, and respiratory tract viral and bacterial infections. His principal research interests are epidemiology, biomathematics, demography, parasitology, immunology, and health economics. He also has a keen interest in science policy and the public understanding of science. He has held a wide variety of advisory and consultancy posts with government departments, pharmaceutical companies, and international aid agencies. Professor Anderson has been a member of SEAC since January 1998.

Steven M. Block, Ph.D., is a biophysicist at Stanford University, where he holds a joint appointment as a professor in the Departments of Biological Sciences and Applied Physics. He is also a Senior Fellow of the Stanford Institute for International Studies, and a member of the JASONs, a group of academicians who consult for the U.S. government and its agencies on technical matters related to national security. Prior to joining the Stanford faculty in 1999, Professor Block held positions at Princeton University (1994-1999), Harvard University (1987-1994), and the Rowland Institute for Science in Cambridge, MA (1987-1994). He received his undergraduate training in both physics and biology at Oxford University, earned his doctorate from the California Institute of Technology (1983), and conducted postdoctoral research at Stanford. Professor Block's technical interests are in interdisciplinary science, particularly the biophysics of motor proteins. His laboratory pioneered the use of laser-based optical traps ("optical tweezers") to study the nanoscale motions of these mechanoenzymes at the level of single molecules, and his group was the first to develop instrumentation able to resolve the individual steps taken by single kinesin motors moving along microtubules. Other biological systems currently under study in his laboratory include RNA polymerase, exonuclease, and helicase, enzymes that move processively along DNA. Professor Block is a strong proponent of nanoscience, but he is also an outspoken critic of the "futurist" element of the nanotechnology movement.

Christopher Chyba, Ph.D., is professor of astrophysics and international affairs at Princeton University, where he co-directs the Program on Science and Global Security in the Woodrow Wilson School of Public and International Affairs. His security-related research focuses on nuclear proliferation and biological terrorism. His planetary science and astrobiology research focuses on the search for life elsewhere in the solar system. A graduate of Swarthmore College, Chyba studied as a Marshall

Scholar at the University of Cambridge and received his PhD in planetary science from Cornell University in 1991. He served on the White House staff from 1993 to 1995, entering as a White House Fellow on the National Security Council staff and then serving in the National Security Division of the Office of Science and Technology Policy (OSTP). After leaving the White House, he drafted the President's decision directive on responding to emerging infectious diseases, and authored a report for OSTP in 1998 on preparing for biological terrorism. He received the Presidential Early Career Award, "for demonstrating exceptional potential for leadership at the frontiers of science and technology during the 21st century." He chaired the Science Definition Team for NASA's Europa Orbiter mission and served on the executive committee of NASA's Space Science Advisory Committee, for which he chaired the Solar System Exploration Subcommittee. Dr. Chyba currently serves on the National Academy of Sciences' Committee for International Security and Arms Control, on the Monterey Nonproliferation Strategy Group, and chairs the National Research Council's Committee on Preventing the Forward Contamination of Mars. He is a member of the Board of Trustees of the SETI Institute. In October 2001, he was named a MacArthur Fellow for his work in astrobiology and international security.

Nancy Connell, Ph.D., associate professor of Microbiology and Molecular Genetics, has been appointed Director of the New Jersey Medical School (NJMS)-Center for Biodefense. She is an NIH-funded basic scientist, a permanent member of the NIH Study Section on Bacteriology and Mycology-1, and serves as Director of the Biosafety Level Three Facility of the NJMS-Center for Emerging and Re-emerging Pathogens. She is a graduate of Harvard Medical School and has been a faculty member at NJMS since 1992.

Freeman Dyson is now retired, having been for most of his life a professor of physics at the Institute for Advanced Study in Princeton. He was born in England and worked as a civilian scientist for the Royal Air Force in World War II. He graduated from Cambridge University in 1945 with a B.A. degree in mathematics. He went on to Cornell University as a graduate student in 1947 and worked with Hans Bethe and Richard Feynman. His most useful contribution to science was the unification of the three versions of quantum electrodynamics invented by Feynman, Schwinger, and Tomonaga. Cornell University made him a professor without bothering about his lack of a Ph.D. He subsequently worked on nuclear reactors, solidstate physics, ferromagnetism, astrophysics, and biology, looking for problems where elegant mathematics could be usefully applied. He has written a number of books about science for the general public. *Disturbing*

the Universe (1974) is a portrait-gallery of people he has known during his career as a scientist. *Weapons of Hope* (1984) is a study of ethical problems of war and peace. *Infinite in All Directions* (1988) is a philosophical meditation based on Dyson's Gifford Lectures on Natural Theology given at the University of Aberdeen in Scotland. *Origins of Life* (1986, second edition 1999) is a study of one of the major unsolved problems of science. *The Sun, the Genome and the Internet* (1999) discusses the question of whether modern technology could be used to narrow the gap between rich and poor rather than widen it. Dyson is a fellow of the American Physical Society, a member of the U.S. National Academy of Sciences, and a fellow of the Royal Society of London. In 2000, he was awarded the Templeton Prize for progress in Religion.

