Life Sciences and Related Fields

Trends Relevant to the Biological Weapons Convention

Committee on Trends in Science and Technology
Relevant to the Biological Weapons Convention:
An International Workshop

Board on Life Sciences
Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

In cooperation with

Chinese Academy of Sciences
IAP—the Global Network of Science Academies
International Union of Biochemistry and Molecular Biology
International Union of Microbiological Societies

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Preface

In 2006 the Royal Society, in cooperation with the International Council for Science, the InterAcademy Panel on International Issues (now IAP—the Global Network of Science Academies), and the U.S. National Academy of Sciences, organized a workshop that surveyed trends in science and technology (S&T). The objective was to provide an independent contribution from the international scientific community to the Sixth Review Conference of the Biological and Toxin Weapons Convention (BWC) that was held in December of that year.

At the time I was serving as chair of the Royal Society standing Committee on Scientific Aspects of International Security and so became chair of the S&T trends workshop. Among the lessons we learned from that workshop were that:

- Inviting researchers to describe the "state of the science" in their fields was a useful and productive strategy. Subsequent discussions drew out the potential implications of these advances and remaining challenges for the BWC.
- Input by technical experts from government and the policy community who engaged with the research scientists at the workshop was extremely valuable.
- The provision of adequate time for small-group discussion was important to enable participants to explore topics in greater depth and detail than was possible in plenary sessions.

- International scientific organizations can make a genuine contribution by assisting the BWC States Parties to gain a greater appreciation of the advances taking place in the life sciences and related fields, including the increasingly global nature of the research enterprise.

We applied the experience we garnered from this meeting when we embarked on organizing the second international workshop held in Beijing in November 2010. Again, this took the form of a partnership between several international scientific organizations and national academies.

The three main themes that emerged from this meeting resonate strongly with my own experience as an active researcher. Take the convergence of disciplines, for example; the major therapeutic advances in my own area (the pharmacology of inflammation) have come from the application of biotechnology, and in particular protein engineering, to the design of anti-inflammatory drugs. The "biologics," as these agents are known, have provided relief to countless sufferers from arthritis and other debilitating diseases. In fact, the very title of my own department—*Biochemical Pharmacology*—was originally chosen to indicate the growing conjunction of two life sciences.

Scientific research has always had a strongly international nature. My own group collaborates with laboratories around the world to take advantage of complementary skills and training facilities that other laboratories can offer. While such endeavors were once dependent upon personal visits or postal exchanges, the advances in communications technologies now enable us to share data and discuss our work in virtual as much as in actual laboratory settings. The many similar international efforts described in the Beijing workshop therefore rang true to me as capturing the reality of a genuinely global scientific enterprise.

I am very pleased to have had the opportunity to serve as the chair of the international committee that organized the second workshop and produced the subsequent report presented here. Planning and mounting such a conference as this is a daunting undertaking, and there are many people I would like to thank.

My colleagues on the committee made numerous suggestions for topics and speakers, helping ensure the broad representation of fields and countries at the workshop. They then played essential roles as session chairs and in some cases as speakers themselves.

We also benefited greatly from the assistance of the staff of three national academies, in particular:

- Neil Davison from the Royal Society;
- Katherine Bowman, Kathryn Hughes, Jo Husbands, and Ben Rusek from the National Research Council of the U.S. National Academy of Sciences (NAS); and

- Our hosts, Tao Xu, Institute Director, and members of his staff Lei Zhang, Xiaoke Xia, and Wei Yang from the Institute of Biophysics of the Chinese Academy of Sciences.

In addition to the practical work of the meeting, they served as rapporteurs for the plenary and breakout sessions, and contributed ideas for the final report. They were joined by James Revill of the University of Sussex, who served as an unpaid consultant and provided valuable support both during the workshop and to the NAS and Royal Society staff in the preparation of a subsequent factual summary of the workshop presentations, which was released in time for the Preparatory Committee of the BWC Review Conference in April 2011.

Everyone on the staff made significant contributions, but I do want to offer special thanks to Katherine Bowman. I first met Katie when she was a Christine Mirzayan Fellow at the National Research Council in 2006 and worked with us in organizing the first trends workshop. In addition to her work on the preparations for Beijing, Katie, along with Jo Husbands and Kate Hughes, made invaluable contributions to the drafting of this report. Their initial work made the committee's task much easier, and I want to express my deep appreciation for their efforts.

Roderick Flower
Chair

Acknowledgments

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

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

Robert Butera, *Georgia Institute of Technology, USA*
R. James Cook, *Washington State University, USA*
Gerald Epstein, *American Association for the Advancement of Science, USA*
Lewis R. Goldfrank, *New York University, USA*
Robert J. Mathews, *Defence Science and Technology Organisation, Australia*
Piers Millet, *United Nations, Switzerland*
Kathryn Nixdorff, *Darmstadt University of Technology, Germany*
Kaiming Ye, *University of Arkansas, USA*

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the

conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Edwin P. Przybylowicz,** *Eastman Kodak Company (retired)*. Appointed by the National Academies, he 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.

The Institute of Biophysics of the Chinese Academy of Sciences served as the host for the workshop in November 2010 and the Director-General, Dr. Tao Xu, welcomed participants to the event. In addition to the able leadership of Dr. Lei Zhang, Director of the International Liaison Office, Mr. Xiaoke Xia and Ms. Wei Yang helped to ensure the smooth and successful operation of the workshop.

Contents

Summary

S.1 INTRODUCTION

Over the past decade, national and international scientific organizations have become increasingly engaged in considering how to respond to the biosecurity implications of developments in the life sciences and in assessing trends in science and technology (S&T) relevant to biological and chemical weapons nonproliferation. The latest example is an international workshop, *Trends in Science and Technology Relevant to the Biological Weapons Convention,* held October 31-November 3, 2010, at the Institute of Biophysics of the Chinese Academy of Sciences in Beijing. The workshop and the subsequent final report are intended to be independent contributions from the international scientific community to the Seventh Review Conference of the Biological and Toxin Weapons Convention (BWC), which will be held in December 2011.

The workshop was planned by an international committee appointed by the National Research Council (NRC) of the National Academy of Sciences and convened in cooperation with IAP—the Global Network of Science Academies, the International Union of Biochemistry and Molecular Biology (IUBMB), the International Union of Microbiological Societies (IUMS), and the Chinese Academy of Sciences. The statement of task for the committee may be found in Box S.1 below; brief biographies of the members of the committee, information about the convening organizations, and the workshop agenda and participant list, may be found in Appendixes A-C of this report.

BOX S.1
Statement of Task

An ad hoc committee with significant international membership will be organized by the NRC to:

- Plan an international workshop to survey key trends in areas of science & technology (S&T) that might be potentially relevant to the development of new or more deadly biological weapons and/or to developments in detection, diagnostics, therapeutics, or vaccines that could affect potential prevention and response to biological attacks. The developments in science discussed at the workshop are likely to be in areas such as immunology, neuroscience, synthetic biology, aerosol and other controlled delivery mechanisms, or others; the specific S&T areas and trends to be discussed during the workshop will be selected by the committee.
- Prepare a report of the workshop that would provide findings, based on the consensus of the committee, about the state of the science in the topics discussed at the workshop. The report will also explore potential implications for the Biological Weapons Convention as an independent input from the scientific community to the treaty's Seventh Review Conference in 2011. The report would not make recommendations about actions to address any of the potential implications.
- In advance of the final report, a brief, staff-authored summary will be produced as a stand-alone document to provide a factual overview of the technical material presented by the speakers.

The workshop provided an opportunity for the scientific community to discuss the implications of recent developments in S&T for multiple aspects of the BWC (a brief description of the key provisions of several relevant BWC articles may be found in Box S.2). For example, a continuing question for the treaty's review conferences is whether scientific developments yield new or novel types of agents or materials that are not captured by Article I, which defines the scope of the treaty's prohibitions as "microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes." More broadly, however, developments in S&T also affect the other key articles of the convention that provide for the treaty's operation, such as the adequacy of national implementation of the convention through national policies and regulatory systems (Article IV), the capabilities to carry out investigations of alleged use of biological weapons (Article VI), and the design of international cooperation to ensure that all States Parties (i.e., those who have signed and ratified the agreement) have access to the benefits of peaceful applications of biology (Article X).

The meeting benefited from being able to draw on the diverse perspectives and active engagement of the participants through both plenary and breakout discussion sessions. Almost 80 scientists and policy makers from 28 countries and several international organizations took part in the workshop, with a mix of scientists and engineers currently engaged in research and technical experts from government and nongovernmental organizations, many of whom are also practicing scientists, who could help draw out potential implications for the BWC. The speakers for the S&T sessions were asked to focus on the "state of the science" with regard to their topics; in a few cases they also offered additional comments on the implications and applications for the BWC. The subsequent plenary discussions, and particularly the breakout sessions, further explored the implications. The workshop participants also discussed ways in which the BWC and its States Parties could continue to follow trends in S&T, including potential mechanisms for more systematic engagement with the scientific community.

Given the immense diversity of current research and development, the report is only able to provide an overview of the areas of science and technology the committee believes are potentially relevant to the future of the BWC, although there is an effort to identify areas that seemed particularly ripe for further exploration and analysis. The report offers findings

BOX S.2
Key Provisions of Several Relevant BWC Articles

- Never under any circumstances to acquire or retain biological weapons (Article I)
- To destroy or divert to peaceful purposes biological weapons and associated resources prior to joining (Article II)
- Not to transfer, or in any way assist, encourage or induce anyone else to acquire or retain biological weapons (Article III)
- To take any national measures necessary to implement the provisions of the BWC domestically (Article IV)
- To consult bilaterally and multilaterally to solve any problems with the implementation of the BWC (Article V)
- To request the UN Security Council to investigate alleged breaches of the BWC and to comply with its subsequent decisions (Article VI)
- To assist States which have been exposed to a danger as a result of a violation of the BWC (Article VII)
- To do all of the above in a way that encourages the peaceful uses of biological science and technology (Article X)

SOURCE: BWC ISU, 2011.

and conclusions organized around three fundamental and frequently cited trends in S&T that affect the scope and operation of the convention:

- The rapid pace of change in the life sciences and related fields;
- The increasing diffusion of life sciences research capacity and its applications, both internationally and beyond traditional research institutions; and
- The extent to which additional scientific and technical disciplines beyond biology are increasingly involved in life sciences research.

The report does not make recommendations about policy options to respond to the implications of the identified trends. The choice of such responses rests with the 164 States Parties to the Convention, who must take into account multiple factors beyond the project's focus on the state of the science.

S.2 PACE OF S&T DEVELOPMENTS

Continued progress is being made in a wide variety of S&T areas, although the committee did not identify any game-changing advances since 2006 that fundamentally alter the nature of life sciences research. Life sciences research continues to advance rapidly and is expected to do so for the foreseeable future. Key advances achieved in one field may also combine with developments in others to achieve new opportunities and new applications. One example is the interaction of research in fields such as immunology, neuroscience, and systems biology with developments in "omics" technologies such as genomics and proteomics, which undertake holistic analyses of a set of biological information to achieve a comprehensive understanding of its structure, function, interactions, and other properties. The results are providing scientists with information to better understand biological processes, helping to support a more complete understanding of human, animal, and plant variability and its relationship to disease, and identifying and characterizing new microbes and their roles in multiple environments. Scientists actively seek to integrate information at multiple levels in order to support rational engineering and design. Although advances in S&T are increasing the overall understanding of biological systems, the extraordinary complexity of biology and the challenges this complexity presents to the effective understanding and design of biological systems remain significant barriers; this complexity is likely to remain a defining feature of the biological sciences for the foreseeable future. Developments in S&T are also changing the nature of biological production, advancing delivery systems, and underpinning the ongoing development of biosensors and detectors.

There has been particularly rapid progress in both the availability and power of enabling technologies that underpin life sciences research, including computational resources, communication resources, and high throughput laboratory technologies. The computational power available to researchers continues to increase, through specialized stand-alone computers and through distributed computing networks. The use of high throughput sample handling and analysis methods has become widespread, and these tools increase the speed with which researchers can conduct studies as well as the volume of data they can obtain. At the same time, new methods of communication and information sharing enhance scientific collaboration and support research progress.

S.3 DIFFUSION OF RESEARCH AND CAPACITY

The increasingly widespread access and ease of use of communications technologies, combined with growing availability of resources to support research, are helping to support the continuing expansion of global research capacity and an ever larger number of international collaborations in science and technology. The workshop highlighted that international S&T collaborations are occurring not only among researchers in scientifically developed countries and between researchers in developed and developing countries, but also among regional networks and increasingly among scientists within developing countries. It also underscored that a growing number of "developing" countries already have impressive scientific sectors. Advanced S&T capacity is far from evenly distributed worldwide, and researchers in developing countries may still face problems in gaining access to resources and knowledge, but these trends are expected to continue and accelerate.

The continuing, rapid diffusion of research capacity and knowledge makes the commitments of States Parties in Article III to restrict access to knowledge, materials, and technologies for anything other than purposes permitted by the Convention more challenging. Given that there is little hope of reversing this trend—and multiple reasons beyond the commitments in Article X to see the diffusion as positive and beneficial—this argues for at least two important findings. First, it suggests the importance of continuing attention to monitoring and assessing the diffusion to try to anticipate any potential negative consequences and to strengthening the capacity of States Parties to address them, for example through their Article IV commitments to national implementation. Second, it underscores the potential for a much larger number of States Parties to contribute to the implementation of the Convention, for example by expanding global public health and disease surveillance capabilities, or playing leadership roles in capacity-building in their regions. Two examples, one current—

global disease surveillance—and one potential—developing scientific capacity in microbial forensics—illustrate the positive aspects of diffusion.

There is also another important form of diffusion: the increasing ability to do life sciences research outside traditional research institutions. In some cases these are trained researchers taking advantage of commercial kits and services, as well as the availability of secondhand equipment, to build their own laboratories and conduct experiments. In others it enables less trained practitioners to perform experiments without having the detailed biological or mechanistic understanding previously required in the life sciences. This is exemplified by innovative approaches to engaging students in hands-on research early in their studies and the expanding interest in what is frequently called "amateur," "garage," or "do-it-yourself" (DIY) biology. There are encouraging examples of initiatives from within and outside these communities to foster cultures of safety, security, and ethics, but it underscores the need to understand how training and know-how are propagated and cultures of safety are developed in such non-institutional environments.

However, although commercial life science kits and services and other advances such as standardized DNA parts provide efficiencies and ease of use, successful achievement of experimental goals generally relies on more than these products. Valuable knowledge and skills are also acquired through experience, and the importance of having these additional levels of knowledge increases with the complexity of the research projects undertaken.

S.4 INTEGRATION OF LIFE SCIENCES WITH OTHER DISCIPLINES

Life sciences research draws on the expertise not only of biologists, but also increasingly of scientists from engineering, physics, mathematics, computer science, chemistry, materials science, and many other disciplines. The multidisciplinary and integrative nature of modern life sciences research and the diversity of fields relevant to the future of the BWC were reflected in the Beijing workshop. The convergence of disciplines, particularly between biology and chemistry, may pose challenges to the operation of regimes like the BWC and the Chemical Weapons Convention (CWC). New scientific developments might alter or expand the types of agents that could be of concern as biological or chemical weapons or might alter or expand the definitions of which molecules fall under the purview of both treaties. As science continues to advance, the convergence of multiple disciplines, including the life, chemical, physical, mathematical, computational, and engineering sciences, will continue and the developments

that this convergence enables will be relevant to the BWC. The science community could play a role in exploring the technical understanding of converging S&T areas to help inform further policy discussions. The monitoring of scientific developments that integrate these fields and the assessment of their implications will need to draw on expertise from a range of disciplines.

S.5 DRIVERS AND ROADBLOCKS

Engaging a range of expertise within the scientific community, from academia, industry, and government, can contribute to efforts both to *monitor the state of science and technology* and to *assess the implications* of developments for the scope and operations of the BWC. In addition to tracking advances across diverse fields, the scientific community can contribute to a better appreciation of both the drivers and the roadblocks that broadly affect how S&T actually develops. Examples include the differential distribution of commercial markets for research products and the current challenge of developing mathematical models able to successfully capture the complexity of biological systems. Tracking and analyzing the impact of these forces should also be considered areas of potential interest for future monitoring of S&T trends. The report notes a number of current examples, and also suggests that an area for future in-depth analysis is the changing nature of tacit knowledge, of which intangible technology is a subset, as kits and other resources make it easier for less skilled individuals to carry out work that once required significant training.

S.6 LOOKING AHEAD: FUTURE APPROACHES TO MONITORING S&T TRENDS FOR THE BWC

The preparations for the Seventh Review Conference have highlighted the potential for adopting a more systematic process to monitor and assess developments in S&T. Whatever sort of mechanism is selected should depend on how the States Parties define their objectives in reviewing areas of S&T and the desired outcomes of the process. These decisions will impact both the types of activities that are undertaken and the timing of activities in order to most effectively meet these objectives. International scientific organizations are one potential resource for gaining access to a wide range of expertise to assist in understanding the "state of the science" and in assessing its implications.

Box S.3 presents the committee's nine findings about the state of science and technology and their relevance to the BWC.

BOX S.3
Findings

I. The committee did not identify any discoveries that fundamentally altered the nature of life sciences research since 2006. However, advances in S&T on many fronts have increased our overall understanding and exploitation of biological systems, despite their daunting complexity.

II. There has been particularly rapid progress in the power of, and access to, enabling technologies, especially those depending upon increased computing power. These include high throughput laboratory technologies and computational and communication resources. This has the following consequences:
- Collaborations between individual investigators, global networks of researchers, and the formation of "virtual laboratories" are growing trends in the life sciences.
- Increasing access to sophisticated reagents such as standardized DNA "parts" and easy-to-use commercial kits and services has placed some hitherto advanced technologies within the reach of less highly trained practitioners, and has expanded the global spread of life sciences research and its industrial applications.
- Although first class research continues to rely heavily upon tacit knowledge, the availability of web-based technologies is facilitating the transfer of tacit knowledge through the creation of worldwide formal or informal learning communities or partnerships.
- These technologies reduce the barriers to the spread of S&T knowledge for responsible, educational purposes, thus creating more favorable conditions for international cooperation in the peaceful application of the life sciences.
- At the same time, we must recognize that these same barriers also serve as impediments to misuse. This is an area that would benefit from more in-depth analysis to gain a more nuanced understanding of the developments and trends and their impact on the norm against biological weapons.