Joshua M. Epstein, Ph.D., is a Senior Fellow in Economic Studies at the Brookings Institution, a member of the Brookings-Johns Hopkins Joint Center on Social and Economic Dynamics, and a member of the External Faculty of the Santa Fe Institute. He holds a Ph.D. in Political Science from MIT and is a member of the New York Academy of Sciences. He is also a member of the Editorial Boards of the journal *Complexity*, and of the Princeton University Press Studies in Complexity book series. His primary research interest is in the modeling of complex social, economic, and biological systems using agent-based computational models and nonlinear dynamical systems. He has taught computational and mathematical modeling at Princeton and the Santa Fe Institute Summer School. He has published widely in the modeling area, including recent articles on the dynamics of civil violence, the demography of the Anasazi (both in the *Proceedings of the National Academy of Sciences*) and the epidemiology of smallpox (in the *American Journal of Epidemiology*). His two most recent books are *Growing Artificial Societies: Social Science from the Bottom Up,* with co-author Robert Axtell, (MIT Press, 1996); and *Nonlinear Dynamics, Mathematical Biology, and Social Science* (Addison-Wesley/Santa Fe Institute, 1997). His book *Generative Social Science: Studies in Agent-Based Computational Modeling* is forthcoming from Princeton University Press.

Stanley Falkow, Ph.D. (NAS, IOM), is professor of Microbiology and Immunology and Professor of Medicine at Stanford University. Dr. Falkow is recognized internationally for his research related to the molecular mechanisms of bacterial pathogenesis. Dr. Falkow is the former President of the American Society for Microbiology and has been elected to the American Academy of Arts and Sciences, the National Academy of Sciences, and the Institute of Medicine. He has received the Squibb Award from the Infectious Diseases Society of America (1978), the Paul Erhlich Award from Germany (1980), the Brisol-Myers-Squibb Award for Infec-

tious Diseases Research (1997), and the Robert Koch Prize from Germany (2000). Dr. Falkow holds a B.S. in Bacteriology from the University of Maine, an M.S. in Biology from Brown University, and a Ph.D. in Biology from Brown University.

Stephen S. Morse, Ph.D., is director of the Center for Public Health Preparedness at the Mailman School of Public Health of Columbia University, and a faculty member in the Epidemiology Department. Dr. Morse recently returned to Columbia from 4 years in government service as Program Manager at the Defense Advanced Research Projects Agency (DARPA), where he co-directed the Pathogen Countermeasures program and subsequently directed the Advanced Diagnostics program. Before coming to Columbia, he was Assistant Professor (Virology) at The Rockefeller University in New York, where he remains an adjunct faculty member. Dr. Morse is the editor of two books, *Emerging Viruses* (Oxford University Press, 1993; paperback, 1996) (selected by *American Scientist* for its list of "100 Top Science Books of the 20th Century"), and *The Evolutionary Biology of Viruses* (Raven Press, 1994). He currently serves as a Section Editor of the CDC journal *Emerging Infectious Diseases* and was formerly an Editor-in-Chief of the Pasteur Institute's journal *Research in Virology*. Dr. Morse was Chair and principal organizer of the 1989 NIAID/NIH Conference on Emerging Viruses (for which he originated the term and concept of emerging viruses/infections); served as a member of the Institute of Medicine's Forum on Microbial Threats to Health (and chaired its Task Force on Viruses), and was a contributor to its report, *Emerging Infections* (1992); was a member of the IOM's Committee on Xenograft Transplantation; currently serves on the Steering Committee of the Institute of Medicine's Forum on Emerging Infections; and has served as an adviser to WHO (World Health Organization), PAHO (Pan American Health Organization), FDA, the Defense Threat Reduction Agency (DTRA), and other agencies. He is a Fellow of the New York Academy of Sciences and a past Chair of its Microbiology Section. He was the founding Chair of ProMED (the nonprofit international Program to Monitor Emerging Diseases) and was one of the originators of ProMED-mail, an international network inaugurated by ProMED in 1994 for outbreak reporting and disease monitoring using the Internet. Dr. Morse received his Ph.D. from the University of Wisconsin-Madison.

Randall S. (Randy) Murch, Ph.D., received a Bachelor of Science degree in Biology from the University of Puget Sound, Tacoma, Washington in 1974, a Master of Science degree in Botanical Sciences from the University of Hawaii in 1976, and a Doctor of Philosophy degree in Plant Pathology from the University of Illinois in 1979. After 23 years of service as a Spe-

cial Agent, he retired from the FBI in November 2002. During his FBI career, he was assigned to the Indianapolis, Los Angeles, and New York field divisions, and to the national security, (forensic) laboratory, and investigative technology (engineering) divisions at FBI Headquarters and Quantico, Virginia. He served as a department head and deputy division head in the FBI Laboratory, as well as a deputy division head of the FBI's electronic surveillance division (investigative technology). He has extensive experience in counterintelligence, counterterrorism, forensic science, electronic surveillance, WMD threat reduction, and outreach to those communities. He created the FBI's WMD forensic investigation/S&T response program in 1996, and served as the FBI's science advisor to the 1996 Olympics. From December 1999 to June 2001, he was detailed to the Defense Threat Reduction Agency as the director of DTRA's advanced systems and concepts office. He has participated in National Academy of Sciences/National Research Council, Defense Science Board and DTRA Threat Reduction Advisory Committee studies and panels and other senior review panels. He joined the Institute for Defense Analyses in December 2002, and now works to deliver creative solutions for difficult national security problems across a range of operational, science, and engineering disciplines.

Paula Olsiewski, Ph.D., is leading the Alfred P. Sloan Foundation's program to reduce the threat of bioterrorism. Since joining the Foundation in 2000, she has created a collaborative network from the public, private, and government sectors that has become critical to the nation's civilian biodefense movement. Among the many projects Dr. Olsiewski has facilitated is the Department of Homeland Security's READY campaign, a public education effort that empowers Americans to prepare for potential terrorist attacks. Another important grant to the Center for Law and the Public's Health at Georgetown and Johns Hopkins Universities produced model legislation for dealing with bioterrorism and catastrophic infectious diseases. Thirty-three states and the District of Columbia have enacted legislation based on the Model State Emergency Health Powers Act. A grant to the National Academies resulted in the Fall 2003 NRC Report *Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma* and led to the establishment of the National Science Advisory Board for Biosecurity by the U.S. Department of Health and Human Services in March 2004. During the 1990s, Dr. Olsiewski founded and directed a consulting practice, Neo/Tech Corp., providing expertise in structuring, implementing, and directing technology development programs. Before that, she was Vice President of Commercial Development at Enzo Biotech, Inc. where she was responsible for overall management of product development, technology licensing, and transfer programs. Dr. Olsiewski serves on

numerous advisory committees and boards. She is a member of the MIT Corporation and was the President of the MIT Alumni/ae Association 2003-2004. She is Chairman of the Board of Trustees of Asphalt Green, Inc., a not-for-profit organization dedicated to assisting individuals of all ages and backgrounds achieve health through a lifetime of sports and fitness. Dr. Olsiewski received a B.S. in Chemistry from Yale College, and a Ph.D. in Biological Chemistry from MIT.

Chandra Kumar N. Patel, Ph.D., a member of the National Academy of Engineering and National Academy of Sciences, is chief executive officer and chairman of the board of Pranalytica, Inc. and professor of physics and former vice chancellor of research at the University of California at Los Angeles. Until 1993, Dr. Patel served as executive director of the Research, Materials Science, Engineering and Academic Affairs Division at AT&T Bell Laboratories. Dr. Patel has an extensive background in several fields, to include materials, lasers, and electro-optical devices. During his career at AT&T, which began in 1961, he made numerous seminal contributions in several fields, including gas lasers, nonlinear optics, molecular spectroscopy, pollution detection, and laser surgery. Dr. Patel has served on numerous government and scientific advisory boards and he is past president of Sigma Xi and the American Physical Society. In addition, Dr. Patel has received numerous honors, including the National Medal of Science, for his invention of the carbon dioxide laser.

Clarence J. Peters, M.D., is the John Sealy Distinguished University Chair in Tropical and Emerging Virology at the University of Texas Medical Branch in Galveston and is Director for Biodefense in the Center for Biodefense and Emerging Infectious Diseases at that institution. Before moving to Galveston in 2001, he worked in the field of infectious diseases for three decades with NIH, CDC, and the U.S. Army. He has been Chief of Special Pathogens Branch at the Centers for Disease Control and Prevention in Atlanta, Georgia and previous to that, Chief of the Disease Assessment Division and Deputy Commander at USAMRIID. He was the head of the group that contained the outbreak of Ebola at Reston, Virginia and led the scientists who identified hantavirus pulmonary syndrome in the southwestern United States in 1993. He has worked on global epidemics of emerging zoonotic virus diseases including Bolivian hemorrhagic fever, Rift Valley fever, and Nipah virus. He received his M.D. from Johns Hopkins University and has more than 275 publications in the area of virology and viral immunology. Dr. Peters is currently also a member of the National Academy of Sciences Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology.

George Poste, D.V.M., Ph.D., is chief executive of Health Technology Networks, a consulting group based in Scottsdale, Arizona and suburban Philadelphia specializing in the application of genetics and computing in healthcare and bioterrorism defense. From 1992 to 1999 he was chief science and technology officer and president, Research and Development of SmithKline Beecham (SB). During his tenure at SB he was associated with the successful registration of 29 drug, vaccine, and diagnostic products. He is chairman of diaDexus and Structural GenomiX in California and Orchid Biosciences in Princeton. He serves on the Board of Directors of AdvancePCS and Monsanto. He is an advisor on biotechnology to several venture capital funds and investment banks. In May 2003 he was appointed as Director of the Arizona Biodesign Institute at Arizona State University. This is a major new initiative combining research groups in biotechnology, nanotechnology, materials science, advanced computing, and neuromorphic engineering. He is a fellow of Pembroke College Cambridge and Distinguished Fellow at the Hoover Institution and Stanford University. He is a member of the Defense Science Board of the U.S. Department of Defense and in this capacity he chairs the Task Force on Bioterrorism. He is also a member of the National Academy of Sciences Working Group on Defense Against Bioweapons. Dr. Poste is a Board Certified Pathologist, a fellow of the Royal Society, and a fellow of the Academy of Medical Sciences. He was awarded the rank of Commander of the British Empire by Queen Elizabeth II in 1999 for services to medicine and for the advancement of biotechnology. He has published over 350 scientific papers; co-edited 15 books on cancer, biotechnology, and infectious diseases; and serves on the Editorial Board of multiple technical journals. He is invited routinely to be the keynote speaker at a wide variety of academic, corporate, investment, and government meetings to discuss the impact of biotechnology and genetics on healthcare and the challenges posed by bioterrorism. Dr. Poste is married with three children. His personal interests are in military history, photography, automobile racing, and exploring the wilderness zones of the American West.