III. Multiple disciplines, including the life, chemical, physical, mathematical, computational, and engineering sciences, are converging. This trend will continue and is relevant to the BWC as well as the CWC. The impact of this convergence on the existing arms control system must be better understood in order to draw conclusions about whether adaptations in the application of the existing regimes may be required, and if so, what they should be.

IV. The field of bioreactor research and the use of transgenic organisms to produce commercially or medically important proteins have seen impressive advances. These have reduced the time needed to produce proteins and have the potential to affect the scale of the facilities required. This has obvious implications for the BWC, for example with regard to the measures States Parties need to take to implement the BWC and to prevent the use of biological or toxin agents for hostile purposes.

V. The development of microbial forensics illustrates one way that life sciences research from around the world can support the BWC and create better

tools to investigate and discriminate between natural and deliberate disease outbreaks.

VI. Notable technical advances have been made at the level of individual-use biosensor detector systems, although there are limitations to what can be achieved given that sensor development must balance factors such as specificity, sensitivity, range of target molecules analyzed, and type of use.

VII. The combination of approaches including improved biosensors, epidemiological monitoring, vaccine research, forensics, and other laboratory investigations can contribute to effective disease detection, investigation, and response systems worldwide.

VIII. These advances underscore the potential for more States Parties to contribute to the implementation of the BWC, for example by expanding their global public health and disease surveillance capabilities, or by playing leadership roles in capacity building in their regions.

IX. Certain scientific and technical roadblocks (e.g., drug delivery technologies) impede future progress, but once overcome, would presage a phase of rapid development. The international scientific community can play a useful role in tracking trends and developments in S&T. Its continued engagement with the BWC is essential to identifying these key scientific hurdles and when they have been overcome.

S.7 CONCLUSIONS

Many of the committee's individual findings about particular developments in S&T will not surprise those who follow trends in research that are potentially relevant to the BWC. Taken together, they represent the S&T reality in which the Convention is now operating and the challenges and opportunities this reality poses for the Seventh Review Conference. They also lead the committee to four general conclusions:

Conclusion 1: None of the trends surveyed for this report currently falls outside the scope of Article I. The language of the treaty, as reinforced by the common understandings reached in prior review conferences, provides a degree of flexibility that has so far allowed it to adapt to progress in the life sciences and related scientific fields. The committee recognizes, however, that as new developments arise, including in fields of research that this report did not assess in depth, there may be surprise discoveries; hence, continued monitoring of advances in the life sciences and evaluation of their relevance for the BWC will be important.

Conclusion 2: Beyond the question of whether these trends pose fundamental challenges to the scope of the treaty, every major article of the treaty will be affected by the developments surveyed. The trends may pose challenges to the implementation of some aspects, but they also offer important opportunities to support the operation of the convention.

Conclusion 3: The three broad trends that provided the organization of the report—the increasing pace, diffusion, and convergence of S&T—will continue for the foreseeable future. The diversity of the fields potentially relevant to the BWC and the potential for surprise discoveries make efforts to predict developments problematic. Within these trends, however, particular fields will be affected in important ways by factors such as commercial interests that drive developments at different rates, as well as roadblocks that impede progress. Gaining a deeper understanding of the drivers and roadblocks would provide a more meaningful picture of how and when continuing S&T developments are likely to affect the convention.

Conclusion 4: There are potential roles for the scientific community in helping to monitor trends in S&T and to assess their implications for the BWC, and there are a number of mechanisms by which input and advice could be provided. The most effective starting point for the Seventh Review Conference, therefore, would be to address the functions that such advice and analysis will serve for the future operation of the convention, including increasing the capacity of States Parties to participate fully in its implementation.

1

Introduction

1.1 BACKGROUND

As part of the preparations for the Seventh Review Conference of the Biological and Toxin Weapons Convention (BWC),[1] a group of national and international scientific organizations held a workshop in Beijing, China, in November 2010 to provide independent input from the scientific community about trends in science and technology (S&T) relevant to the convention. The workshop provided an opportunity to discuss the implications of recent developments in S&T in diverse fields such as immunology, neuroscience, synthetic biology, and drug and gene delivery mechanisms that are potentially relevant to new or more deadly biological weapons or bioterrorism, as well as for detection, diagnostics, therapeutics, and vaccines that affect potential prevention and response to biological attacks. The workshop drew on the scientific community's expertise in identifying the state of research in the life sciences. It did not address the question of policy options to respond to the implications of the identified trends, because the choice of such responses rests with the 164 States Parties to the Convention, who must consider multiple factors beyond the state of the science.

As described below, the workshop is the most recent example of the continuing engagement by national academies, international scientific organizations, and individual scientists and engineers in assessing trends

[1] The full name of the agreement is the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction.

in S&T relevant to nonproliferation and disarmament. It also reflects the increasing involvement of the scientific community in addressing the broader implications of continuing advances in the life sciences that, while yielding great benefits for health, the economy, and the environment, are producing knowledge, tools, and techniques with the potential to cause greater physical and psychological damage and loss of life than many natural disasters.[2]

The workshop was convened under the auspices of IAP—the Global Network of Science Academies, the International Union of Biochemistry and Molecular Biology (IUBMB), the International Union of Microbiological Societies (IUMS), the Chinese Academy of Sciences (CAS), and the National Research Council (NRC) of the U.S. National Academies. The CAS Institute of Biophysics hosted the workshop, and an international steering committee assembled by the NRC organized the workshop in collaboration with the other partners. The steering committee also took responsibility for preparing a final report that would draw on the workshop and other information to reach findings and conclusions about S&T trends and developments and their implications for the BWC (see Box 1.1 for the committee's statement of task). Brief biographies of the steering group members may be found in Appendix A; information about the convening organizations as well as other important international science bodies may be found in Appendix B. Support for the workshop came from a variety of public and private sources.[3]

Almost 80 participants from 28 countries and several international organizations took part in the workshop. The participants included practicing scientists from a variety of research institutions as well as technical and policy experts from governments and nongovernmental organizations. The 2.5-day meeting combined plenary sessions featuring talks by researchers about current developments across a range of S&T areas and smaller discussion groups to allow for more in-depth exploration of the implications of these developments for the BWC. Toward the end of the workshop the participants also discussed the impact of improved communication technologies on scientific collaboration and examined options for providing input from the scientific community to the BWC on a more structured and sustained basis. The workshop agenda and a list

[2] For further information about this engagement, see the introductory chapters of the reports arising from two earlier international workshops (NRC, 2009a, 2011a). The current benefits and promises of advances in the life sciences are addressed, for example, in *A New Biology for the 21st Century* (NRC, 2009b) and *The Bioeconomy to 2030: Designing a Policy Agenda* (OECD, 2009).

[3] Support was provided by the Alfred P. Sloan Foundation, IAP, U.S. National Academies, CAS, U.K. Global Partnership Programme, U.S. Defense Threat Reduction Agency, U.S. National Institutes of Health, and U.S. Department of State.

BOX 1.1
Statement of Task

An ad hoc committee with significant international membership will be organized by the NRC to:

- Plan an international workshop to survey key trends in areas of science & technology (S&T) that might be potentially relevant to the development of new or more deadly biological weapons and/or to developments in detection, diagnostics, therapeutics, or vaccines that could affect potential prevention and response to biological attacks. The developments in science discussed at the workshop are likely to be in areas such as immunology, neuroscience, synthetic biology, aerosol and other controlled delivery mechanisms, or others; the specific S&T areas and trends to be discussed during the workshop will be selected by the committee.
- Prepare a report of the workshop that would provide findings, based on the consensus of the committee, about the state of the science in the topics discussed at the workshop. The report will also explore potential implications for the Biological Weapons Convention as an independent input from the scientific community to the treaty's Seventh Review Conference in 2011. The report would not make recommendations about actions to address any of the potential implications.
- In advance of the final report, a brief, staff-authored summary will be produced as a stand-alone document to provide a factual overview of the technical material presented by the speakers.

of participants may be found in Appendix C. A factual summary of the plenary workshop presentations was published previously (NRC, 2011c) and presented at the meeting of the Preparatory Committee for the Seventh Review Conference in April.[4]

Given the vast and growing diversity of research in the life sciences and other relevant areas of S&T, the workshop and this report necessarily represents a selection and a snapshot of developments that may be relevant to the future of the BWC. The organizing committee selected the topics and speakers for the workshop by

- Drawing on the committee members' own expertise;
- Seeking the advice of others in the scientific community; and
- Consulting with experts in government and international organizations with responsibility for the BWC and broader biological and chemical nonproliferation and disarmament.

[4] The report is available at http://www.nap.edu/catalog.php?record_id=13113; most of the presentations may be found at http://dels.nas.edu/Past-Events/Trends-Science-Technology-Relevant/DELS-BLS-09-06/4752.

In addition to new and cutting-edge developments, the committee also included updates on a number of the topics addressed in the earlier workshops on S&T relevant to the BWC and the Chemical Weapons Convention (CWC) described below. As noted above, the S&T sessions featured talks on the "state of the science" while the subsequent discussions and breakout sessions were designed to put the developments into context and bring out the implications for the BWC. The report is built on the presentations in Beijing but draws on additional sources.

1.2 THE BIOLOGICAL WEAPONS CONVENTION AND S&T

1.2.1 An Overview of the Biological Weapons Convention

The BWC, which was opened for signature in 1972 and entered into force in 1975, was the first international disarmament agreement to ban an entire class of weapons. It built upon the 1925 Geneva Protocol, which banned the use of chemical and biological weapons.[5] Together these agreements embody the international legal norm against the use of disease as a weapon. A short (approximately four-page) document, the BWC's major articles call upon member states:

- Never under any circumstances to acquire or retain biological weapons (Article I)[6]
- To destroy or divert to peaceful purposes biological weapons and associated resources prior to joining (Article II)
- Not to transfer, or in any way assist, encourage or induce anyone else to acquire or retain biological weapons (Article III)
- To take any national measures necessary to implement the provisions of the BWC domestically (Article IV)
- To consult bilaterally and multilaterally to solve any problems with the implementation of the BWC (Article V)
- To request the UN Security Council to investigate alleged breaches of the BWC and to comply with its subsequent decisions (Article VI)

[5] The Geneva Protocol's formal title is the Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare. Reservations filed by some States Parties meant that, for them, the Protocol became in effect a no-first-use undertaking.

[6] "The Fourth and Sixth Review Conferences reaffirmed *that the use by States Parties, in any way and under any circumstances, of microbial or other biological agents or toxins, that is not consistent with prophylactic, protective* or other peaceful purposes, is effectively a violation of Article I [VI.I.3, IV.I.3]" (United Nations, 2007:4).

- To assist States which have been exposed to a danger as a result of a violation of the BWC (Article VII)
- To do all of the above in a way that encourages the peaceful uses of biological science and technology (Article X).[7] (BWC ISU, 2011)

As of early 2011, 164 nations had become States Parties and an additional 13 countries had signed but not ratified the BWC.[8]

As with other international agreements related to weapons of mass destruction, conferences are held at regular intervals, in this case every five years, to review the operation of the BWC and to make plans for its future. In addition, for the past decade the BWC has carried out a unique set of activities. After efforts to negotiate a protocol to provide verification of treaty compliance failed in 2001, the States Parties agreed in 2002 to a series of annual meetings before the next full treaty review conference in 2006. Each year's meeting focused on a different topic and included both a one- or two-week meeting of experts and a one-week meeting of the States Parties. This program of intersessional meetings was continued between 2007 and 2010.[9]

1.2.2 S&T Reviews and Assessments

Developments in S&T affect the BWC in several important ways. One key issue is the impact of S&T on the treaty's scope: Could developments yield new or novel biological agents or toxins that are not captured by Article I, which covers "[m]icrobial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes"?[10] S&T developments can affect the balance between potential offensive and defensive applications of biology for purposes of warfare, and therefore the risks associated with new discoveries. Furthermore, developments can impact all of the major articles of the convention by assisting or complicating the tasks associated with the treaty's operation, such as the design of national policies and regulatory systems, investigations of alleged use, and the forms and types of international cooperation to promote peaceful applications of biology.

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[7] The full text of the convention is available at http://www.un.org/disarmament/WMD/Bio/pdf/Text_of_the_Convention.pdf.

[8] Another 18 countries have not signed, ratified, or acceded to the treaty.

[9] Information about intersessional meeting topics and an extensive collection of materials from the meetings are available at http://www.unog.ch/80256EE600585943/(httpPages)/92CFF2CB73D4806DC12572BC00319612?OpenDocument as well as in Millet (2011).

[10] The series of understandings reached at various review conferences that the general purpose criterion in Article I does capture all relevant S&T may be found in United Nations (2007).

Article XII of the Convention called for a review conference to assess progress in the treaty's implementation within five years of its entry into force. The review was to "take into account any new scientific and technological developments relevant to the Convention." Although the treaty text called for only the initial review, such conferences have been held at regular intervals, with the Sixth Review Conference in 2006 and the Seventh Review Conference to be held in December 2011. Discussions of S&T developments take place primarily as part of the preparations for the review conferences; for example, some States Parties contribute formal background papers related to S&T and the United Nations (UN) secretariat unit assigned to support the treaty may offer other papers and material as well. At the review conference itself, the final documents typically note the papers and the importance of S&T but do not address the question of potential effects of new developments on the treaty's scope (Article 1).

The range and variety of discussions within the BWC relevant to S&T have grown in recent years. The intersessional meetings are good examples. They have covered topics that touch directly on the interests of the scientific community (e.g., codes of conduct in 2005, education and research oversight in 2008) and topics where advances in S&T are integral to the discussions (e.g., public health and disease surveillance in 2004 and 2009, investigations of alleged use in 2010). Prominent scientists have been invited to address the meetings as guests of the chair, panels have been organized to examine particular S&T topics, either in plenary sessions or as side events, and poster sessions have provided the opportunity to explore topics in greater depth and detail. In addition, an increasing number of countries have included scientific and technical experts from outside government in their delegations. A quick review of the materials from the meetings posted on the BWC's website underscores the extent of these connections.[11] The intersessional meetings have been invaluable in catalyzing discussions within the international scientific community with respect to scientific responsibility—between scientists about their responsibilities under the Convention, between scientists from different countries, and between scientists and their own countries' policy makers (NRC, 2009a, 2011a).

There is also a sense that the pace and scale of advances in S&T—not only in the life sciences but also in increasingly connected areas of the physical sciences, such as chemistry and engineering—will have a growing impact on the BWC in the future. The reports of the 2006 review conference and the 2008 States Parties meeting, for example, include calls for greater attention by the States Parties to the potential impact of these

[11] See http://www.unog.ch/80256EE600585943/(httpPages)/92CFF2CB73D4806DC12572BC00319612?OpenDocument.

developments (BWC, 2006, 2008). In his message to the BWC Meeting of States Parties in December 2010, UN Secretary General Ban Ki-moon emphasized S&T.

> Next year, the Seventh Review Conference will consider how to build upon this work [the intersessional process]. Indeed, that meeting offers the best chance in a decade or more to reach significant agreements on the future of the Convention. With the pace of advances in biological science and technology growing ever quicker, there is a pressing need for a structured and regular means of monitoring developments and assessing their implications.
>
> While much is being done to promote assistance and cooperation for the peaceful uses of biological science and technology, more could still be done to improve coordination and communication. I wish you well as you consider various proposals aimed at exploring practical approaches for strengthening the Convention and promoting its full implementation. (Ban, 2010)

1.3 ADVISING ABOUT S&T: THE GROWING ROLE OF INTERNATIONAL SCIENTIFIC ORGANIZATIONS

Taking account of the developments in S&T in ways that are useful to the BWC will require an understanding of the details within broad trends, including the forces that drive different aspects at different rates and the inevitable roadblocks that hamper progress. It also requires engaging a range of experts within the scientific community, including academic, industrial, and government experts who can contribute to efforts both to *monitor the state of science and technology* and to *assess the implications* of developments for the scope and operations of the BWC.

Over the past decade, a number of national and international scientific organizations have taken an increasing interest in the implications of S&T developments for security. One of their contributions has been a series of workshops designed to provide independent input into the treaty review conferences for the BWC and CWC.

1.3.1 The First IUPAC-OPCW Workshop (2002)

The Organisation for the Prohibition of Chemical Weapons (OPCW) has a formal Scientific Advisory Board (SAB), whose members are appointed by the OPCW Director General based on nominations provided by member states of the Convention. As the First Review Conference for the CWC approached, the SAB and OPCW staff recognized the benefits of engaging the wider chemical sciences community to offer

perspectives on trends in chemical sciences and technology. OPCW approached the International Union for Pure and Applied Chemistry (IUPAC; see Appendix B for further information) to organize a workshop to provide input into the preparations for the review conference. This was the first time an independent scientific organization had been invited to contribute directly to an arms control treaty review conference.

IUPAC had limited experience with arms control and disarmament, but had worked previously with OPCW on CW destruction technologies.[12] Because IUPAC did not have the staff to support the workshop, its headquarters was in the United States, and the U.S. National Academy of Sciences (NAS) was the formal U.S. adhering body to IUPAC, the NAS served as the workshop secretariat. Private foundations and the NAS funded the workshop.

The workshop, held in July 2002 in Bergen, Norway, was attended by 79 participants from 34 countries, including several members of the SAB, as well as a number of representatives from National Authorities and other government technical experts.[13] The workshop addressed both advances in S&T that could potentially be misused for weapons development and terrorist purposes and advances in areas such as analytical methods that could enhance the implementation of the convention. Later in 2002, a detailed report to OPCW was sent to all States Parties and reprinted, along with papers from the workshop lectures, in the IUPAC journal *Pure and Applied Chemistry* (IUPAC, 2002).

1.3.2 The IAP-ICSU-Royal Society Workshop (2006)

In anticipation of the Sixth BWC Review Conference, a number of scientific organizations decided to use the model from the IUPAC workshop to undertake an effort to provide independent input. The international

[12] See, for example, Pearson and Magee (2002).