C. Kameswara Rao, Ph.D., initially taught at the Department of Botany, Andhra University, Waltair, and served the Bangalore University from 1967 to 1998. He received the B.Sc. (Hons.), M.Sc., and Ph.D. degrees from the Andhra University, and a D.Sc. (honoris causa) from the Medicina Alternativa Institute, Open International University for Complementary Medicines, Colombo. He was a professor of Botany and the chairman of the Department of Botany, and the Department of Sericulture at the Bangalore University. Currently, he is executive secretary for the Founda-

tion for Biotechnology Awareness and Education. On a Commonwealth Academic Staff Fellowship and a Royal Society and Nuffield Foundation Bursary, Professor Kameswara Rao worked on the computer applications in plant systematics, at the Natural History Museum, London, and the Royal Botanic Gardens, Kew, in the UK, besides some other institutions. Professor Kameswara Rao was the President of the Indian Association for Angiosperm Taxonomy for 1999. He is a member of the Indian Subcontinent Plant Specialist Group of the Species Survival Commission, IUCN. He is a member of the Programme Advisory Committee of the Botanical Survey of India and the Zoological Survey of India, Ministry of Forests and Environment, Government of India. He is the executive secretary of the Foundation for Biotechnology Awareness and Education. Professor Rao's research interests are applications of computers and phytochemistry in plant systematics and databases of medicinal plants. Recently, he was awarded a Certificate of Merit by the World Peace Foundation, Beijing, an affiliate of the UN, for his research work on Indian medicinal plants.

Julian Robinson is a chemist and patent lawyer by training. He had previously held research appointments at the Stockholm International Peace Research Institute (SIPRI), the Free University of Berlin, and the Harvard University Center for International Affairs. He has been active in the Pugwash Conferences on Science and World Affairs since 1968. He has served as an advisor or consultant to a variety of national and international organizations, governmental and nongovernmental, including the World Health Organization, other parts of the United Nations system, the International Committee of the Red Cross, and the UK National Authority for the Chemical Weapons Convention. In association with the Belfer Center for Science and International Affairs of the Kennedy School of Government at Harvard, he directs the UK end of the Harvard Sussex Program (HSP), which is a collaborative research, teaching, and publication activity focused on chemical/biological-warfare armament and arms limitation. This is a subject on which he has published some 400 papers and monographs since 1967, including much of the six volume SIPRI study *The Problem of Chemical and Biological Warfare* (1971-76), *Effects of Weapons on Ecosystems* (1979), *Chemical Warfare Arms Control* (1984), *NATO Chemical Weapons Policy and Posture* (1986), and *The Problem of Chemical-Weapon Proliferation in the 1990s* (1991). Since 1988, he has been editing, with Matthew Meselson of Harvard University, one of the few journals in the field, *The CBW Conventions Bulletin,* now published quarterly from the Sussex end of HSP.

Peter Singer, Ph.D., is the Sun Life Financial Chair in Bioethics and Director of the University of Toronto Joint Centre for Bioethics and the

Program Director of the Canadian Program on Genomics and Global Health. He directs the World Health Organization Collaborating Centre for Bioethics at the University of Toronto. He is also professor of Medicine and practices Internal Medicine at Toronto Western Hospital. He studied internal medicine at the University of Toronto, medical ethics at the University of Chicago, and clinical epidemiology at Yale University. A Canadian Institutes of Health Research Investigator, he has published 140 articles on bioethics. He holds over $16 million in research grants from the U.S. National Institutes of Health, Ontario Research and Development Challenge Fund, Genome Canada, and Canadian Institutes of Health Research. He is a member of the ethics committee of the *British Medical Journal,* and a Director of The Change Foundation. His current research focus is global health ethics.

Christopher L. Waller, Ph.D., received his Ph.D. in Medicinal Chemistry and Natural Products from the University of North Carolina in Chapel Hill in 1992. His graduate research efforts were directed at the design, synthesis, and biological evaluation of anti-edema agents. Following graduation, Dr. Waller accepted a post-doctoral fellowship under the direction of Dr. Garland Marshall at Washington University in St. Louis where he focused his efforts on the design HIV protease inhibitors. In 1993, Dr. Waller accepted a position with the U.S. EPA in which he was responsible for the development of structure-activity relationship and pharmacokinetic models as a research chemist and leader of a team of analytical, computational, and synthetic organic chemists, toxicologists, and biomedical engineers. From 1996 to 1999, Dr. Waller served as a Research Manager at OSI Pharmaceuticals. In this role, he managed a group of computational chemists, scientific application developers, and robotics engineers. In early 1999, Dr. Waller joined Eli Lilly- Sphinx Laboratories as a computational chemist and Head of Cheminformatics in the Discovery Chemistry group. Since 2001, Dr. Waller has been Associate Director of Research Informatics for Pfizer Global Research and Development, Ann Arbor Laboratories. Dr. Waller has published over 25 peer-reviewed articles and has received numerous honors and awards including the Board of Publications Award for the Best Paper in Toxicology and Pharmacology in 1996.

BIOSKETCHES OF INVITED PARTICIPANTS

Charles Arntzen was appointed to the Florence Ely Nelson Presidential Endowed Chair at Arizona State University (ASU) in Tempe in 2000. He also served as the Founding Director of the Biodesign Institute at ASU, and currently serves as the Co-director of the Center for Infectious Dis-

eases and Vaccinology, a component of that Institute. Prior to joining ASU, Dr. Arntzen was a Director of Research at the Dupont Company in Delaware from 1984 to 1988, and in 1988 he was appointed Deputy Chancellor for Agriculture, Dean, College of Agriculture and Life Sciences and Director, Texas Agricultural Experiment Station in the Texas A&M University System. He moved to New York in 1995 to serve as President and CEO of Boyce Thompson Institute—a not-for-profit corporation affiliated with Cornell University. He has served on many national and international committees including service as Chairman of the National Institutes of Health's Biotechnology Policy Board and as Chair of the Biobased Industrial Products Committee for the National Academy of Sciences. He was elected to the U.S. National Academy of Sciences in 1983 and to the National Academy of India the following year. He currently serves as a member of President George W. Bush's Council of Advisors on Science & Technology.

David Banta graduated from Duke University (M.D. degree) and Harvard University (M.P.H., M.S.). He was program manager and Assistant Director of the U.S. Congressional Office of Technology Assessment from 1975 to 1983. In 1983, he joined the World Health Organization as Deputy Director of PAHO in Washington, DC. In 1985, he moved to the Netherlands to head a Ministry of Health/WHO study of future health care technology, continuing as a staff member of the WHO. He took Dutch citizenship and resigned from the WHO in 1993. From then until formal retirement in 2003, he worked from the Netherlands Organization for Applied Scientific Research (TNO), the largest research program in the Netherlands. He has worked extensively as a consultant in other countries, mostly in Europe and the more developed countries of the developing countries of the world (China, Brazil, India, Malaysia). Since his retirement, he has worked as a consultant for WHO and for the World Bank on special projects in Serbia, Russia, and Slovenia. He has written and edited more than 10 books on subjects related to health technology assessment.

Abdallah Daar is professor of Public Health Sciences and of Surgery at the University of Toronto, where he is also director of the Program in Applied Ethics and Biotechnology at the University of Toronto Joint Centre for Bioethics. He is also the director for Ethics and Policy at the McLaughlin Centre for Molecular Medicine. After medical school in London, England, he went to the University of Oxford where he did postgraduate clinical training in surgery and also in internal medicine, a doctorate in transplant immunology/immunogenetics, and a fellowship in transplantation. He was a clinical lecturer in Oxford for several years before going to the Middle East to help start two medical schools. He took

up the foundation Chair of Surgery in Oman in 1988, where he also headed the research labs. Professor Daar has been an expert advisor to WHO and OECD. He is a fellow of the New York Academy of Sciences and is on the Ethics Committee of the (International) Transplantation Society and of the Human Genome Organization. Professor Daar is also a member of the Institute Advisory Board, Institute of Infection and Immunity of the Canadian Institutes of Health Research. He was awarded the Hunterian Professorship of the Royal College of Surgeons of England in 1999 and in 2000 he was appointed to the Roster of Experts for the Food and Agriculture Organization of the United Nations/WHO Joint Consultations on Foods Derived from Biotechnology. Dr. Daar has been a visiting scholar in Bioethics at Stanford University and Visiting Professor in the Faculty of Law at the University of Toronto. Editorial Boards include *World Journal of Surgery, Kidney Forum, Clinical Transplantation Proceedings,* and *Bioethics*. His current research interests are in the exploration of how genomics and other biotechnologies can be used effectively to ameliorate global health inequities.

Miguel Gomez Lim is a Full Professor at the Department of Plant Genetic Engineering of CINVESTAV-Irapuato. He majored in Biology at the National University of Mexico and then obtained his Ph.D. at the University of Edinburgh, UK. After a postdoc at the University of California, Los Angeles, he joined CINVESTAV-Irapuato where he has been working in the plant Genetic Engineering for almost 15 years and for the past 5 he has been actively working in the field of Molecular Farming. He received the National Award for Young Investigators from the Mexican Academy of Sciences in 1998 and is currently a member of the National System for Investigators.

Peter Herby is head of the Mines-Arms Unit in the Legal Division of the ICRC. He has written and spoken extensively on the norms of humanitarian law applicable to the use of arms and, more specifically, on landmines, blinding laser weapons, and small arms. He is co-author of an ICRC study on "arms availability and the situation of civilians in armed conflict" (1999). From 1983 to 1993 he worked with chemical, biological, and nuclear arms control negotiations for the Quaker United Nations Office, Geneva. Mr. Herby has represented the ICRC in all arms-related negotiations since 1994 and is responsible for overall development of the ICRC's initiative on "Biotechnology, Weapons and Humanity." His holds a Master of Philosophy degree in International Relations from Cambridge University in the United Kingdom and a Masters in Peace and Conflict Studies from the Univesity of Bradford, UK.

Mauricio Hernandez-Avila has a Medical degree from the National Autonomous University of Mexico (UNAM), with a residency in Pathology at the Salvador Zubiran National Institute of Health Sciences and Nutrition (HSNI). He has a Master's degree in Statistics from UNAM, Applied Mathematics and Systems Research Institute. He has a Master's Degree and D.Sc. in Epidemiology from the Harvard School of Public Health, 1988. Dr. Hernandez developed his labor trajectory at the Ministry of Health as Attending Physician in the Nutrition Division of the Community in the INNSZ (1981). Dr. Hernandez was incorporated to the General Direction of Epidemiology of the Mexico Ministry of Health as Director of the area of Epidemiological Alertness of Chronic Illnesses and Accidents (1988-1991). In April 1991, Dr. Hernandez was appointed as Director of the Centre of Public Researches in Health. To the completion of his Academic activity, he rejoins to his activities as Director of the Centre of Investigation in Population Health, developing activities of management and teaching, in addition to leading projects of research. On April 1st, 2004, he was appointed Executive Director of the INSP. Dr. Hernandez-Avila is a researcher of recognized prestige at both the national and international levels. He has been a Member of the National Academy of Medicine since 1993 and of the National System of Researchers (Level III National Investigator) since 1990. He sits on the Committee of Biomedical Sciences of CONACyT. His scientific production includes the publication of 187 articles, 7 articles for diffusion, 29 chapters of books, and 6 books, internationally and nationally recognized.