[13] "To make sure that the CWC is implemented effectively, States Parties are obliged to designate or establish a National Authority. This body escorts OPCW inspections of relevant industrial or military sites; submits initial and annual declarations; assists and protects those States Parties which are threatened by, or have suffered, chemical attack; and fosters the peaceful uses of chemistry. In addition, the National Authority acts as the focal point in the State Party's interaction with other States Parties and the Technical Secretariat of the OPCW" (OPCW website, http://www.opcw.org/about-opcw/member-states/national-authorities/, accessed February 3, 2011).

partners were the Biosecurity Working Group of IAP[14] and the International Council for Science (ICSU), the parent body for IUPAC and the many unions in the life sciences (see Appendix B for further information). The Royal Society served as the workshop's host and lead organizer, and the NAS took an active part in the workshop planning.

Held at the Royal Society in September 2006, the workshop included 84 people from 23 countries and several international organizations. It provided an opportunity for scientists as well as governmental and nongovernmental technical and policy experts to discuss the potential implications of recent developments in the life sciences. Topics at the meeting included "post-genomic" technologies,[15] immunology, drug discovery and delivery, agricultural and environmental biotechnology, diagnosis and surveillance of infectious diseases, and responsible stewardship of scientific research. Among the workshop's conclusions was the increasing convergence of technological developments relevant to both the BWC and the CWC, complicated by the great difficulty of predicting what technological developments will be and where they will occur. The workshop underscored the need to consider a broader threat spectrum, which requires "thinking beyond bugs" and further blurs the boundaries among areas of emerging technologies. An initial summary of the meeting's key findings was circulated to all the BWC States Parties (Royal Society, 2006a). A report based on discussions from this workshop was disseminated prior to the Sixth Review Conference and was presented at a lunch seminar during the conference (Royal Society, 2006b).

[14] In 2004 IAP had created a Biosecurity Working Group composed of the academies of China, Cuba, the Netherlands (chair until 2009), Nigeria, the United Kingdom, and the United States. (In early 2010 the Polish Academy of Sciences became the chair of the Biosecurity Working Group. Current members of the Working Group also include the academies of Australia, Egypt, and India.) The Working Group has undertaken a number of activities related to security issues in the life sciences, including preparing the 2005 IAP Statement on Biosecurity, which was presented to the 2005 BWC Meeting of Experts and Meeting of States Parties, and organizing two International Forums on Biosecurity, one in 2005 and one in 2008. A more detailed account of the activities of the Working Group may be found in two reports of meetings organized in collaboration with other international scientific organizations (NRC, 2009a, 2011a).

[15] Topics included the potential to identify previously uncultured microorganisms using metagenomics approaches; efforts to understand gene regulation, protein synthesis, and biological pathways using transcriptomics, proteomics, bioinfomatics, and systems biology; the potential of synthetic biology to engineer microorganisms with designed properties; and the possibility of employing genetic targeting.

1.3.3 The Second IUPAC-OPCW Workshop (2007)

As the Second CWC Review Conference approached, OPCW again asked IUPAC to organize a workshop on trends in chemical sciences and technologies as an independent contribution. This time the preparations began in late 2006 to ensure that the report would be completed in time to support the preparations for the review conference in 2008, and OPCW provided support for a substantial portion of the workshop costs. The NAS again served as secretariat, which offered an opportunity to continue some of the substantive discussions begun at the IAP-ICSU-Royal Society meeting. The meeting also provided an opportunity to discuss issues and mechanisms for providing scientific advice to international bodies.

The workshop, held in Zagreb, Croatia, in April 2007, in collaboration with the Croatian Academy of Sciences and Arts and under the auspices of the Zagreb city government, was attended by 68 participants from 30 countries, again including members of the SAB, as well as representatives of National Authorities and other government technical experts. Workshop sessions included a wide range of presentations on the context of the CWC; trends in the chemical industry; developments in chemical synthesis, analysis and production technology, including microreactors; and advances in fields such as nanotechnology and decontamination technology. Expert commentary on the presentations helped link the scientific and technical developments to policy issues facing the CWC. The summary report of the meeting was delivered to OPCW in July 2007 and later published in *Pure and Applied Chemistry* (Balali-Mood et al., 2008).

The 2010 workshop in Beijing follows directly from the experience gained by the international scientific organizations involved in planning these previous workshops on S&T trends. Although IUPAC was not one of the convening organizations, several of the key leaders from the CWC workshops took part in the workshop.

1.4 POTENTIAL POSITIVE AND NEGATIVE APPLICATIONS OF ADVANCES IN THE LIFE SCIENCES

A starting point for the committee's report is the longstanding recognition among scientists, policy makers, and civil society that the application of scientific knowledge and skills, which promises enormous benefits, also potentially enables the creation of products that may cause injury or death. This potential extends beyond the security implications addressed in this report to include other effects on human, plant, and animal health, the environment, the economy, and the safety of those conducting scientific and technical work. With regard to security, as depicted in Figure 1.1, there is a hierarchy of increasingly advanced life sciences techniques, beginning with basic laboratory skills and moving toward sophisticated areas of

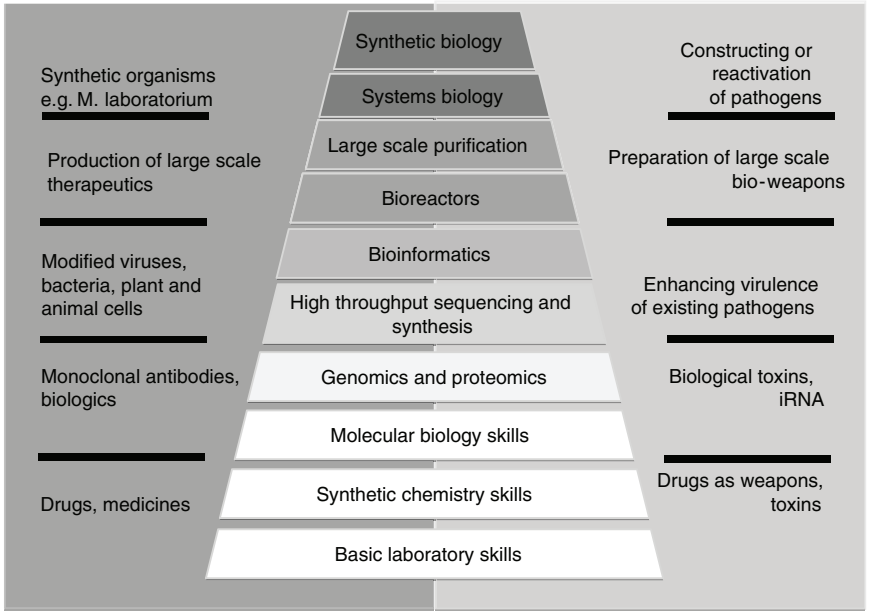

FIGURE 1.1 Dual use in the life sciences.
SOURCE: Flower (2011).

research such as systems and synthetic biology. At each level of increasing sophistication, science could be applied to yield fundamental advances in understanding and create products such as new therapeutics. These advances could also have a "dual use" potential by being directed toward the creation of toxins or pathogens that might serve as bioweapons or of improved ways to deliver them. The pyramid also illustrates the wide range of life sciences research beyond microbiology that is potentially relevant to BWC discussions.

At the pyramid's base, laboratory and synthetic chemistry skills can be employed to create new medicines and other beneficial drugs. Alternatively, such skills could be directed toward synthesizing chemicals used for weapons. Farther up the pyramid, modern "omics" sciences like genomics and proteomics coupled with molecular biology techniques in areas like recombinant DNA and cell transfection[16] can be used to generate beneficial biological products like monoclonal antibodies and therapeutic proteins. Knowledge of these techniques can also be used to

[16] *Transfection* refers to the transfer of genetic material such as DNA into a cell, particularly by nonviral means. When a virus is used to transfer genetic material (for example, for the purpose of viral gene therapy), this process is frequently referred to as *transduction*.

produce protein toxins derived from pathogens, whose cell-damaging properties can be harnessed to combat cancer (Cimini et al., 2011; Lorberboum-Galski, 2011; Weldon and Pastan, 2011), for example,[17] but could also be misapplied as toxin weapons. Advances in the understanding of mechanisms that influence gene expression, such as RNA interference (RNAi), can be employed to silence targeted genes but can potentially be used to manipulate gene expression systems for harm. At the next level of the pyramid, the growth of high throughput sequencing and synthesis and the analysis of the massive amount of data generated by these technologies using bioinformatics tools have formed the basis for more sophisticated biological modification. Life sciences production technologies such as bioreactors also have dual uses—enabling the large-scale production either of therapeutics or of materials for biological weapons in ways that can be hard to detect. Finally, toward the top of the pyramid, rapidly developing fields like systems and synthetic biology integrate knowledge in many of the areas represented on the diagram along with converging areas of chemistry and engineering. Research in these fields holds the promise of greater physiological understanding and, ultimately, the rational design and manipulation of organisms. The current states of development in many of the areas of life sciences and related enabling S&T that form the blocks of the Figure 1.1 pyramid, along with some of their potential implications, are discussed in more detail in the subsequent chapters of the report.

Several additional important points must be kept in mind with regard to Figure 1.1. First, a given scientific technique or field of study is not *in itself* either beneficial or harmful; rather, scientific knowledge can be applied to more than one purpose. Research that leads to the creation of a modified virus or toxin, or seeks a deeper understanding of its mechanism of action, might have legitimate and beneficial purposes, but might in some cases require additional biosafety and oversight measures.

Over the years, recognition of this potential for benefits and risks has led to the development of a variety of approaches to address the risks while ensuring that scientific and technological progress can continue. The approaches affect:

- whether particular experiments or in some cases particular lines of research are undertaken, e.g., experiments involving aspects of recombinant DNA, stem cells, or gene therapy;

[17] A number of experiments with so-called "dual use" potential, that is, to be used for harmful purposes even though the research is intended for beneficial ends, are discussed in NRC (2004) and presented as case studies in online education modules from the Federation of American Scientists (see http://www.fas.org/biosecurity/education/dualuse/index.html).

- how research is carried out, e.g., with regard to biosafety and biosecurity, as well as the treatment of animals and human subjects; and
- what is considered appropriate conduct by the researchers themselves.

Laws, regulations, and guidelines from national, regional, and international sources are all included, as is a significant component of self-governance by the scientific community.[18] The approaches evolve over time, for example, in response to factors such as increasing knowledge of relative risks and changing attitudes toward what level of risk is acceptable.

The potential dual use of life sciences knowledge, tools, and techniques reinforces the need for the scientific community to be aware of the norms of responsible and appropriate scientific conduct, as well as international and national legal requirements. Over the past decade, national and international scientific organizations having become increasingly engaged in issues related to the responsibilities of the scientific community to help reduce the risks of misuse of life sciences research (Bowman et al., 2011; IAP, 2005; NRC, 2004, 2006a, 2009a,c, 2011a; OECD, 2004; Royal Society and Wellcome Trust, 2004; WHO, 2005, 2007a). Scientists can also play a useful role in communicating with policy makers and civil society to help them understand the nature, applications, and potential positive and negative implications of developments in their field. Perspectives from the scientific community can contribute to discussions of how to create the best mix of policies and practices to achieve safety and security without unduly hampering global scientific progress for beneficial applications. This is the motivation and foundation for the workshop and the committee's report.

1.5 ORGANIZATION OF THE REPORT

This report represents the findings and conclusions of the ad hoc international committee organized by the National Research Council of the U.S. NAS under its standard procedures. It draws heavily on the discussions at the Beijing workshop but also on the committee members' expertise and additional data gathering. Chapters 2–4 discuss three fundamental trends that appear frequently in discussions of how advances in S&T may affect the convention:

- The rapid pace of change in the life sciences and related fields;
- The increasing diffusion of life sciences research capacity and its applications, both internationally and beyond traditional research institutions; and

[18] The discussions at the 2008 Meetings of Experts and State Parties highlighted many of the approaches; see BWC (2008) and the materials at http://www.unog.ch/80256EE600585943/(httpPages)/92CFF2CB73D4806DC12572BC00319612?OpenDocument.

- The extent to which additional scientific and technical disciplines beyond biology are increasingly involved in life sciences research.

These themes are discussed in more detail in the following three chapters and illustrated with representative examples. The selection of topics for each chapter is necessarily somewhat arbitrary. Many of the topics could appear in more than one chapter, and cross references are provided where appropriate.

Chapter 5 addresses a number of topics. As an introduction, it provides a discussion of the drivers of S&T development, along with roadblocks to progress, that span the various trends examined in the report and that have important implications for how they will develop in the future. It also reviews some of the ideas about how the BWC might most usefully address continuing S&T developments in the future. The chapter then provides the committee's overall findings and conclusions about the trends in S&T and their implications. Again reflecting the committee's charge—and the pattern successfully established in the other trends workshops—the report considers the state of life sciences research but does not make recommendations for national or international policy in response to the identified findings and conclusions.

2

The Pace of Developments in the Life Sciences

As the range of presentations covered at the workshop illustrates, the meeting surveyed developments in the life sciences broadly. Although it was not able to cover all possible topics in depth, the committee sought to identify major themes and trends and then to consider ways in which these scientific developments might relate to the Biological and Toxin Weapons Convention (BWC). The committee's discussions were guided by the three major trends identified in Chapter 1:

- The pace of relevant advances in science and technology (S&T) and in related, enabling technologies;
- The diffusion of S&T research and its applications; and
- The breadth of fields now engaged in the "life sciences."

This chapter examines the first of these trends.

2.1 ADVANCES IN SCIENCE AND TECHNOLOGY

2.1.1 Developments Since 2006

As the message from United Nations Secretary General Ban Ki-moon to the BWC States Parties in 2010 (see Chapter 1) illustrates, one of the important trends that potentially affects the future of the BWC is the rapid pace of advances in S&T. The 2010 workshop provided the international scientific community with an opportunity to review major developments in S&T since the 2006 meeting organized by IAP, the International Council

for Science, and the Royal Society. Many of the subject areas discussed in 2010 echoed those that were highlighted in 2006, including the "omics" fields,[1] synthetic biology, delivery technology, and vaccine and countermeasures development. The workshop reviewed not only the potential to apply areas of S&T to the creation or delivery of biological agents that could be employed as weapons, but also to prevention, defense, and response against the misuse of biological agents, and to the promotion of beneficial uses of biology. Progress continues to be made in many of the research areas discussed in 2006 and 2010. Examples of key developments in advancing areas of life sciences are highlighted below. Particularly rapid developments have also occurred in enabling technologies and are discussed in more detail in Section 2.2.

2.1.2 Genomics, Systems Biology, and Synthetic Biology

Developments

Since the draft sequence of the human genome was published in 2001 and the completed sequence announced in 2003 (HHS and DOE, 2003; International Human Genome Sequencing Consortium, 2004), the sequencing of additional human genomes has proceeded rapidly. A variety of large-scale collaborative genome sequencing initiatives have been undertaken, such as the international 1000 Genomes Project to catalogue human genetic variation as a resource for future biomedical research, which was mentioned at the workshop (The 1000 Genomes Project Consortium, 2010). A recent article on worldwide human genome sequencing efforts notes, "although far from comprehensive, the tally indicates that at least 2,700 human genomes will have been completed by the end of this month [October 2010], and that the total will rise to more than 30,000 by the end of 2011" (Nature, 2010). A significant proportion of this increased sequencing capacity is expected to come from China, where BGI (formerly the Beijing Genomics Institute) is now one of the

[1] "Omics" fields in the life sciences generally refer to the holistic analysis of a set of biological information, in order to achieve a comprehensive understanding of its structure, function, interactions, and other properties. Omics fields include genomics, the study of the complete DNA sequence of an organism; metagenomics, the identification and analysis of the genomes of a community of organisms without first culturing and separating them; transcriptomics, the analysis of the set of RNA transcripts expressed by a cell, tissue, or organism; proteomics, the study of the set of expressed proteins that result from these transcripts; interactomics, the analysis of interactions among the molecules in a cell; metabolomics, the study of the cellular metabolites produced by the cell, tissue, or organism; and many others.

world's largest sequencing centers[2] and reportedly predicted in 2010 that it would complete 10,000 to 20,000 human genomes by the end of 2011 (Nature, 2010). Beyond human genome sequencing, international collaborations are under way to sequence 1,000 plants and animals of economic and scientific importance (Fox and Kling, 2010) and to characterize the earth's microbial communities from the soil, air, and water through the Earth Microbiome Project. The project, launched in 2010, plans to "analyze 200,000 samples from these communities using metagenomics, metatranscriptomics and amplicon sequencing to produce a global Gene Atlas describing protein space, environmental metabolic models for each biome, approximately 500,000 reconstructed microbial genomes, a global metabolic model, and a data-analysis portal for visualization of all information" (http://www.earthmicrobiome.org/; accessed June 1, 2011).[3]

As several workshop presenters explained, additional omics fields continue to advance steadily and build on the understanding gained through genomics, providing researchers with functional information to annotate the more static genomic data (de Villiers, 2010; Dhar, 2010; Pitt, 2010a,b). The field of systems biology seeks to integrate these multiple levels of biological knowledge into descriptive, and ultimately predictive, mathematical models, combining experimental knowledge with computational tools in order to study the interactions between the components that make up a particular biological system. As a result, a primary goal of systems biology is to understand how the system being studied functions, what its properties are that arise from the interactions of its individual components (also referred to as emergent properties), and the design principles on which it operates (Bruggeman and Westerhoff, 2007; Ferrell, 2009).

The field of synthetic biology seeks to use the knowledge gained through these other biological disciplines in order to design new pathways[4] having defined functions. Perhaps of all the S&T areas examined during the workshop, synthetic biology has received the greatest public and policy attention, both for its potential contributions to health, the economy, and the environment and for the security risks that misuse of

[2] Second generation sequencers at BGI include 137 HiSeq 2000 systems from Illumina and 27 SOLiD 4 systems from Applied Biosystems, along with multiple, earlier generation capillary electrophoresis ("Sanger method") sequencers (http://www.genomics.cn/en/). BGI has locations in China, the United States, and Europe.

[3] Descriptions of genomic sequencing projects are derived from articles current at the time of committee discussions. With rapid development in research and sequencing capacity, the state of these projects and the numbers of genomes sequenced also change rapidly.

[4] "A biological pathway is a series of actions among molecules in a cell that leads to a certain product or a change in a cell. Such a pathway can trigger the assembly of new molecules, such as a fat or protein. Pathways can also turn genes on and off, or spur a cell to move" (U.S. National Human Genome Research Institute, Fact Sheets: Biological Pathways, http://www.genome.gov/27530687, accessed August 29, 2011).

its discoveries could pose.[5] Given this, the committee addressed synthetic biology in the context of all three major trends it identified, and discussions of aspects of synthetic biology are found in Chapters 3 and 4 as well as here.