Luis Herrera-Estrella is director of the Centro de Investigación y de Estudios Avanzados del IPN-Unidad Irapuato, Irapuato, Gto, Mexico. He graduated with a B.Sc. degree in Biochemical Engineering from the Mexican National Polytechnic Institute and received a Ph.D. from the State University of Ghent, Belgium. Dr. Herrera-Estrella has made important contributions to the field of plant molecular biology, especially in the study of gene regulation and in the development of gene transfer methods. While still working as a Ph.D. student he published the first report on the genetic manipulation of plant cells and pioneered the development of dominant selectable markers for plant transformation. His current research is now primarily focused on the development transgenic plants better adapted to marginal soils. Dr. Herrera-Estrella has been awarded several national and international prizes, among them the award in biology from the Mexican Academy of Sciences, the Minoru and Ethel Tsutsui Research Award of the New York Academy of Sciences, and the Javed Husain prize from UNESCO. He was elected foreign associated member of the National Academy of Sciences (US) in 2003.

Gerardo Jimenez-Sanchez is professor of Genomic Medicine at the UNAM and Resident Investigator of the Mexican Health Foundation (FUNSALUD). He is also Acting Director of the National Institute of Genomic Medicine of Mexico, affiliate member of the Institute of Genetic Medicine of Johns Hopkins University. His actual work focuses on the study of the human genome, particularly in human disease causing genes, production of animal models for the study of monogenic diseases, and the development of genomic medicine. He has led the efforts being done in Mexico to establish the National Institute of Genomic Medicine. He served as Director of the Consortium for the Institute of Genomic Medicine from 2002 to 2004. He obtained his Medical Doctor degree from the National Autonomous University of Mexico (UNAM). He did his residency in Pediatrics at the National Institute of Pediatrics and earned his Ph.D. degree in Human Genetics and Molecular Biology from the Johns Hopkins University in Baltimore, MD. He received his training in business administration from the IPADE Business School. In August 2003, he was elected Founding President of the Mexican Society of Genomic Medicine and he served as President of the I National Congress of Genomic Medicine in August 2004. Dr. Jimenez-Sanchez is a certified pediatrician and a member of the Mexican Academy of Pediatrics, the Mexican Society of Pediatrics, the Mexican Association of Human Genetics, the Mexican Society of Biochemistry, and the American Societies of Human Genetics, Inborn Errors of Metabolism and Gene Therapy, the European Society of Inborn Errors of Metabolism, and the Human Genome Organization (HUGO), National Commission for the Human Genome.

Elliott Kagan is professor of Pathology, Emerging Infectious Disease, and Preventive Medicine & Biometrics at the Uniformed Services University of the Health Sciences in Bethesda, MD. His expertise is in the area of lung biology and his research has centered on the role of cytokines and reactive oxygen and nitrogen species in the pathogenesis of pleural and pulmonary injury induced by inhaled particulates such as asbestos and silica. For approximately the last year, his research focus has changed and has concentrated on biodefense against a possible aerosolized Ebola virus threat. He also has written on the potential of bioregulators to be used as future biological threat agents. Dr. Kagan has served on several NIH study sections and other scientific panels.

Robert Mathews is a principal research scientist in the Chemical, Biological, Radiological and Nuclear (CBRN) Defence Centre of the Australian Defence Science and Technology Organisation (DSTO). His main current scientific research interest is the development of analytical methods to support verification of the Chemical Weapons Convention (CWC) and

the Biological Weapons Convention (BWC). Dr. Mathews served as scientific adviser to the Australian Delegation to the Conference on Disarmament from 1984, and since 1993 he has provided scientific support to the Australian delegation to the Organisation for the Prohibition of Chemical Weapons (OPCW), based in The Hague. He has also been actively involved in other Australian government efforts towards non-proliferation of weapons of mass destruction, including providing scientific support to the meetings of the Australia Group (CB export licensing measures) since its inception in 1985, and in the efforts to develop a Verification Protocol and other methods to strengthen the BWC. He has also made many visits to regional countries for arms control consultations, including guidance in their preparations for national implementation of the BWC and CWC. In 2002, he was appointed an associate professor and member of the Advisory Board of the Asia Pacific Centre for Military Law at the University of Melbourne. He is also Deputy-Chair of the Australian Red Cross International Humanitarian Law (IHL) National Advisory Committee, and provides advice on a range of arms control issues in that capacity. Dr. Mathews was elected Fellow of the Royal Australian Chemical Institute in 1995, and became a member of the International Verification Consultants Network of the Verification Research, Training and Information Centre (VERTIC, London) in 1998. In 2003, he was awarded a D.Sc. for his published work and other contributions to chemical and biological defence and arms control.

Michael Morgan is a graduate of Trinity College, Dublin and obtained his Ph.D. (Leicester University) in 1968. He joined the staff of Leicester University in 1971 where he set up a somatic cell facility studying interferon and carbohydrate metabolism. He joined the Wellcome Trust in 1983 and as director of Research Partnerships and Ventures was responsible for the development of new enterprises such as the Synchrotron Project, the SNPs Consortium, and the structural genomics consortium. He played a major role in the international coordination of the Human Genome Project and was chief executive of the Wellcome Trust Genome Campus; he is now a Consultant for Special Projects at the Wellcome Trust. He is chairman of the Board of the Structural Genomics Consortium, a director of Diamond Light Source and the Conway Institute, and a trustee of the Institute of Cancer Research and the Scottish Crop Research Institute.

Janet K.A. Nicholson is associate director for Laboratory Science, National Center for Infectious Diseases (NCID), Centers for Disease Control and Prevention (CDC). Previous positions include deputy chief, Immunology Branch, Division of HIV/AIDS, NCID; Research Chemist, Immunology Branch, Division of Immunologic, Oncologic, and Hemato-

logic Diseases, NCID; postdoctoral fellow, Division of Immunology, Bureau of Laboratories, CDC; research scientist, Emory University; Research Technician, University of Texas Medical Branch; research technician, University of Nebraska Medical Center. Dr. Nicholson received a B.S. from Buena Vista College and a Ph.D. from Emory University. She is a member of the Interagency Working Group for Select Agents, and the Interagency Biosecurity Subcommittee of Select Agents. She was a delegate for the National Committee for Clinical Laboratory Standards (NCCLS). Other memberships include the Biosecurity subcommittee for the Biomedical and Microbiological Biosafety Manual revision, 2004, the Infectious Diseases Committee, Association of Public Health Laboratories. She was coordinator of the ASM/NCID Postdoctoral Fellowship, a member of the Laboratory Response Network (LRN) Steering Committee, and past president of the Clinical Cytometry Society. Dr. Nicholson's international activities include a role as a U.S. representative for the Global Health Action Group Laboratory Network, and an expert for the Biological Weapons Convention Expert Meeting on Biosecurity, 2003. She is involved in efforts to develop alternative technologies for CD4 enumeration through the WHO. Dr. Nicholson's current scientific interests include emerging infectious diseases and laboratory response to bioterror threats.

Mikeljon P. Nikolich is a microbiologist working with Dr. Luther Lindler and managing plague research in the Department of Homeland Security's Biological Threat Characterization Program in the National Biodefense Analysis and Countermeasures Center laboratory at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland. Dr. Nikolich earned his Ph.D. at the University of Illinois at Urbana-Champaign in 1994 and has since done research at the WRAIR, devoting the past 8 years to developing live attenuated vaccines to protect humans against the bacterial biothreat agent *Brucella melitensis*.

Kathryn Nixdorff studied microbiology and biochemistry at the University of Florida and did postdoctoral research as an Alexander von Humboldt Fellow at the Max-Planck-Institute of Immunobiology in Freiburg, Germany. She was an instructor in the Department of Cell Biology, University of Kentucky Medical School, and is at present a professor in the Department of Microbiology and Genetics at Darmstadt University of Technology, Germany. She teaches microbiology and immunology and carries out research on molecular aspects of the interaction of microorganisms with cells of the immune system, in particular the regulation of proinflammatory cytokine production in macrophages. In addition, she is a founding member of the interdisciplinary research group concerned with science, technology and security (IANUS) at the university. In this

group she works on problems involving the development of biotechnology and its relevance for the control of biological weapons.

Jacques Ravel is an assistant investigator at the Institute for Genomic Research (TIGR), Rockville, MD, an innovative leading non-profit institution in the field of genomics and bioinformatics. He is a member of the Federal Bureau of Investigation's sponsored Scientific Workgroup on Microbial Genetic and Forensics (SWGMGF), which aims at establishing the baseline procedures for the emerging field of Microbial Forensics. His main research interests are in the fields of comparative genomic of microbial biothreat agents and the application of genomic technologies in microbial forensics. He is leading TIGR's effort in the FBI investigation of the anthrax mail attacks of the Fall 2001. Dr. Ravel received a Ph.D. degree in Microbial Molecular Ecology from the University of Maryland College Park. He also holds an adjunct appointment as an assistant professor at the Center of Marine Biotechnology, University of Maryland Biotechnology Institute in Baltimore.

Decio Ripandelli graduated in 1981 in Natural Sciences and Experimental Geology at the Pierre and Marie Curie University of Paris. In January of 1982 he joined AGIP, the Italian national oil company, and started his career with the United Nations system in August of 1984, by joining a technical assistance project in Tanzania. Other overseas assignments brought him to Niger (1987-1988) and the Philippines (1988-1989). In mid-1989 he entered the Italian Ministry for Foreign Affairs, where he was in charge of all the programs financed by the government of Italy through the UN specialized agencies in the fields of scientific, technological, and industrial cooperation. He joined ICGEB in 1991 and has been instrumental in organizing the Centre's autonomy from UNIDO. Presently, as Director for Administration and External Relations of ICGEB, he supervises the management of the Centre and of its two Components of Trieste and New Delhi, while being in charge of all ICGEB's external and international relations. He also directs the Institutional Services implemented by ICGEB, with major emphasis on biosafety, intellectual property rights, and international cooperation in the framework of the Biological Weapons Convention.