Synthetic biology has now resulted in the successful creation of individual components or elements that can be used as building blocks within a larger genetic network or pathway (Khalil and Collins, 2010; Purnick and Weiss, 2009),[6] bringing ever closer the promise of practical applications based on synthetic biology principles. Examples of successful engineering of specific cellular pathways derived from existing genetic sequences have already been reported, notably the design of a terpenoid biosynthesis pathway in yeast to produce the plant-derived antimalarial drug precursor artemisinic acid (Ro et al., 2006). Terpenoids are a very large class of molecules with diverse functions, many of which may have potential pharmaceutical uses (statin drugs, for example, inhibit an enzyme in a terpenoid synthesis pathway resulting in decreased downstream production of cholesterol). Understanding and manipulating terpenoid pathways, the enzymes involved in those pathways, and pathway regulation also hold promise for the development of novel antimicrobial drugs (Muntendam et al., 2009).

In 2010, yet another milestone in synthetic biology was reported—the design and synthesis of a functioning bacterial genome and its insertion into a cell from which the natural genetic material had been removed (Gibson et al., 2010). This advance was notable because it represented the creation of a fully synthetic genome able to successfully direct the range of activities needed for the bacterial cell to survive, grow, and reproduce

[5] For example, SYNBIOSAFE, a project supported by the European Commission, examines issues of safety, security, and ethics in synthetic biology (http://www.synbiosafe.eu/). Ethical and security issues in synthetic biology have also been addressed in reports from the U.S. Presidential Commission for the Study of Bioethical Issues (2010) and the U.S. National Science Advisory Board for Biosecurity (2010). The Implementation Support Unit (ISU) of the BWC has co-hosted workshops on synthetic biology in partnership with the United Nations Interregional Crime and Justice Research Institute (UNICRI) and with the Geneva Forum, as well as delivered presentations on biosecurity issues at synthetic biology conferences (reports of the activities of the ISU are available at http://www.unog.ch/bwc/isu).

[6] These include, for example, various promoters and regulators to influence gene expression. Building on roots in both molecular biology and traditional engineering disciplines, synthetic biologists frequently conceive of cellular systems through the framework of electronic circuit design. As a result, biological modules may be viewed as functioning like switches, oscillators, logic-gates, and other electronic components; the framework is used as an aid in trying to design and conceptualize biological systems similar to the manner in which engineers design machines. Synthetic biologists have also borrowed terminology from the computational sciences, referring to the ability of genetic material to operate as the "software" of living systems and to "boot up" the operations of a cell (which can analogously be thought of as the hardware).

itself. It also represented progress along the pathway toward "synthetic life," although the study itself did not create a fully synthetic organism from scratch (i.e., from a pool of chemical precursors to create not only the genetic information but also the cell membrane and necessary cellular machinery), an achievement that still remains out of reach.

Discussion and Implications

The combination of enabling tools, particularly high throughput measurement techniques (see Section 2.2), and the number of omics projects being undertaken results in the creation of vast amounts of biological data to be analyzed and converted into information that will be useful to systems and synthetic biologists. Based on the workshop discussions, the committee emphasizes, however, that the complexity of biological systems remains a significant obstacle to the ability to construct accurate mathematical models, even at the level of a single signaling pathway. For example, Dr. Andrew Pitt of the University of Glasgow in the United Kingdom[7] noted at the workshop that solving a mathematical model of the epidermal growth factor receptor pathway requires equations for 322 components and the 211 reactions in which they are involved (Oda et al., 2005). As a result, truly rational systems design in biology remains a goal of the field (Pitt, 2010a). As a recent review of developments in synthetic biology notes,

> Whereas traditional engineering practices typically rely on the standardization of parts, the uncertain and intricate nature of biology makes standardization in the synthetic biology field difficult. Beyond typical circuit design issues, synthetic biologists must also account for cell death, crosstalk, mutations, intracellular, intercellular and extracellular conditions, noise and other biological phenomena. A further difficult task is to correctly match suitable components in a designed system. As the number of system components grows, it becomes increasingly difficult to coordinate component inputs and outputs to produce the overall desired behavior. (Purnick and Weiss, 2009)

Nevertheless, advances in omics, systems, and synthetic biology have potential implications for the BWC in several overarching areas. On a fundamental level, these fields continue to advance the understanding of biological systems—including human, animal, plant, and microbial physiology. These fields provide information on how systems function, on networks of interactions (for example, between receptors, ligands that bind to them, and resulting cascades of signaling molecules), and on points at

[7] Dr. Pitt is currently affiliated with Aston University.

which such systems might be modified or acted upon to cause specified biological effects. In addition to the goal of improving the understanding of existing systems, scientists are exploring how to control these systems in ways that we currently cannot and to enable the design of completely new systems. The knowledge that results from these discoveries might eventually be used to explore new targets and mechanisms of action of biological agents, or new agents themselves, with implications for both protective and prophylactic purposes or for bioweapons. For example, understanding of immune pathways gained through systems biology approaches can be applied to the development of new vaccines (Oberg et al., 2011), while studies of drugs and their networks of interactions in the body can aid in the identification of new drug targets (Chua and Roth, 2011). Laboratories in synthetic biology are already working toward designing and synthesizing new microorganisms by manipulating metabolic and biosynthetic pathways, work that is being conducted for socially beneficial ends such as biofuel production (Alper and Stephanopoulos, 2009; Keasling, 2010). However, advances in synthetic biology may also enable the synthetic re-creation of known pathogens, the combination of sequences from several microorganisms to create new chimeric pathogens, or even the design and synthesis of novel pathogens (NRC, 2010b; Tucker and Zilinskas, 2006).[8]

2.1.3 Immunology

The workshop surveyed the state of life sciences research broadly and considered both whether S&T developments might have the potential to be misused and how advances in science could help provide solutions to BWC concerns. Developments in understanding the immune system have potential relevance to both of these themes.

Developments

Advances in molecular biology, high throughput techniques, and bioinformatics tools for data analysis are moving the field from empiri-

[8] Discussion continues about the relative risks and extent to which advances in areas such as DNA synthesis and synthetic biology enable the construction of novel viral or bacterial pathogens. Design issues arising from the complex nature of biological systems are noted above (Purnick and Weiss, 2009), suggesting that creating a novel genome that yields specifically desired pathogen functions and virulence, either by de novo design or by combining sequences derived from existing microorganisms in new ways, would continue to take significant time and effort. To create a functional pathogen also requires additional, nontrivial steps beyond the construction of a nucleic acid genome. These include packaging the genome into a viral capsid or a bacterium, replication and production of larger quantities of the pathogen, and possibly steps to protect the pathogen from environmental degradation and render it more suitable for delivery (Tucker, 2011a). Further discussion about tacit and explicit knowledge required to conduct complex scientific experiments may be found in Section 5.1.2.

cal, trial-and-error design of vaccines and drugs toward rational design (Adams et al., 2011; Bagnoli et al., 2011; Bowick and Barrett, 2010; Connell, 2010; Plotkin, 2009). To accomplish this goal, scientists characterize the pathogens, their hosts,[9] and systems of pathogen-host interactions that occur during infection and subsequent immune responses. For example, by comparing the genomic sequences of multiple strains of a pathogen, researchers may identify genetic alterations that correlate with greater or lesser virulence. In fact, increasing virulence of a pathogen is a useful experimental approach to understanding pathogenic mechanisms (Shimono et al., 2003). Yet such manipulations of even mildly virulent organisms could lead to the creation of novel pathogens, which could result in some States Parties questioning whether the project could be a possible violation of Article I. By using high throughput microarrays, scientists can also identify the patterns and changes of gene and protein expression that occur in the pathogen and the host. All of these techniques are directed toward determining the specific molecules and signaling pathways involved in host responses to a pathogen and the ways that pathogens disrupt effective host immune reactions in both plant and animal species,[10] ultimately enabling scientists to move toward a systems-level understanding of the infection process. This expanded base of knowledge is used to identify proteins, nucleic acids, or attenuated pathogen strains for testing as vaccine candidates, to design vaccines and countermeasures that will stimulate aspects of the host immune response that are predicted to be effective in eliminating the pathogen, or to disrupt the mechanisms that a pathogen uses to bypass an effective host response. The increased DNA sequencing and characterization of individual genomic data and the correlation of different genetic variations with different responses to a pathogen or to a vaccine are also moving the field toward "personalized vaccinology" (Connell, 2010).

Researchers developing vaccines and countermeasures are actively studying new expression and delivery systems (see Section 2.1.6), along

[9] Because potential biothreat agents could be used not only to cause human disease but also to act against veterinary or agricultural targets, the relevant "host" for a pathogen could be a human, a nonhuman animal, or a plant.

[10] Many pathogens employ strategies designed to diminish the effectiveness of a host's immune response against them. For example, almost all human cells display Major Histocompatibility Complex (MHC) class II molecules on their surfaces, and certain cells also display MCH class I molecules. These molecules present antigens derived from infecting pathogens to the immune system. Some pathogens decrease MHC I or II expression on cell surfaces, diminishing the resulting immune response. Other pathogens directly target and kill frontline immune sentinel cells such as macrophages and dendritic cells. Plant pathogens also employ strategies to decrease the effectiveness of plant immune responses directed against pathogen-associated molecular patterns and virulence factors. Although plants lack some types of immune responses exhibited by mammals, they employ similar types of "innate" immune responses (Jones and Dangl, 2006).

with options to enable more rapid development and manufacturing (Bagnoli et al., 2011; Plotkin, 2009). One example mentioned during the workshop is the use of nonpathogenic latent viruses as transgene vaccine delivery systems (Connell, 2010). Such viruses result in an ongoing but nonsymptomatic and nondisease-causing infection and so can provide a more long-lived boost to the immune system through continued production of immunogens. For example, altered strains of Herpes Simplex Virus-1 (HSV-1) are being developed to deliver foreign antigens (i.e., immunogenic proteins for protection against infection by bacteria and non-Herpes viruses) (Manservigi et al., 2010; Marconi et al., 2009). An added advantage of this approach is that HSV-1–based vaccines are capable of eliciting a strong cellular immune response.[11] DNA-based vaccines are another option, particularly when combined with adjuvants or as the first (prime) immunization in a two-pronged prime and boost strategy (Liu, 2011). The DNA that encodes pathogen proteins against which an immune response is desired can be delivered to cells using viruses or bacteria as vectors or using lipid or polymer-based nonviral particles, as discussed in Section 2.1.6. The immunoprotective proteins encoded by the DNA are subsequently produced within host cells and expressed as antigens on host cell surfaces, generating immune responses (Ledgerwood and Graham, 2009; Plotkin, 2009).

There is also significant interest in the development of new human and veterinary adjuvants, which work in conjunction with vaccines to boost immune responses (Heegaard et al., 2011; Reed et al., 2009). All adjuvants appear to act by stimulating components of the innate immune system, thereby affecting the outcome of adaptive immunity. Thus as more is learned about innate immunity, adjuvants can be designed in ways that direct the efficacy of a given vaccine toward a specific outcome. These studies will greatly enhance vaccine development in the future.

New vaccine platforms are another major focus of countermeasures research. Platforms are flexible systems of vectors (whether viruses, bacteria, or particles) that deliver genes for the pathogen-associated proteins against which immunity is desired, are adaptable so that genes of interest can be swapped in and out of the base platform system, and are optimized for rapid production (Drew, 2007; Ledgerwood and Graham, 2009). Finally,

[11] The mammalian immune system includes innate immune responses (which are rapid in response and are frequently directed against conserved pathogen signals such as bacterial lipopolysaccharides) and adaptive immune responses. The adaptive immune system includes two broad pathways—one that results in the generation of circulating antibodies directed against an extracellular pathogen or toxin ("humoral immunity"), and one that directs the immune system to kill cells that have been infected with an intracellular pathogen such as a virus ("cellular immunity"). The nature and extent of immune system responses are influenced by many factors, including the type and location of immune cells that first encounter the pathogen and by chemical signals such as cytokines that preferentially direct the immune response toward one or the other pathway.

the global prevalence of antimicrobial resistance remains a significant and growing concern, including the spread of multidrug resistant strains, and new antibiotic and antiviral countermeasures are clearly needed. Although the introduction of high throughput screening has greatly reduced cost and increased efficiency of drug discovery and the search for new antibiotics, the length of time, regulatory hurdles, and costs of bringing new compounds into the clinic remain high (Hamad, 2010; IDSA, 2011; IOM, 2010).

Discussion and Implications

Advances in vaccine design and production, in particular those associated with rapid manufacturing methodologies, will have obvious benefits for global health and for preparedness for and response to the potential use of bioweapons or bioterrorism, as well as serving an important public health function. Advances in understanding plant immune systems and plant defenses against infection similarly have relevance to the protection of crops against both natural disease outbreaks and potential intentionally introduced pathogens. Article X of the BWC, which addresses cooperation in the prevention of disease, promotes the sharing of materials and knowledge in the development of infectious disease therapeutics. However, advanced understanding of the immune system has potential dual use implications because it could be misapplied to create pathogens with increased virulence or to decrease the effectiveness of a human, animal, or plant immune response. A concern has been raised, for example, that as synthetic biology continues to advance it could be used to design novel pathogens for these functions.

Effectively modulating and controlling the immune system whether for beneficial or harmful purposes remains a challenge because of the complexity of the immune system itself and because of the complexity of immune system interactions with other physiological systems like the endocrine and nervous systems. Biological systems exist in an "exquisite balance" (Connell, 2010), and although scientific knowledge continues to expand, it is still not possible to predict with certitude the downstream effects of disrupting these biological control systems (Connell, 2010; Nixdorff, 2010). The well-known mousepox case study represents one example in which immune modification provoked unintentional negative effects, creating a lethal vaccine (Jackson et al., 2001).[12]

[12] Researchers seeking to create a contraceptive vaccine used a nonpathogenic strain of the Ectromelia virus, which causes mousepox, to deliver DNA encoding a mouse egg protein to mice. The goal was to induce an immune response against the egg protein, preventing fertility. In order to boost the effectiveness of their vaccine, researchers also co-delivered DNA for the cytokine IL-4, which modulates the immune system. By influencing the immune system in such a way that it mounted a less effective response to the vaccine virus, the researchers unintentionally created a mousepox virus that was lethal to the mice.

Other significant challenges are associated with the development of new vaccines and countermeasures against infectious diseases. Sophisticated laboratory containment systems are required to safely handle certain pathogens, particularly ones of concern as potential bioweapons and as new emerging diseases. Developing and testing vaccines against these pathogens often requires the use of animal models because of ethical considerations that prevent experimental infection in humans and make conducting clinical trials problematic. In many cases, suitable animal models may not currently exist or the specific types and levels of immune responses that correlate with protection in humans are not well known (Matheny et al., 2007; NRC, 2006b). There are also few significant commercial markets for vaccines, and this fact coupled with the regulatory requirements necessary to develop a licensed product result in low commercial interest. As a result, incentives and government and philanthropic investments have been used to drive the creation of new vaccines and medical countermeasures.

Many pathogens of concern as bioweapons and as emerging infectious diseases are zoonoses (e.g., *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), Rift Valley fever virus (Rift Valley fever), *Coxiella burnetii* (Q fever), *Burkholderia mallei* (glanders), equine encephalitis viruses (Eastern, Western, and Venezuelan equine encephalitis), Ebola virus (Ebola hemorrhagic fever), influenza viruses such as H5N1 (avian influenza), and others).[13] This fact highlights the fundamental importance of cooperation among human, animal, and plant health research communities to support new medicine and vaccine development efforts and global disease surveillance; natural partners include the World Health Organization (WHO), the World Organisation for Animal Health (OIE), and the United Nations' Food and Agriculture Organization (FAO). The creation of appropriate animal models to support the development and testing of new licensed human products against pathogens of concern is an obvious area for collaboration. The committee noted that contact already exists between the BWC, WHO, FAO, OIE, and other potential partners.[14] Further descriptions of this engagement may be found in Chapter 3 as part of a broader discussion of international collaboration on public health.

2.1.4 Neuroscience

The ability to target and deliver substances to the brain and central nervous system brings great promise to the treatment of diseases like brain cancer. Delivery of therapeutics to influence mood and cognition

[13] A zoonotic disease is one that can be transmitted between wild or domesticated animals and humans.

[14] Reports of the activities of the BWC ISU reference relevant meetings with a variety of intergovernmental and nongovernmental organizations and are available at http://www.unog.ch/bwc/isu.

also play roles in treating a range of neurological disorders like depression, attention deficit disorder, and many others.

Developments

Neuroscience research is providing new insights into gene expression, variability, and phenotypic plasticity at the level of individual nervous system cells, knowledge that is helpful to understanding the functions of cells in the nervous system as well as exploring improved options for drug screening platforms (Eberwine, 2010). It is also helping scientists to better understand processes in disease development and pathology, for example in elucidating the role of genetics and molecular interactions in Alzheimer's disease (Holtzman et al., 2011). Advances in delivery methods and formulations intersect with neuroscience research in, for example, developing improved therapeutics to cross the blood brain barrier (BBB).[15] Finally, research continues to actively explore the brain-machine interface, which could have positive applications for the replacement of motor or sensory system functions lost due to injury and the creation of functional prosthetics. Signals captured from neurons in the brain can be processed computationally, for example, to allow a subject to move a cursor on a screen or to move a robotic hand (Leuthardt et al., 2009; Warwick, 2011). This area has received significant civilian and military attention and some overstatement of current levels of development. Commercial games using noninvasive methods to capture neural output (for example, by wearing a helmet that monitors brain electrical signals) have been on the market for several years (Li, 2010). Small numbers of patients have received initial prototypes of invasive or noninvasive neural interfaces, several companies are actively developing neural systems (e.g., BrainGate, http://www.braingate.com/), and clinical trials are ongoing (e.g., the U.S. study "Microelectrode Brain-Machine Interface for Individuals with Tetraplegia," http://www.clinicaltrials.gov, accessed August 18, 2011). A variety of scientific and technical hurdles remain to be overcome, however, in creating more sophisticated and accurate medical devices (Lega et al., 2011).

Advances in the delivery of molecules to the brain also raise the possibility of delivering substances that could influence brain and body pathways as bioregulators and that could either enhance or degrade aspects of cognition, performance, and mood. Oxytocin, for example, is a 9 amino acid peptide found naturally at high levels in women following

[15] The blood brain barrier inhibits the movement of most molecules from the body's bloodstream into the brain and central nervous system, although small molecules such as dissolved oxygen can pass, and some molecules, such as glucose needed by brain cells, are actively transported across. The barrier consists largely of tight junctions between the endothelial cells that line the capillaries.

childbirth and has been associated with a variety of effects including social behaviors, bonding, and the promotion of trust (Ebstein et al., 2010; Lee et al., 2009). Several recent studies on the intranasal administration of oxytocin in situations of group competition have found more complex effects, including promotion of "in-group trust and cooperation, and defensive, but not offensive, aggression toward competing out-groups" (De Dreu et al., 2010, 2011). The suggestion that oxytocin "enhances the cognitive availability of salient information in the social environment" (Chen et al., 2011) has been raised as an alternative explanation for the results, and further research may be needed to clarify the details of oxytocin's effects. It has been suggested that there could be dual use military applications for oxytocin because of its trust-promoting properties (Dando, 2011; Nixdorff, 2010), which could perhaps play a role in reinforcing social cohesion and bonding within a military unit. Significantly, it has also been noted that experiments such as those delivering oxytocin demonstrate the theoretical feasibility of employing a bioregulatory molecule to produce changes to a subject's mood or behavior (Dando, 2011). Understanding the complexity of a particular bioregulator's effects and issues of dosing and delivery would remain as challenges to actual use (additional discussion of bioregulators may be found in Chapter 4).

A variety of advances in the understanding of human neuroscience could conceivably be used to enhance military performance (e.g., use of the antisleepiness drug modafinil to maintain alertness in pilots [Caldwell et al., 2004; Eliyahu et al., 2007]) or might be considered for law enforcement purposes (e.g., the development of neuroimaging techniques with the goal of detecting lying).[16] International frameworks and conventions address appropriate uses of chemical and biological agents under treaties such as the BWC and CWC, under international human rights and humanitarian law, and in human subjects for medical research. The association of neuroscience with personality and with the integrity and dignity of a person seems to raise particular social and ethical issues that should be carefully considered. Science is still far from understanding many details of the brain, and the scientific community can contribute to discussions not only on what is possible (including offering a "reality check" of what is truly feasible, when warranted), but also on the potential implications of emerging neuroscience research.

[16] It is important to note that limitations continue to exist in the ability of neuroimaging technologies to accurately detect states such as deception or memory. Methods such as magnetic resonance imaging, positron emission tomography, and other techniques aggregate signals from multiple neurons, and spatial and temporal resolution vary depending on the particular technology. How closely imaging studies in controlled laboratory conditions on compliant, healthy volunteers would correlate with other populations also remains unknown. The current state of neuroimaging techniques is discussed in a recent series of modules from the Royal Society (2011a) and the NRC (2008) as well as in presentations from the Second Raymond and Beverly Sackler USA-UK Scientific Forum: Neuroscience and the Law, March 2011 (http://sites.nationalacademies.org/PGA/stl/PGA_062477).

Discussion and Implications

The social, ethical, and military implications of neuroscience research across many areas of research have garnered increasing attention in recent years (NRC, 2008, 2009d; Royal Society, 2011a). Developments in this field have the potential to raise complex issues about the types of applications that are feasible, ethical, and acceptable for military or law enforcement purposes in the context of international legal frameworks. In the context of the BWC, the improving systems-level understanding of the nervous system and its interactions with other physiological systems, methods that enable improved delivery of drugs and genes to the central nervous system, and the delivery of drugs or peptides to influence cognition or motivation, are all areas of potential relevance should such advancing knowledge be used to cause harm. It appears that the science has not yet developed to a point where many of the potential applications of emerging neuroscience research are imminent, but progress continues to be made and interest in these areas is significant. The Beijing workshop, which surveyed developments in S&T broadly, did not allow potential neuroscience issues to be examined in detail. Additional scientific dialogues to examine topics in neuroscience in the context of social and policy issues are ongoing (for example, The Royal Society's Brain Waves project; see http://royalsociety.org/policy/projects/brain-waves/), and this may be an interesting area for further monitoring as research progresses and developments move closer to applications.

2.1.5 Production Systems

Another area of active research in the life sciences is protein production, whether through the process of translation in transgenic organisms and cell culture systems, through the use of "cell-free" extracts, or by means of chemical synthesis. The increasing importance of biologics to the pharmaceutical and biotechnology industries is helping to drive this trend, and a variety of scientific and enabling technical developments are expanding efficient production options for proteins and peptides.[17]

Developments

Transgenic Organisms

As highlighted during the workshop, multiple options exist for protein production in transgenic organisms. Factors such as cost, required

[17] Proteins and peptides are both composed of a series of amino acid building blocks. Molecules containing less than approximately 50 amino acids are generally referred to peptides; larger molecules are generally referred to as proteins.

production yield and scale, the need for post-translational protein modifications,[18] safety concerns related to potential contaminants, and regulatory requirements influence the selection of a production system (Ma, 2010; Slomski et al., 2010). In general, cell culture systems (both bacterial and mammalian) remain the most popular means of producing large quantities of a particular protein, and these systems are relatively straightforward to scale up in bioreactors, as discussed further below.

Therapeutic proteins are also produced in a variety of animal models, including rabbits, sheep, pigs, and goats. However, the creation of transgenic animals and the optimization of protein production in these systems generally require collaboration among teams of scientists and are both more expensive and more time consuming than is creation of a cell culture–based protein expression system (Slomski et al., 2010). The silkworm, an insect-based system, also serves as a feasible model for protein production because fairly high expression levels can be achieved (Kato et al., 2010). Plants, which are already grown economically at very large scale for agriculture, offer another interesting option for the production of recombinant proteins, have already demonstrated proof of principle in a variety of systems, and may be coming closer to practical application (Ma, 2010; Rybicki, 2010).

The use of plant-based production systems has been explored for the creation of edible, lower-cost vaccines that would not require cold-chain transport; however, concerns about reproducible dosing and potential environmental escape of the transgenic crop remain. As a result, recent efforts have focused increasingly on transient protein expression in nonedible plant species, such as tobacco, using viral or bacterial infiltration to carry the genes encoding the desired proteins into the plant tissues (Rybicki, 2010). These systems can result in very fast production times—for example, virus-like particles in tobacco, made from H1N1 influenza hemagglutinin (HA) protein for testing in mice as an anti-influenza vaccine, have reportedly been produced in only 18 days from the starting HA DNA sequence (D'Aoust et al., 2008). The current system of influenza vaccine production in chicken eggs takes months. Although biotechnology and pharmaceutical companies have existing investments in cell culture–based production facilities and may be less likely to switch in the near term to plant-based systems for major drugs, it has been suggested

[18] Eukaryotic organisms like animals and plants frequently modify proteins after they have been translated from mRNA—well-known modifications include the addition of phosphate groups (phosphorylation) and the addition of specific carbohydrate molecules (glycosylation). Bacteria lack the ability to conduct many post-translational modifications, and different eukaryotic systems (yeast, different plant and animal species) also vary in the details of the specific modifications they conduct. The influences that these post-translational modifications have on protein properties, including on correct folding and protein activity, are also ongoing areas of life sciences research.

that plant production systems could gain a foothold in the production of veterinary drugs and in the rapid production of vaccines against emerging pathogens, including against potential biothreat pathogens (Rybicki, 2010). The field is still developing, but as Julian Ma of the University of London noted during the workshop, the demonstrated ability to rapidly produce active therapeutic proteins and vaccines from plant systems may increasingly provide a "low-tech high-tech" option for economical, massive-scale production (Ma, 2010).

Bioreactors

Another notable trend is the increasing sophistication of small, laboratory-scale benchtop bioreactors for cell culture production. These systems, which vary in their construction materials and in the design of components like stirrers and mixers, are used to culture bacterial, mammalian, and insect cell lines to express a desired protein, such as a monoclonal antibody therapeutic. Benchtop bioreactor systems generally hold several liters of cell culture (up to approximately 20L), and typical protein yields may be milligrams to grams of protein per liter. Real-time sensors are increasingly being integrated into bioreactors to measure parameters that affect cell growth such as temperature, pH, and dissolved oxygen. The data gathered by these sensor systems are also being fed back to computerized control systems to increase process optimization and automation. There is a similar trend toward use of disposable bioreactors, such as wave-mixed culture bags, which decrease sterilization requirements when switching from one product or cell line to another and decrease equipment lead time (Bareither and Pollard, 2011).

Bioreactor process optimization remains an important step in culture-based protein production, and it can take several months or more to optimize production in a lab-scale system by adjusting environmental conditions, cell density, and concentrations of nutrients or enzymes that might be needed to produce the protein. Production is generally optimized in small-scale systems (micro reactors and bench-scale reactors) and gradually scaled up to pilot manufacturing and full manufacturing capacity in very large bioreactor tanks. However, scale-up of cell cultures is not always an easy process. Smaller scale bioreactors offer the ability to more rapidly optimize production conditions. It is also possible to subsequently operate multiple smaller scale bioreactors in parallel to produce desired protein quantities, assuming that very large scale manufacturing capacity is not needed, and the small size of micro- and bench-scale bioreactors would make them difficult to monitor or detect.

Cell-free Systems

Increasingly feasible options also exist for creating biological molecules like peptides and proteins in cell-free systems and through chemical

synthesis. Cell-free systems rely on the principal biological machinery used to translate proteins (e.g., mRNA, ribosomes, amino acids, and tRNAs), but the steps are carried out in solution rather than inside a cell. These systems may facilitate subsequent protein purification and reduce potential contamination, and may also be advantageous if the protein being produced causes toxicity in the producing cell line at high concentrations. A desired protein can also be fully chemically synthesized, eliminating entirely the need for cell culture or transgenic expression and production. Furthermore, chemical synthetic systems offer the possibility of more easily incorporating unusual or non-natural amino acids or otherwise modifying the protein to include desired functional groups or other chemistry. Chemical synthesis of significant quantities of a product still remains limited to peptides rather than to larger proteins, and the complexity of the chemistry needed to synthesize a particular peptide can vary widely, affecting time and cost (Thayer, 2011). However, a chemically synthesized peptide therapeutic, Fuzeon, has been on the market since 2003 and is produced in industrial-scale quantities. The scalability and purification of peptide synthesis have improved, and the market for synthesized peptides is expected to grow (Thayer, 2011).

Discussion and Implications

The pharmaceutical market for biological products is currently more than $100 billion a year and continues to grow (Bain and Shortmoor, 2010). Monoclonal antibodies are a significant component of this market, along with other protein and peptide drugs. The potential magnitude of these markets will continue to drive developments in protein production, although, as with all biological products, substantial investments of knowledge, time, and money in research, development, and clinical trials are required in order to develop a licensed therapeutic, regardless of the production method.

The creation and optimization of transgenic animal and plant models and the design of sophisticated chemical synthetic pathways require significant scientific expertise. Continuing developments in plant-based production systems, however, are expanding the options for rapid, economical, and large-scale protein production. These systems may turn out to be useful for the rapid production of vaccines against emerging pathogens or other disease agents of concern, although such systems could theoretically also be misapplied to create protein toxins for bioweapons. Laboratory-scale cell culture bioreactors are already widely available and enable fairly rapid production of smaller quantities of proteins as well as the ability to scale up production by operating multiple bioreactors in parallel. The small size of laboratory-scale bioreactors also renders it

difficult to detect protein production capacity. All of these production systems (transgenic animals and plants, small-scale cell culture bioreactors, and chemical synthesis) thus have the potential to expand the definition of production facilities relevant to the BWC beyond traditional industrial-scale operations.

2.1.6 Delivery Systems for Biological Molecules

The prohibitions embodied by the BWC also apply to the means of delivery of biological agents. Developing effective delivery methods is often cited as a key technological hurdle for the creation of a bioweapons or bioterrorism program (see, for example, Danzig et al., 2011). As a result, the committee considered both aerosol science and recent developments in viral and nonviral delivery technology as part of its analysis of the overall picture of trends in the life sciences.

Developments

The delivery of drugs or vaccines through an aerosol route (such as through the use of individual inhalers) has been widely studied as an alternative method to injection. Only a thin wall separates the air spaces from the bloodstream in the alveolar cells of the deep lung, and this can enable drugs or other molecules to pass into the body. Aerosol delivery may also increase the concentration of an agent reaching the bloodstream by avoiding the "first pass" metabolism that occurs in the liver following oral absorption. As described during the workshop, the fluid dynamics of particles in inhaled air, whether droplets of drugs, viruses, or dust, reach and deposit into different regions of the respiratory system based on factors such as particle size and density.[19] Researchers study and optimize these parameters in order to create successful inhaled-delivery systems (Roy, 2010).

As several workshop presenters discussed, research on the development of delivery systems that protect drugs, vaccines, and even bacterial

[19] Gravitational settling of a particle is affected by its *aerodynamic diameter*, which depends on a particle's geometric diameter and density and which represents the diameter of an equivalent spherical particle with a density of 1 gram per cubic centimeter that settles at the same rate. Particles with aerodynamic diameters of 2-10 micrometers generally deposit in the trachea and bronchi while particles of less than 2 micrometers reach the alveoli of the lungs (NRC, 2011c). This concept has been employed to develop novel aerosol delivery systems using, for example, porous polymer particles over 5 micrometers in size but having relatively low density (producing an aerodynamic diameter of approximately 2 micrometers) (Edwards et al., 1997). Such particles were inhaled into the deep lung and showed prolonged systemic drug levels compared to smaller and denser particles with the same aerodynamic diameter.

or viral vectors from degradation in the environment and in the body, that increase uptake, and that target delivery to specific cells and tissues is actively ongoing (Nixdorff, 2010; Roy, 2010; Ying, 2010). One delivery option is the use of various DNA and RNA viruses as vectors, because viruses have evolved specific strategies to infect target cells and deliver the nucleic acids they contain.[20] These viral properties can be harnessed to deliver therapeutic, nonviral DNA. Genes and drugs can also be encapsulated or embedded in various types of lipids and polymers as both nano- and micro-particles. These systems protect the molecules from degradation in the body and can be chemically functionalized to target particular cell and tissue types (e.g., through the conjugation of ligands on their exterior to interact with cellular receptors and promote particle uptake into cells via receptor-mediated endocytosis, or through many other strategies). As a result, functionalized nanoparticle delivery systems seek to mimic some of the types of properties that make viruses such efficient delivery vehicles (such as mechanisms for uptake into target cells and for effective transfer of the payload they contain) (Nixdorff, 2010). Nonviral materials can also be designed so that their properties change in response to relevant physiological signals like temperature or glucose concentration (Ying, 2010). Advances in delivery technology, such as the use of liposomal nanoparticles or carriers targeted to transport pathways, may help achieve more effective delivery of drugs, genes, and imaging agents across the blood brain barrier, although effective delivery to the brain remains a challenge. In particular, nanoparticulate drug delivery systems are under development that can be targeted to specific cells and organs, such as those of the reticuloendothelial system, by incorporation of surface recognition molecules from viruses or other infectious agents that normally hone to these cellular targets. The nanoparticulates may be lipid- or polymer-based and have been modified to carry antibiotics, siRNAs, peptides, nucleic acids, and other small molecules for immunogenic, therapeutic, or antimicrobial effects.

Pulmonary delivery systems are under intensive development because this route lacks many of the barriers to successful drug delivery found in the intestinal tract, such as low pH and mucosal surfaces. Pulmonary vehicles include aerosols and aerosol inhaler systems, dry powder inhalers, and nebulizers. The treatment of respiratory diseases and efficient systemic dissemination of aerosolized drugs make the lung an attractive target; in fact, more than 30 percent of the global drug delivery market consists of aerosol delivery (Kaparissides et al., 2006).

[20] Many viruses have been studied as potential delivery systems. Some of the most commonly studied are retroviruses (particularly lentivirus), vaccinia virus, adenoviruses, and adeno-associated viruses.

Thus, active research is expected to continue on methods to protect therapeutic molecules such as genes, proteins, and other drugs from premature biological degradation and to increase the delivery of these molecules to target cells and tissues. In particular, aerosol delivery is playing an expanding role in the pharmaceutical enterprise. As with protein production technology, the healthcare industry is expected to remain a significant driver of the delivery technology field. However, formidable biological challenges like protection from physiological degradation and clearance mechanisms, immune system responses, and achievement of therapeutic levels of targeting, uptake, and expression remain, despite continued progress. As a result, the creation of these systems continues to require training and expertise.

Discussion and Implications

Article I of the BWC addresses "means of delivery designed to use such [biological] agents or toxins for hostile purposes or in armed conflict." This provision relates to means of delivery *specifically* developed for the dissemination of biological and toxin agents for warfare purposes. But new biological weapons delivery methods may also come about as the result of legitimate research and development into means and methods of dissemination and administration of treatments for entirely legitimate purposes, for example to administer improved therapeutics and vaccines. Although the focus of that work is on better control of the dose, improvement of patient compliance, and better absorption and targeted delivery of the treatment, some of the underlying physical and engineering principles may well be adaptable to biological weapons delivery systems. Advances in delivery of small and large molecules, both protein and nonprotein, along with targeting, would place this research within the purview of Article I. On the other hand, the pharmaceutical industry, which drives much of this research, is largely focused on the individual having easy access to aerosolized therapeutics.

There may also be significant hurdles to scaling up these new delivery systems. Advances in traditional lower technologies for delivery might also require monitoring. For example, it was noted during the workshop that the simplest "delivery system" could consist of an infected human used as a vector to spread disease. Incidents of disease transmission in airline passengers seated within several rows of a SARS-infected traveler illustrate this possibility (ECDC, 2010). It is worth noting that the ease with which a disease is transmitted varies, potentially rendering this method less effective at spreading disease to large numbers of people. However, it may still be possible to create public disruption even if only small numbers of people are directly affected.