Amy Sands has been dean of the Graduate School of International Policy Studies at the Monterey Institute of International Studies since August 2003. Before assuming the position of dean, she had been deputy director of the Center for Nonproliferation Studies, also at the Monterey Institute, for the previous seven years. From August 1994 to June 1996, she was assistant director of the Intelligence, Verification, and Information Man-

agement Bureau at the U.S. Arms Control and Disarmament Agency (ACDA). Upon leaving the government, Dr. Sands received ACDA's Distinguished Honor Award and the On-Site Inspection Agency's Exceptional Civilian Service Medal. Before joining ACDA, she led the Proliferation Assessments Section of Z Division at the Lawrence Livermore National Laboratory. She is a member of the Council on Foreign Relations and the International Institute of Strategic Studies.

Nadrian C. Seeman received a B.S. in biochemistry from the University of Chicago and then went on to receive his Ph.D. in biological crystallography from the University of Pittsburgh in 1970. His postdoctoral training, at Columbia and MIT, emphasized nucleic acid crystallography. He obtained his first independent position at SUNY/Albany, where his frustrations with the macromolecular crystallization experiment and his awareness of the fatal series—no crystals, no crystallography, no crystallographer—led him to the campus pub one day in the fall of 1980. There, he realized that the similarity between six-arm DNA branched junctions and the flying fish in the periodic array of Escher's "Depth" might lead to a rational approach to the organization of matter on the nanometer scale, particularly crystallization. Ever since, he has been trying to implement this approach and its spin-offs, such as nanorobotics and nanoelectronics; for the past 16 years he has worked at New York University.

Jerome Amir Singh is Head of the Bioethics and Health Law Programme at the Center for the AIDS Programme of Research in South Africa (CAPRISA), Nelson R. Mandela School of Medicine, Durban, South Africa; Adjunct Professor in the Department of Public Health Sciences and Joint Center for Bioethics at the University of Toronto, Canada; and Course Director for Bioethics and the Law at Howard College School of Law, University of KwaZulu-Natal, Durban, South Africa. He serves on the International Research Ethics Board of Médecins Sans Frontières, the United States National Institutes of Health International Therapeutic Data Safety Monitoring Board, the Research Ethics Committee of the South African Human Sciences Research Council, and the Executive Committee of CAPRISA.

Patrick Tan holds a joint appointment as group leader at the Genome Institute of Singapore and principal investigator at the National Cancer Centre of Singapore. His research interests lie in the application of genome-level targeted technologies to understand how genetic differences at both the cellular and organismal level can influence the development of various diseases and other complex phenotypes. He received his B.A. (summa cum laude) from Harvard University, and M.D. and Ph.D. degrees

from Stanford University, where he received the Charles Yanofsky prize for Most Outstanding Graduate Thesis in Physics, Biology or Chemistry. Prior to joining GIS, Dr. Tan was a senior research fellow at the Defence Medical and Environmental Research Institute (Medical Biodefence Program) of the Defence Science Organization (DSO) in Singapore. He has published numerous articles in scientific journals such as *Cell*, *Science*, *Molecular Microbiology*, and *Genome Research*. Dr. Tan is also the chief scientific officer of Agenica Research, a cancer genomics joint venture between NCC, Mitsui Corp., and Shimadzu Corp., and the first collaborative research company established between Singapore and Japan.

Terence Taylor is president and executive director of the International Institute for Strategic Studies-US (IISS-US). He is also assistant director of the IISS in London. He studies international security policy, risk analysis, scientific and technological developments and their impact on political and economic stability worldwide. Mr. Taylor is one of the Institute's leading experts on issues associated with nuclear, biological, and chemical weapons and their means of delivery. He was one of the Commissioners to the UN Special Commission on Iraq for which he also conducted missions as a Chief Inspector. He was a research fellow on the Science Program at the Center for International Security and Cooperation at Stanford University where he carried out, among other subjects, studies of the implications for government and industry of the weapons of mass destruction treaties and agreements. He has also worked as a consultant for the International Committee of the Red Cross on the implementation and development of the laws of armed conflict and as a consultant for private companies on political risk analysis (both regional and country-specific). Prior to joining IISS Mr. Taylor worked as a political affairs officer at UN Headquarters in the Department for Disarmament Affairs and earlier for the UK Ministry of Defence as a member of the staff for the development of policy on arms control and non-proliferation measures on nuclear, biological, and chemical weapons. In this capacity he was a member of the UK negotiating team for Nuclear Nonproliferation Treaty review conferences, the Chemical Weapons Convention, and also a member of joint US/UK inspection teams in Russia investigating the biological weapons program in that country. He has also been a member of the UK delegation at the UN General Assembly's Committee on Disarmament and the UN Disarmament Commission. He served as a career officer in the British Army on operations in many parts of the world, including counterterrorist operations and UN peace keeping.

Tibor Toth is the Permanent Representative of Hungary to the United Nations Office and Other International Organizations in Geneva and the

Permanent Representative of Hungary to the Conference on Disarmament. For the past 20 years Ambassador Toth has been participating in a wide variety of multilateral conferences and bodies related to political, disarmament, economic, human rights, and humanitarian activities of the UN. He has served in various office-holder capacities in those fora. Since 1980 he has been participating in the work of the UN General Assembly and numerous codification and review conferences of political and arms control agreements. He served as permanent representative to the OPCW Preparatory Commission and as governor of the IAEA's Board of Governors. He has been the chairman of the CTBT Preparatory Commission's subsidiary body on administrative, financial and legal issues since 1997. In 1991, he began chairing a number of diplomatic conferences related to the Biological Weapons Convention.