2.1.7 Biosensors

Developments

As described during the workshop, a wide array of strategies can be employed to create biosensors (Kurochkin, 2010; Resnick, 2010), which also help to support and enable life sciences research. As noted above, sensors incorporated into cell culture production systems are used to control and optimize culture conditions. However, biosensors are also used as diagnostic tools in medicine (Mascini and Tombelli, 2008; Rapp et al., 2010), as tools to support public health disease surveillance (Hajslova et al., 2011; Kamikawa et al., 2010; Pejcic et al., 2006; Rodrigues Ribeiro Teles et al., 2010), and as detection tools for biosecurity monitoring (Cirino et al., 2004; Fischer et al., 2007). Many different technologies are used for these purposes, each with its own advantages and limitations.

Roughly speaking, a wide range of biosensor configurations is possible, and the responsive elements of a sensor may employ direct observation of the material or employ antibodies, enzymes, nucleic acids, physical adsorption, or other techniques. When the sensing element is triggered, the response is translated into changes in electrical, magnetic, chemical, or optical signals that are amplified and separated from background noise and displayed in a form that can be read by end users. One of the goals of biosensors is the rapid identification of molecules or organisms, such as pathogens, without first needing to isolate and culture them (steps which generally require both laboratory conditions and time). In addition to rapid identification, general trends in the field include miniaturization and efforts to develop sensors that can detect multiple and/or complex substances under real-time and real-world conditions. A truly robust, broadly sensitive, handheld system would revolutionize biosensor development, but there are still a number of technical hurdles to overcome before this goal is achieved.[21]

Considering the role that biosensors play in the areas listed above, it is important to recognize that the same technology is not appropriate for all applications. For example, within a medical setting and if technical support is available, it may not be important that the analysis of biological material be automated. For environmental sensors in the field or in a remote setting, automation of analysis is a higher priority. Within a medical setting, personnel attempting to identify a pathogen may seek

[21] Two concepts of relevance to the development of biosensors are *sensitivity* and *specificity*. Sensitivity refers to the ability of a sensor to accurately identify true positive signals (i.e., it does not miss cases). Specificity, on the other hand, refers to the ability of a sensor to accurately distinguish true negatives (i.e., it does not give false positive readings). In general, development reflects a balance between these two goals and it would be extremely difficult, if not impossible, to design a sensor to be both perfectly sensitive and perfectly specific.

a sensor that is sensitive to a broad range of organisms. In addition, it may be acceptable for a sensor to identify multiple possible organisms if the patient is symptomatic, because this is additional information that can be brought into the overall evaluation of the situation. In a setting where the primary concern is exposure to a specific, known pathogen, a selective biosensor with high sensitivity and a low false-positive and -negative rate may be the preferred choice to allow for a greater chance of detection to warn exposed populations. A fixed-site facility may not require the same device portability as does a mobile diagnostics laboratory. Thus, the strong drivers that influence the development of devices for the public health community, for example, will not necessarily result in the development of devices that are appropriate for any other community.[22]

As noted above, there are strong commercial drivers for the development of improved biosensors, particularly in the area of healthcare diagnostics as well as in detection systems for national security applications. The field continues to advance rapidly, although workshop participants noted that developing sensor systems requires making compromises among variables such as sensitivity, specificity, cost, size, and portability. The particular balance of variables chosen to create a cancer diagnostic for use in a hospital setting, for example, may not be the same as the optimal balance for creating a pathogen detector for use in the field during a disease outbreak. In some cases, for example, a preliminary positive response from a sensor is subsequently confirmed through a more specific, often slower, secondary screening test. As a result, a "one size fits all" sensor platform does not exist. Limits in data analysis and interpretation, such as amplification of true signal from background noise and minimization of false positives and false negatives, also remain. Sensors are thus one from a range of identification and monitoring tools.

The increased sequencing speed described previously is a recent development that could improve the overall efficacy of biosensors and detectors and has two main effects: first, high-speed sequencing can be incorporated into the analysis, whether as part of the device itself or as part of secondary analysis after collection of biological material; second, the pace of genetic sequencing allows researchers to create information databases that can be accessed by analysts to assist in identification of known bacteria and viruses. As the known genetic universe expands, both in the area of pathogens and environmental microecology, more sensitive, targeted analysis systems can be developed, and the risk of false positives can be reduced. In addition, antigen-based sensors con-

[22] A variety of portable biosensors exist, including "electronic noses" for applications ranging from industry to law enforcement. Such sensors can, for example, detect cocaine molecules (Stubbs et al., 2003) or help to identify bacterial species (Dutta and Dutta, 2006).

tinue to improve, allowing for the development of systems that more closely mimic human immune responses than previously possible (Ma et al., 2011). If fully developed, these sensors have the potential to allow for responses based on known and unknown pathogens, which is currently difficult to achieve.

Discussion and Implications

Certainly advances in biosensor technology represent an improvement in the tools available to provide advance warning of the release or emergence of a biological threat to human health. However, it is important to remember that in order to interpret results from a biosensor, it is necessary to understand the limitations of the device and the context in which it is being used. For example, a system that relies on collection of culturable material on a surface or in liquid will only be effective if the virus or bacterium survives collection and impact. A detector based on identification of genetic material will identify species that do not survive impact, but it could also issue unnecessary alerts by identifying material that belongs to dead bacteria or viruses posing no immediate risk to human or animal health. One must also be aware of the fact that every biosensor can result in false positives or negatives, misidentification of species, and other instrumental failures.

Even if an ideal biosensor were to be developed (one that could combine attributes such as being portable, sensitive and accurate for a broad range of pathogens, able to determine viability of the material, having a low false-positive rate, etc.), having a robust administrative structure in place to respond to positive reports from the device will still be necessary. Information transfer from one group to another—for example, local to national authorities, or defense to public health officials—is critical. Who has responsibility for the information, who has the right to access it, and who decides the actions to take in a geographic area are all questions that might be addressed in advance of an alert. The population being protected by the device, military vs. general public, for example, could be considered because it will likely change the chosen response. Does the area being monitored contain particularly vulnerable populations, such as elderly or young children? What systems of emergency preparedness and public health infrastructure are in place in the area and what are the vaccination policies? How will the response differ if the alert is a result of a natural disease outbreak, the unintentional release of a pathogen (such as escape from a laboratory), or the intentional introduction of a pathogen? Although at the policy level, the need for these decisions may be triggered by the result from a piece of sophisticated technology, and thus are presented here for consideration.

Workshop participants noted that understanding the scientific basis for biosensor mechanisms has the potential to raise dual use concerns,

because such knowledge could theoretically be used to try to evade or take advantage of the biosensors' limitations. For example, a system employing identification based on genetic material as described above could be manipulated to create a positive result and trigger an emergency or community response that could reveal weaknesses in the response infrastructure, waste resources, reduce confidence in the overall system, and cause fatigue in responders.

Because broad response biosensors pose serious technical challenges (loss of selectivity leading to high false-positive rates, for example), most biosensors today are based on a specific biological or biochemical response to the presence of the target molecule/protein/organism, and this specificity presents a potential target for manipulation or misdirection. For example, at the simplest level, material from threat organisms that have been rendered inactive could be introduced to a targeted sensor to trigger a positive response. At a more sophisticated level, as the ability to change the surface characteristics of organisms becomes more commonplace and easier to accomplish, the ability to change the surface characteristics of potential threat organisms also becomes easier, which could reduce the efficacy of existing detection systems. Acting as a barrier to actually accomplishing this task is the complexity of biology itself: changing the surface characteristics can also change the response of a human being to an organism, so any modification could kill the organism or enhance or negate the anticipated risk to a given population.

Another possible option involves encapsulation of the threat organism or agent within material designed for easier delivery. As discussed earlier in this chapter, this technology advances drug delivery options, allowing for improved uptake of therapeutics. However, such encapsulation technology could also present a challenge for biosensors because it could hide the very surface characteristics being used to identify organisms of concern. This is one example of how advances in technology may result in the emergence of new threats that were not anticipated when the sensor was designed. Technology can be created to respond to known or predicted threats, but the "unknown threat," whether an emerging infectious disease or an engineered pathogen, will be difficult to identify in this manner.

2.1.8 Discussion and Implications of the Pace of Advances in Science and Technology

Continued progress is being made in a wide variety of S&T areas, although the committee did not identify any advances since 2006 that fundamentally alter the nature of life sciences research. Life sciences research continues to advance rapidly and is expected to do so for the foreseeable future, driven by a combination of academic, commercial, and

government influences. The enormous amounts of data and information being generated from research in omics technologies and fields such as immunology, neuroscience, and systems biology are providing scientists with information to better understand processes within biological systems. Research in these fields is helping to support a more complete understanding of human, animal, and plant variability and its relationship to disease and is also identifying and characterizing new microbes and their roles in multiple environments. Scientists are actively seeking to integrate information at multiple biological levels (from genes, to proteins, to networks of intra- and inter-cellular interactions, to community dynamics) in order to improve biological understanding and to support rational engineering and design. As a result, advances in S&T are increasing the overall understanding of biological systems.

Important milestones have been achieved in molecular biology and synthetic biology, and very active research in these areas is expected to continue worldwide. The extraordinary complexity of biological systems and the challenges this complexity presents to the effective understanding and design of biological systems remain significant barriers even as applications building on these research fields draw closer to fruition. This complexity is likely to remain a defining feature of biological systems for the foreseeable future. As a result of this complexity, for example, *ab initio* design of biological organisms will likely be unachievable for a number of years to come. Well-funded and well-organized research programs are making significant steps toward this goal, but their efforts remain far from commonplace. Although genetic modifications of organisms are already possible and relatively straightforward today, the complexity and stochastic nature of many biological interactions can also render the outcome of novel modifications unpredictable. Understandings reached by the Sixth Review Conference of the BWC include "that all naturally or artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of their origin and method of production and whether they affect humans, animals or plants, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes, are unequivocally covered by Article I" (BWC, 2006). This suggests that any forms of artificial biological systems (such as might be created by synthetic biology), or synthetic chemical analogs of biological molecules, would be covered under the prohibitions enshrined in Article 1. However, as science continues to advance rapidly new research developments may provide additional opportunities for further clarification and understandings to be reached.

Developments in S&T in areas such as transgenic animal expression systems, production of proteins in plants through "pharming," availability and sophistication of small-scale bioreactors, and chemical

synthetic methods to produce biological molecules also affect the ways in which biological materials are produced or reduce the time, space, or cost requirements needed to produce them. These advances raise the possibility that molecules that have previously been very difficult or expensive to obtain may be more readily produced in larger amounts (for example, extraction in the 1960s of several grams of the neurotoxin saxitoxin reportedly required processing tons of affected clams [Tucker, 2011b]). The changing nature of biological production systems thus expands the understanding of potentially relevant production capabilities beyond the traditional model of fixed, industrial-scale, cell culture fermentation tanks.

Advances also continue in the development of effective injectable, implantable, and inhalable delivery systems for molecules such as genes and drugs. The medical industry is a primary driver of this development, and the most notable advances are being made at the level of individual-use systems (for example, the delivery of nanoparticles encapsulating chemotherapeutic agents to a cancer patient or the implantation of materials able to release insulin in a diabetic patient in response to glucose levels). In the context of the BWC, questions on the potential for advanced or targeted delivery systems to be scaled up and delivered to multiple people, such as through environmental aerosol dispersal, are particularly relevant. The committee interpreted the obligations contained in Article 1(b) as covering advanced forms of delivery systems, should such systems be used to deliver biological agents in violation of the other provisions of the BWC, but noted that delivery systems developed for medical (veterinary, pest control, etc.) purposes may be relevant to the overall assessment of risks posed to the objectives of the BWC by new technological advances. Detailed discussions on these questions were beyond the scope of the Beijing workshop and current report, but may be areas for further discussions and monitoring.

Biosensors and detectors are another area that has seen significant interest since 2006. The biological and engineering advances that underpin the development of these sensors continue to move forward, although there are still limitations in what can be achieved, and sensor development balances factors such as specificity, sensitivity, range of target molecules analyzed, and type of use (for example, sampling environmental components such as a building's air supply or sampling fluids such as blood from a single individual for diagnostic purposes). Biosensors are also only one tool and are used with information provided by other scientific and policy tools in order to make decisions.

Finally, the committee noted that multiple, parallel S&T fields are developing and advancing. As key advances are achieved in one field, they may be combined with developments in others to achieve new opportunities and new applications.

2.2 ENABLING TECHNOLOGIES

Some of the most notable developments since 2006 can be found in the enabling technologies that underlie and support significant advances in life sciences research, particularly the availability of high throughput systems and powerful computational resources. Access to these resources and the availability of large amounts of data storage capacity underpin many of the developments in the omics fields and in systems and synthetic biology (see Section 2.1.1). Increasing global access to computational and data resources is also cited in the Chapter 3 discussion on diffusion of research capacity and applications. These enabling technologies have general implications relevant to the BWC because they are helping to push the overall life sciences research enterprise forward at an ever more rapid pace. Unlike in the previous section, specific implications for the BWC are not drawn out within each subsection; rather a broader discussion of the potential implications of enabling technologies is provided in Section 2.2.4.

2.2.1 High Throughput Systems

Significant research and development are taking place in new technologies for high throughput sample analysis. High throughput systems generally rely on robotics, computer-based control systems, and detector technologies to automate sample handling and analysis, emphasizing the multidisciplinary nature of modern life sciences research. Although an initial investment in such systems can be significant, they have the ability to greatly increase speed and capacity by analyzing multiple samples in parallel.

DNA sequencing technology is one area that has experienced particularly rapid advances (de Villiers, 2010; Dhar, 2010; Pitt, 2010a,b; Taylor, 2010).[23] Next or "second generation" DNA sequencing systems, such as the Illumina HiSeq 2000 released in 2010, have significantly increased DNA throughput capacity. The HiSeq 2000, for example, can reportedly read up to 25 billion bases of DNA per day in 100 base pair read lengths using a modified method of sequencing during synthesis (Illumina.com, http://www.illumina.com/documents/products/datasheets/datasheet_hiseq2000.pdf). Second generation sequencing technology such as the

[23] "First generation" DNA sequencing was based on a method initially developed by Frederick Sanger in the 1970s and on the fact that double-stranded DNA is synthesized using its complementary strand as a template. As this synthesis is conducted, regular deoxynucleotide triphosphates (the building blocks of DNA) are mixed with labeled dideoxynucleotides that will terminate an extending DNA chain. The result is a series of DNA molecules that each differ by one nucleotide in length; these are separated by capillary electrophoresis and the terminal nucleotide identified, allowing the DNA sequence to be read.

HiSeq generates relatively short lengths of DNA sequence, which are aligned and assembled into the complete sequence using software and computer systems. This process is made significantly easier when a previously sequenced reference genome is available to help guide the alignment, such as the reference human genome sequenced in 2003. A variety of new ("third" or "fourth" generation) DNA sequencing technologies are also on the horizon, some of which might produce longer DNA sequence lengths and higher accuracy than the current technology or might further increase speed and decrease costs (Niedringhaus et al., 2011; Shendure and Ji, 2008). In some cases, these technologies streamline steps in the sequencing process so that each nucleotide is directly read as it is incorporated into a single molecular DNA chain (e.g., Pacific Biosciences) (Niedringhaus et al., 2011). In other cases, very different technical processes are being explored for sequencing, such as the detection of alterations in current as individual bases of a DNA molecule pass through a nanopore (e.g., Oxford Nanopore) (Niedringhaus et al., 2011).

Along with the increase in speed has come a dramatic decrease in DNA sequencing costs. Figure 2.1 analyzes data from the U.S. National Human Genome Research Institute (NHGRI). Since 2008, costs have decreased even more rapidly than would be predicted by Moore's Law,[24] reflecting the use of second generation sequencing systems combined with the availability of the existing human genome reference (Wetterstrand, 2011). As a result, human genome sequencing can now be accomplished for approximately $0.10 per million bases of DNA or less than $10,000 per human whole genome, with costs dependent on factors like the sequencing coverage and error rates, as well as which specific costs are factored into the calculation. In 2010, the company Complete Genomics announced that it had sequenced a genome for a cost of approximately $4,400 in consumables such as reagents (Drmanac et al., 2010). Science may be approaching the $1,000 genome in the not too distant future, a price that may in turn bring the concept of personalized medicine closer to reality (Pitt, 2010b; Venter, 2010).

High throughput systems are also available to analyze gene and protein expression. For example, gene microarrays consist of small pieces of DNA attached to a solid surface to act as probes. Pieces of nucleic acid from a biological sample will hybridize with the fixed probes if they have a complementary sequence, and through this process researchers identify those genes that are expressed (turned into messenger RNA) in a particular cell and their relative expression levels.

[24] "Moore's Law" is the observation by Gordon Moore, the founder of Intel Corporation, that the number of transistors on a computer chip roughly doubles every two years. The comparison has frequently been drawn between this exponential growth and a comparable growth in DNA sequencing and synthesis capabilities.

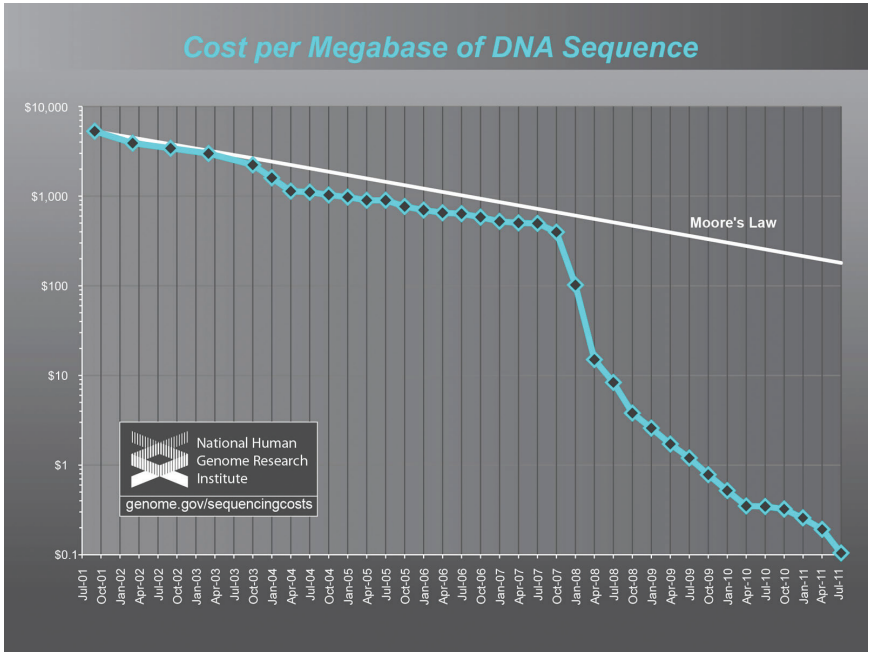

FIGURE 2.1 Decreasing costs of DNA sequencing.
NOTE: Based on "production cost" data from the Large-Scale Genome Sequencing Program of the U.S. National Human Genome Research Institute. Costs include labor, reagents and consumables, DNA preparation, amortization of instrument costs, and initial data processing, but not expenses such as technology and bioinformatics development and subsequent data analysis and interpretation.
SOURCE: Wetterstrand (2011).

Similarly, a variety of protein microarrays exist to identify and quantify the proteins found in a biological sample (Chandra et al., 2011). The use of mass spectrometry (MS), which ionizes proteins and measures the mass-to-charge ratio of the intact protein molecules and fragment ions, has also become a powerful and widely used tool to characterize the proteins and peptides in biological samples and to support proteomics research (Domon and Aebersold, 2006). Improvements in techniques to generate ions from biological molecules, including matrix assisted laser desorption/ionization (MALDI), have enabled improvements in analysis methods that can provide more detailed structural information about peptides. Examples include time-of-flight (TOF) analysis, in which the mass-to-charge ratio of ions is determined by measuring the time it takes the ion to travel through a vacuum after being accelerated by an electric field, and tandem mass spectrometry (MS/MS), which makes use of multiple stages of MS analysis. These techniques

can enable the rapid and sensitive identification of microorganisms as well as their toxins; MS can also be applied to detect a microorganism's nucleic acids amplified through techniques such as polymerase chain reaction (PCR), which may be useful in cases in which a microorganism cannot be cultured (Boyer et al., 2011; Ho and Reddy, 2011). As a result, these advances can contribute to areas relevant to the BWC including monitoring, diagnostics, and bioforensics.

These types of high throughput systems all function as tools to help support active research in many of the areas discussed at the workshop, including genomics, proteomics, systems biology, and synthetic biology (de Villiers, 2010; Dhar, 2010; Pitt, 2010a). The characterization of changes in gene and protein expression during the progress of different diseases helps researchers identify new targets for the development of diagnostics and therapeutics, while the ability to analyze gene and protein expression in individuals helps advance the concept of personalized medicine.

2.2.2 Computational Technologies and Data Resources

Increasingly powerful stand-alone supercomputers are being constructed, including specialized computers to investigate computationally intensive problems in the life sciences. For example, Anton, constructed by D.E. Shaw Research in 2008, is a massively parallel machine designed specifically to enable atomic-level simulations to be conducted of biological molecules up to millisecond-length time scales and up to 100 times faster than previously possible (Shaw et al., 2008; http://www.deshaw-research.com/). These molecular dynamics simulations can be used to investigate the folding and interactions of proteins and nucleic acids, for example to examine predicted interactions between cellular receptors and drug candidates in efforts to advance biological understanding and improve therapeutics development. Supercomputing resources are also now available in regions beyond the United States and Europe. Until June 2011, the world's fastest stand-alone supercomputer, Tianhe-1A, was located at the National Supercomputing Center in Tianjin, China, surpassing the U.S.-developed supercomputer, Jaguar, in the November 2010 rankings published by the Top500 Project. In June, a computer at the RIKEN Advanced Institute for Computational Science in Japan bumped Tianhe-1A to number two on the list and four of the top five fastest supercomputers are now located in Asia.[25]

[25] Supercomputer rankings by the Top500 project are released twice a year based on the use of a benchmark performance measure. See http://www.top500.org/.

An alternative strategy to the use of ever more powerful individual supercomputers is the use of distributed computing.[26] This strategy allows a network of smaller computers to create the equivalent of a supercomputer, thus enabling wider research access to significant computational resources and the analysis of far more complex problems. In his presentation to the workshop, Dr. Etienne de Villiers of the International Livestock Research Institute (ILRI) in Kenya cited the successful distributed computing example of Folding@Home, a project based at Stanford University that is devoted to understanding protein folding and the relationship of misfolding to disease (De Villiers, 2010). By downloading project software, participants donate a portion of their unused computing resources; the project website notes that "since October 1, 2000, over 5,000,000 CPUs throughout the world have participated in Folding@Home" (http://folding.stanford.edu/), making it the equivalent of the largest computer in the world. Similar types of volunteer distributed computing networks are available worldwide. The Asia@home project promotes the use of volunteer computing resources in Southeast Asia, and a recent "Asia@home hackfest" was held during the International Symposium on Grids and Clouds 2011 in Taiwan and focused on applications for earthquake science (http://event.twgrid.org/isgc2011/asiaathome.html). Project websites generally describe the motivations, goals, and problems being undertaken and may subsequently publish results. Although participants in these networks control how much of their computing capacity they are willing to make available to the project, they do not know the specific uses to which it is put.

More specialized distributed computing networks, such as the Teragrid system supported by the U.S. National Science Foundation, also provide the research community with access to high-performance computing and data analysis. Teragrid, coordinated through the Grid Infrastructure Group at the University of Chicago, links computers from 11 U.S. partner sites to provide computing capability, online and archival data storage, and access to more than 100 discipline-specific databases (https://www.teragrid.org/). Similarly, EGI in Europe "maintain[s] a pan-European Grid Infrastructure (EGI) in collaboration with National Grid Initiatives (NGIs) and European International Research Organisations (EIROs), to guarantee the long-term availability of a generic e-infrastructure for all European research communities and their international collaborators" (http://www.egi.eu/). These increasingly available distributed comput-

[26] Distributed computing "is any computing that involves multiple computers remote from each other" (de Villiers, 2010); the systems exist in various configurations with slightly different properties (e.g., cloud computing, grid computing). For further examples on the uses of distributed computing in life sciences research, see Burrage et al. (2006), den Besten et al. (2009), Schatz et al. (2010).

ing networks provide researchers with access to computing power, databases, software, and other tools. As a result, they can be thought of as evolving toward "knowledge grids," a term that has come into use in the past decade to represent virtual social environments that enable access to resources and information as well as the sharing and creation of knowledge (Konagaya, 2006; Zhuge, 2004).

2.2.3 Communication Technologies

Changes in communication technologies, including access to the Internet, email, blogs, social media, mobile communication platforms, and open access publishing, are also enabling widespread dissemination of data and viewpoints and have the potential to change the ways in which scientists work (Meadway, 2010; Royal Society, 2011b).

Internet usage has grown very rapidly. For example, China and Tunisia have experienced 1,800 and 3,000 percent user growth, respectively, since 2000 (Meadway, 2010). A recent report from the Royal Society on international scientific collaborations notes that "the countries showing the fastest rate of growth in publication output and those rising up the global league tables as collaborative hubs show strong trends of growth in mobile phone usage and in internet penetration" (Royal Society, 2011b). Internet penetration is not yet universal and continues to vary widely even among countries in the same region.[27] Despite some remaining access challenges, however, the growth in connectivity enables scientists from multiple countries to search and access information, communicate more easily and informally with each other through means like email and video conferences, and share documents for collaborative editing.

Communication tools have enhanced researchers' access to information in several ways. The ability to search widely used online journal databases such as PubMed, operated by the U.S. National Library of Medicine, coupled with the ability to link to and download journal articles, has become more global as Internet usage has expanded, although

[27] The International Telecommunication Union (ITU) monitors global trends and has created an ICT Development Index (IDI) that reflects multiple factors such as fixed and mobile telephone and Internet infrastructure, access, usage, and skills combined into a single score. Among 159 countries in 2008, Sweden had the highest IDI score (7.85), but significant country-to-country variation is present. Argentina, for example, had an IDI score of 4.38 (number 49 on the list), while Bolivia had a score of 2.62 (number 101); in Africa, Morocco had an IDI score of 2.68 (number 97), while Uganda had a score of 1.30 (number 145) (ITU, 2010). Other groups also monitor trends in world Internet usage. For example, although 66 percent of the general population in Argentina reportedly had access to the Internet as of March 2011, only 10.9 percent did in Bolivia. The rate was 41.3 percent in Morocco, versus 9.2 percent in Uganda and only 0.5 percent in Ethiopia (http://www.internetworldstats.com/stats.htm, accessed July 10, 2011).

institutional subscriptions may be required to access an article's full text. Several online-only life sciences journals also exist (e.g., PLoS One, Nature Communications). These journals frequently employ some system of peer review, but their online-only format can speed up traditional publishing times. In addition, articles that will appear in future issues of a print journal are frequently available electronically in advance of print publication. The Internet also helps scientists identify specialists with whom to collaborate, although it has been reported that 90 percent of all collaborations are initiated in person (Royal Society, 2011b). However, the Internet and other communication tools certainly help collaborations to develop and move forward once established. In these ways, advances in communications technology continue to improve the ease, speed, and global reach of the traditional ways in which science has been done (in particular, the establishment of individual investigator-to-investigator collaborations that might be initiated at a scientific conference and then carried over to the Internet, ideally leading to the joint publication of a peer-reviewed journal article).

As discussed during the workshop, an additional level of interaction involving greater social participation and networking can also be increasingly facilitated with "Web 2.0" technologies. Sites such as Wikipedia, for example, rely on user-generated content and collective wisdom, and other possibilities include science blogging, direct commenting on scientific articles, tagging of articles of interest to share with fellow users of a particular social networking site, posting updates on Twitter, or others. It is not yet clear the extent to which use of these types of tools has become widespread among practicing life scientists. Reportedly, fewer than 10 percent of a sample of 19,800 blogs tagged "science" were written by scientists, and only low percentages of U.K. researchers in 2009 used Twitter (10 percent) or regularly wrote a blog (4 percent) (Meadway, 2010). The challenges involved in creating new Web 2.0 resources that will be useful to life scientists and that can effectively integrate with the existing ways in which science is done have been noted by several authors (Crotty, 2008; Stafford, 2009). David Crotty, formerly an executive editor at the Cold Spring Harbor Laboratory Press, suggested in 2008 that some of these tools, such as blogging or tagging, take investments of time and currently yield insufficient benefits for a scientist, given the continuing emphasis on peer-reviewed journal publications as the gold-standard by which academic productivity is judged (Crotty, 2008). There are also variations in the uses of technology by discipline, with fields such as computer science and mathematics reportedly making more widespread use of newer communications technologies than fields such as medical science (Meadway, 2010). Within the biosciences, it appears that the synthetic biology community may have adopted some of these newer communications tools—the teams participating in the International Genetically Engineered

Machine (iGEM) competition, for example, all develop wiki pages as one of the competition requirements.

2.2.4 Discussion and Implications of Enabling Technologies

There has been particularly rapid progress in both access to and power of enabling technologies that underpin life sciences research, including computational and communication resources and high throughput laboratory technologies. The computational power available to researchers continues to increase, through both specialized stand-alone computers and distributed computing networks. The use of high throughput sample handling and analysis methods has become widespread, and these tools increase the speed with which researchers can conduct studies as well as the volume of data they obtain.

As discussed above, the uses of high throughput analysis tools and computational resources are enabling faster and cheaper developments in the life sciences while the rapid global spread of the Internet and other forms of electronic and mobile communication significantly enable global scientific collaboration and the dissemination of scientific information. Some of the newer "Web 2.0" tools also have the potential to provide a greater social context to the process of scientific knowledge creation, and dissemination and the use of these types of tools in the life sciences may become more widespread as ways to integrate them into the existing system of science become more clearly defined.

These developments have several general implications for the BWC. First, the technologies underpin other developments in the life sciences and contribute to the pace and nature of advances being made in fields that might have specific relevance to the treaty. For example, high throughput techniques yield large amounts of data to advance systems biology understanding in areas like immunology and neuroscience, while computational capacity is used to address problems such as protein structure as part of screening drug candidates for therapeutics development. Second, the global and widespread use of communication technologies, along with models such as online and open access publishing of experimental results, make efforts to control or restrict access to scientific knowledge ever harder. Finally, the same types of mobile and electronic tools that scientists can use to collaborate and share information could also be used by other types of distributed groups, whether state- or non-state actors, to trade information and knowledge. Technological resources that enable the life sciences are now available worldwide, although access to them is not yet evenly distributed. However, the life sciences community is only one of many communities that use computational and communication technologies. As a result, rapid progress in these fields is driven by many factors beyond the life sciences.

2.3 SUMMARY REMARKS ON CHALLENGES AND OPPORTUNTIES RELATED TO THE PACE OF S&T DEVELOPMENTS

Developments in advancing and enabling areas of S&T provide both opportunities and potential challenges relevant to the BWC. One potential challenge posed by advancing S&T is the possibility that a novel development will fall outside the scope of the treaty. As discussed in Section 2.1, the committee did not identify any developments among those it surveyed that did so, a finding also reached by the scientific community at a workshop held prior to the Sixth BWC Review Conference in 2006 (Royal Society, 2006a,b). However, rapid advances in the life sciences on many fronts will likely continue to pose challenges for tracking and assessing future research progress—in establishing priorities for which areas to monitor, anticipating new combinations of advances drawn from progress in multiple fields, and expanding the types of expertise required to assess new developments.

Advances in S&T also provide opportunities to address specific BWC concerns. For example, knowledge derived from omics, systems biology, and immunology, and the high throughput tools, computational resources, and bioinformatics that enable these fields can support rational vaccine and drug design, along with efforts to better understand the immune system, pathogen virulence, and how to modulate these factors. This understanding is critical for effective vaccine and countermeasures development.

As has already been widely recognized, there is a potential dual nature to advances in many fields of the life sciences, because the information that could enable scientists to better understand and manipulate fundamental life processes could potentially also be misused to create harm, and a clear dividing line cannot be drawn between the knowledge, skills, and equipment that would be needed for beneficial or for harmful purposes (Atlas and Dando, 2006; Azzi, 2009; NRC, 2004; van der Bruggen, 2011). It has also been widely recognized that engaging the scientific community in discussions on the safety, security, and ethical implications of research are inherently international, given the global nature of the life sciences research enterprise. This global research capacity and growing numbers of international collaborations in the life sciences are discussed further in the following chapter.

3

Diffusion of Life Sciences Research Capacity and Applications

Chapter 3 addresses the second of the major trends considered by the committee: the increasing diffusion of life sciences research and its implications for the Biological and Toxin Weapons Convention (BWC). The chapter first examines the growing diffusion of research capacity and applications around the globe, illustrated by the rise in international research collaboration, and briefly discusses some of the specific developments enabling these collaborations. It then presents two examples of how the BWC can take advantage of global diffusion to enhance the effective implementation of the treaty. The final section of the chapter discusses a different sort of diffusion: the increasing ability to carry out life sciences research outside traditional institutional settings.

3.1 GLOBAL R&D CAPACITY AND INTERNATIONAL COLLABORATIONS IN SCIENTIFIC RESEARCH

3.1.1 The Growth of International S&T Collaboration

The increasingly widespread access and ease of use of communications technologies, combined with the growing availability of resources to support research (see Section 3.1.2), support the continuing expansion of global research capacity and an ever larger number of international collaborations in science and technology (S&T). Workshop presentations illustrated how global capacity in the life sciences has become; examples included studies at the International Livestock Research Institute (ILRI) in Kenya on Rift Valley fever (de Villiers, 2010) and at the Centre for Systems

and Synthetic Biology at the University of Kerala, which organized the first synthetic biology conference in India and created a wiki to encourage information sharing among Indian laboratories engaged in synthetic biology research (Dhar, 2010).

Data from studies in the United States and the United Kingdom (Adams et al., 2007; NSB, 2010; Royal Society, 2011b) indicate that the number of international collaborations, as measured by jointly authored scientific papers, continues to increase; in 2008 more than one-third of scientific articles included authors from more than one country (Royal Society, 2011b). Although the absolute numbers of scientific papers remain highest for the United States and scientifically developed countries in Europe, countries such as China and India are experiencing particularly rapid growth in output. A recent report comparing the number and growth rate of collaboratively authored papers among a sample of six countries (United States, United Kingdom, France, Germany, China, and India) over two time periods—1996 to 2000 and 2001 to 2005 found that, in all cases, more jointly authored papers were released in 2001-2005 than in 1996-2000. Although there were higher total numbers of papers from the United States and European countries, the rate of increase in joint papers was highest for China and India (Adams et al., 2007). A recent analysis by the U.S. National Science Foundation similarly observed that U.S. and European Union researchers' "combined world share of published articles decreased steadily from 69% in 1995 to 59% in 2008 as Asia's output increased. In little more than a decade, Asia's world article share expanded from 14% to 23%" (NSB, 2010). The additional observation that, as a general pattern, "collaboration usually creates an increase in the indexed bibliometric impact" of a journal article, such as through an increased number of citations (Adams et al., 2007), suggests that collaborative research is producing valuable science.

The workshop also highlighted that international S&T collaborations are occurring not only among researchers in scientifically developed countries and between researchers in developed and developing countries (sometimes referred to as North-South collaboration). The impressive growth of scientific capacity among countries once considered "developing" has enabled collaborations among regional networks and increasingly among scientists (South-South collaboration) (Hassan, 2007; Royal Society, 2011b; Sáenz et al., 2010; Thorsteinsdóttir et al., 2010; WHO, 2009). The growing numbers of such regional and South-South collaborations appear to be an important trend that is expected to continue (UNESCO, 2010).

Examples of effective international and regional collaborations presented at the workshop included multi-partner genomic sequencing efforts (de Villiers, 2010; Pitt, 2010b), the global Human Genome Organi-

zation (HUGO),[1] and related initiatives like the Pan Asian SNP Consortium (HUGO Pan-Asian SNP Consortium, 2009; Sudoyo, 2010). The SNP Consortium links scientists in 11 Asian countries in efforts to catalogue regional human genetic variation, fosters the exchange of knowledge among partner countries, and enables knowledge transfer from more scientifically advanced countries to partner countries seeking to increase their scientific capacity.

The three additional examples described briefly below underscore the growing role that regional and South-South collaborations are playing in S&T and emphasize how truly global life sciences research has become:

- *Cooperation between Cuba and Brazil in Biotechnology*: The Finlay Institute in Cuba and the Immunobiological Technology Institute (Bio-Manguinhos) of the Oswaldo Cruz Foundation in Brazil partnered to develop and manufacture a meningitis vaccine for distribution in Africa, building on the scientific expertise both countries have in biotechnology. Reportedly, "between 2007 and 2009, some 19 million doses were produced and distributed in Burkina Faso, Ethiopia, Mali and Nigeria. The vaccine's price is much lower than on the international market and lower than would be possible without Cuba-Brazil cooperation" (Sáenz et al., 2010)
- *Pan-African Cooperation in Health*: The African Network for Drugs and Diagnostics Innovation (ANDI) was recently established as a partnership among national African organizations, the African Development Bank, and the World Health Organization "to promote and sustain African-led health product innovation to address African public health needs through efficient use of local knowledge, assembly of research networks, and building of capacity to support economic development" (http://www.andi-africa.org/). The ANDI initiative will support projects undertaken by networks of research centers, provide an information technology and database backbone, and support the purchase of advanced laboratory equipment such as nuclear magnetic resonance (NMR) and mass spectrometry instruments (WHO, 2009). The project will tap into and help connect existing R&D capacity in a variety of centers within Africa (see Figure 3.1).

[1] HUGO, created in 1998 as part of the earliest planning for the Human Genome Project, promotes international coordination and collaboration in the study of the human genome. It has grown from an initial membership of 42 scientists from 17 countries to more than 1,200 members from 69 countries. See HUGO website at http://www.hugo-international.org/aboutus.php.

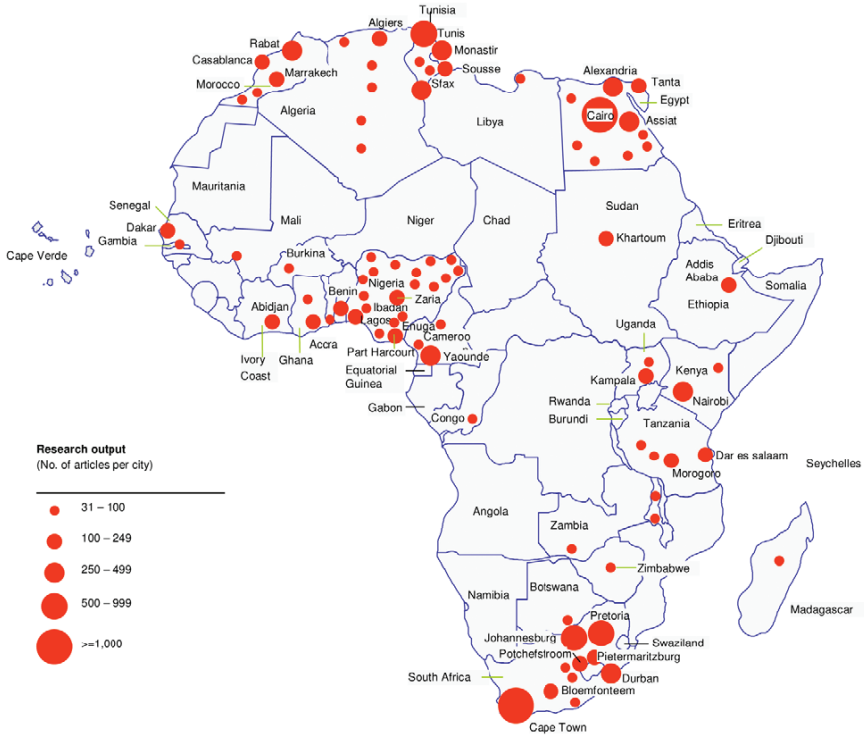

FIGURE 3.1 Distribution of R&D capacity in Africa based on analysis of journal articles from 2004-2008 having corresponding authors located in Africa. The size of the circles correlates with the numbers of published articles.
SOURCE: Nwaka et al. (2010).

- *Cooperation among India, Brazil, and South Africa (IBSA)*: Although health and health-related biotechnology is clearly an area of active international collaboration, it is by no means the only scientific one. IBSA was established in 2003 as a trilateral partnership between the governments of India, Brazil, and South Africa. Within this framework, a variety of cooperative S&T activities have been fostered. The IBSA nanotechnology initiative, for example, is a partnership between the ministries of science and technology of the countries that undertake nanotechnology-based projects in the areas of advanced materials, energy, health and water, and human-capacity building. The initiative has conducted several nanotechnology schools, including one on health applications of nanotechnology (held in November 2009 in South Africa) and one on sensor applications of advanced materials (held in November 2010 in India) (http://www.ibsa-nano.igcar.gov.in/).

As these examples illustrate, there can be multiple motivations for life sciences researchers to engage in international collaborations beyond joint publications. Regional and South-South collaborations, for example, may involve alignment of shared research needs and priorities (e.g., in seeking treatments for diseases endemic to a particular region, but rare elsewhere), opportunities to bring together complementary types of expertise in "South-South partnerships that synergize strengths and bolster competitiveness" (Thorsteinsdóttir et al., 2010), or information sharing by scientifically advanced countries in the South to support capacity building in partner counties (Hassan, 2007). Ideally, all partners in a given collaboration benefit, and one of the strongest incentives seems to be a desire to work with the best people and facilities in a particular field. As a recent analysis of international S&T collaborations noted:

> Collaboration enhances the quality of scientific research, improves the efficiency and effectiveness of that research, and is increasingly necessary, as the scale of both budgets and research challenges grow. However, the primary driver of most collaboration is the scientists themselves. In developing their research and finding answers, scientists are seeking to work with the best people, institutions and equipment which complement their research, wherever they may be. (Royal Society, 2011b:6)

The value of international collaboration is not limited to academic research, as the Cuba-Brazil vaccine development example shows. Industry also participates and benefits. As an examination of collaborations by biotechnology companies in six developing countries concluded:

> Collaboration between firms in the North and South can also facilitate access to strategic knowledge and resources. This flow of resources is not solely North to South, with developed countries being the providers of knowledge; developing countries have been increasing their expertise in this field and possess other resources, such as indigenous materials, important for health biotech development. Furthermore, South-North collaboration can open firms' access to each other's markets. For developing countries, it can be key to gain access to the rich markets in the North, but market opportunities are also flourishing in the South. (Melon et al., 2009:229)

3.1.2 Availability of Resources to Support Collaboration

Investments and Support for S&T

As mentioned in Chapter 1, advances in the life sciences are expected to yield great benefits for health, economic growth and well-being, and the environment. For many countries, they are a key element of invest-

ments in S&T as part of national strategies for development. As early as 1992, *Agenda 21* from the United Nations Conference on Environment and Development forecasted that:

> By itself, biotechnology cannot resolve all the fundamental problems of environment and development, so expectations need to be tempered by realism. Nevertheless, it promises to make a significant contribution in enabling the development of, for example, better health care, enhanced food security through sustainable agricultural practices, improved supplies of potable water, more efficient industrial development processes for transforming raw materials, support for sustainable methods of afforestation and reforestation, and detoxification of hazardous wastes. (United Nations Conference on Environment and Development, 1992:223)

More recently, in 2009 the Organisation for Economic Co-operation and Development (OECD) released a major study on the potential contributions of a "bioeconomy" in 2030, which it defined as "a world where biotechnology contributes to a significant share of economic output. The emerging bioeconomy is likely to involve three elements: the use of advanced knowledge of genes and complex cell processes to develop new processes and products, the use of renewable biomass and efficient bioprocesses to support sustainable production, and the integration of biotechnology knowledge and applications across sectors" (OECD, 2009:8).

For developing countries, one of the key conclusions from the *UNESCO Science Report 2010* is worth quoting at length:

> [T]he increase in the stock of "world knowledge", as epitomized by new digital technologies and discoveries in life sciences or nanotechnologies, is creating fantastic opportunities for emerging nations to attain higher levels of social welfare and productivity. It is in this sense that the old notion of a technological gap can today be considered a blessing for those economies possessing sufficient absorptive capacity and efficiency to enable them to exploit their "advantage of relative backwardness". Countries lagging behind can grow faster than the early leaders of technology by building on the backlog of unexploited technology and benefiting from lower risks. They are already managing to leapfrog over the expensive investment in infrastructure that mobilized the finances of developed countries in the 20th century, thanks to the development of wireless telecommunications and wireless education (via satellites, etc), wireless energy (windmills, solar panels, etc) and wireless health (telemedicine, portable medical scanners, etc). (UNESCO, 2010:25)

Moreover, the substantial trend over the past decade or more by multinational corporations to diversify their research and development facilities beyond their traditional bases in the West (Zanatta and Queiroz, 2007), combined with the growth of significant industries in countries

such as India and China that are investing in the West (UNESCO, 2010) provides another significant driver for the development of life sciences capacity. AstraZeneca, for example, has research facilities in Shanghai, China, and Bangalore, India.[2] The effects of these commercial drivers on particular areas of life sciences research are discussed in Chapter 2 and examined more generally in Chapter 5.

Significant challenges remain to making this potential globally available, and the financial crisis of 2008 and its continuing perturbations have slowed progress for some (UNESCO, 2010). Numerous reports from international and regional organizations recognize the challenges and offer lessons and strategies for overcoming them (see, for example, InterAcademy Council, 2004; Juma and Serageldin, 2007). Efforts to take advantage of S&T to support development and improved well-being can be expected to continue to provide a powerful impetus for the diffusion of research capacity.

Access to Computational and Data Resources

As discussed in Chapter 2, the availability of large amounts of data storage capacity and powerful computational resources supports many of the S&T developments surveyed at the workshop, particularly in the omics fields and in systems and synthetic biology (see Section 2.1). Access to computational resources continues to expand as the underlying infrastructure is put in place worldwide. The ILRI research project on Rift Valley fever described by Dr. de Villiers will generate large amounts of sample meta-data in parallel with the storage of the samples themselves in a biobank (De Villiers, 2010). The project plans to take advantage of the possibilities offered by the completed installation of high-speed fiber-optic cables along the east coast of Africa. The East Africa Submarine Cable System (EASSy), completed in 2010, currently provides 4.72 terabits per second network capacity (http://www.eassy.org/); additional regional bandwidth is now provided by the East African Marine System (TEAMS) and SEACOM cables completed in 2009, as well as by national cable infrastructure. These networks will enable the project to use distributed computing (see Section 2.2.2), providing capacity equivalent to the largest supercomputers.

Availability of Sophisticated Kits, Reagents, and Commercial Services

Global research capacity in the life sciences is also enabled by the commercial availability of kits, reagents, and services to conduct scien-

[2] Further information may be found at http://www.astrazeneca.com/Research/our-global-reach.

tific protocols for cutting-edge research. A large number of multinational suppliers produce kits containing reagents, enzymes, and step-by-step instructions to conduct many of the basic laboratory techniques a life sciences researcher might use, including nucleic acid and protein expression, purification, detection, and analysis.[3] Commercial services are also available for tasks like sequencing, DNA and protein synthesis, microarray construction, mass spectrometry analysis, and others. The availability of smaller, more automated, and easier to use bioinstrumentation also facilitates the performance of laboratory research. In addition to commercial high throughput sequencing services, for example, benchtop DNA sequencers are now available for use within individual laboratories. These tools, which can help increase the speed and efficiency of laboratory research, are available to scientists worldwide, although direct commercial suppliers largely remain clustered in Europe, North America, and parts of Asia.

Qualifying Comments: Continuing Limits on Access and Availability

Although life sciences research capacity is now globally distributed in a very real sense, a variety of barriers remain for scientists in developing countries (InterAcademy Council, 2004). One example, as discussed in Chapter 2, is access to the Internet and other communications technologies, which facilitates global scientific collaboration. Despite continued growth in usage, however, this access remains uneven.[4] A recent report from the Royal Society in the United Kingdom found, for example, that "access to the net is growing very rapidly in some middle-income developing countries, such as South Korea (where access is almost universal) and Brazil. But it is rising only very slowly in low-income countries: 0.06% of the population in low-income countries had access to the web in 1997, rising to 6% 10 years later" (Royal Society, 2011b). However, the same report also noted that statistics on access among the general population of a country are not the entire picture, because "scientists are one community who are most likely to have good access. More troublesome for researchers is internet bandwidth which may be limited, or infrastructure issues which may hinder the ability to communicate effectively. For example,

[3] Major life sciences supply companies include Invitrogen (http://www.invitrogen.com), Promega (http://www.promega.com), Qiagen (http://www.qiagen.com), Ambion (http://www.ambion.com), Clontech (http://www.clontech.com), Sigma-Aldrich (http://www.sigmaaldrich.com), Roche Applied Science (http://www.roche-applied-science.com), Affymetrix (http://www.affymetrix.com), and many others.

[4] As noted by participants in a 2009 workshop on the use of online resources for education about biosecurity issues, it is not just developing countries that suffer from uneven access to the Internet. Substantial parts of the rural United States, for example, either do not have access to the Internet or have only very basic services (NRC, 2011a).

power cuts are frequent in many universities across Africa and the internet connection speed is low" (Royal Society, 2011b).

As noted above, direct suppliers of commercial life sciences kits, tools, and services largely remain clustered in Europe, North America, and parts of Asia, although networks of local distributors may exist. In addition to the financial cost of ordering from commercial suppliers, researchers in areas of the developing world may still experience challenges associated with regulations and shipping times. A detailed discussion of these forces is beyond the committee's task. A major purpose of this section has been to highlight the increasingly global nature of current life sciences research and the growing role of regional and South-South scientific collaborations, while recognizing that advanced S&T capacity is not yet evenly distributed worldwide.

3.1.3 Discussion and Implications

The diffusion of research capacity and its applications is directly relevant to two articles of the BWC:

- Article III, which states: "Each State Party to this Convention undertakes not to transfer to any recipient whatsoever, directly or indirectly, and not in any way to assist, encourage, or induce any State, group of States or international organizations to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or means of delivery specified in Article I of this Convention." (United Nations, 2011:2)[5]
- Article X, which states: "(1) The States Parties to this Convention undertake to facilitate, and have the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. Parties to the Convention in a position to do so shall also cooperate in contributing individually or together with other States or international organizations to the further development and application of scientific discoveries in the field of bacteriology (biology) for prevention of disease, or for other peaceful purposes. (2) This Convention shall be implemented in a manner designed to avoid hampering the economic or technological development of States Parties to the Convention or international cooperation in the field of peaceful bacteriological (biological) activities, including the international exchange of

[5] "The Second, Third, Fourth and Sixth Review Conferences affirmed that Article III is sufficiently comprehensive to cover any recipient whatsoever at the international, national or sub-national levels. [VI.III.8, IV.III.1, III.III.1, II.III.1]." (United Nations, 2007:6)

> bacteriological (biological) and toxins and equipment for the processing, use or production of bacteriological (biological) agents and toxins for peaceful purposes in accordance with the provisions of the Convention." (United Nations, 2011:3)

The relationship between Article III and Article X has been the source of debate since the BWC's entry into force; the list of common understandings achieved at various review conferences reflects the continuing effort to find a satisfactory mix of policies to address both aspects of this common disarmament bargain.[6] The debates have sharpened since the early 1990s, when the Australia Group expanded its focus from chemical weapons to include biological weapons and placed export controls on certain dual use biological equipment and a number of pathogens and toxins.[7] The Chemical Weapons Convention and the Nuclear Non-Proliferation Treaty contain similar provisions and debates, but the pervasively dual nature of life sciences research discussed in Chapter 1 makes this problem particularly difficult for the BWC.[8]

The continuing, rapid diffusion of research capacity and knowledge poses a profound challenge to those aspects of nonproliferation policy that rely on controlling access to knowledge, materials, and technologies. Given that there is little hope of reversing this trend—and multiple reasons beyond the commitments in Article X to see it as positive and

[6] For example, with slightly different wording the Second, Third, Fourth, and Sixth Review Conferences all "noted States Parties should not use the provisions of this Article to impose restrictions and/or limitations on transfers for purposes consistent with the objectives and provisions of the Convention of scientific knowledge, technology, equipment and materials under Article X. [VI.III.10, IV.III.4, III.III.2, II.III.2]" (ibid., p. 7).

[7] "The Australia Group (AG) is an informal forum of countries which, through the harmonisation of export controls, seeks to ensure that exports do not contribute to the development of chemical or biological weapons. Coordination of national export control measures assists Australia Group participants to fulfill their obligations under the Chemical Weapons Convention and the Biological and Toxin Weapons Convention to the fullest extent possible" (Australia Group, http://www.australiagroup.net/en/index.html, accessed October 20, 2011). The AG membership currently includes 40 countries as well as the European Commission.

[8] Chemical and nuclear weapons also involve dual use technologies; one distinguishing feature of biological weapons is that the dual use relationship is deeper and more extensive than in these other fields. For biological weapons, it is much harder to identify S&T that is primarily "weapons relevant" or primarily "legitimate." The issue of scaling up is even more important; for CW, agent quantity can play a key role in distinguishing between offensive and defensive intentions (the definition of CW refers to consistency of types and quantities of toxic chemicals with regard to permitted purposes); in BW that is less relevant given the nature of biological agents, including self-replicating organisms, and the different scenarios of hostile use, some of which require relatively small quantities.

beneficial[9]—this argues for at least two important findings. First, it suggests the importance of continuing attention to monitoring and assessing the diffusion to try to anticipate the potential negative consequences and of strengthening the capacity of States Parties to address them, for example through their Article IV commitments to national implementation. Second, it underscores the potential for a much larger number of States Parties to contribute to the implementation of the convention, for example by expanding global public health and disease surveillance capabilities, or by playing leadership roles in capacity building in their regions. The next two sections of the chapter provide examples of this second finding in more detail.

3.2 DISEASE SURVEILLANCE AND RESPONSE SYSTEMS: A RESEARCH AREA THAT EXEMPLIFIES GLOBAL LIFE SCIENCES CAPACITY AND INTERNATIONAL COLLABORATION RELEVANT TO THE BWC

3.2.1 Introduction

In 2007 the *World Health Report* from the World Health Organization (WHO) warned

> Today's highly mobile, interdependent and interconnected world provides myriad opportunities for the rapid spread of infectious diseases … Infectious diseases are now spreading geographically much faster than at any time in history. It is estimated that 2.1 billion airline passengers travelled in 2006; an outbreak or epidemic in any one part of the world is only a few hours away from becoming an imminent threat somewhere else … Infectious diseases are not only spreading faster, they appear to be emerging more quickly than ever before. Since the 1970s, newly emerging diseases have been identified at the unprecedented rate of one or more per year. There are now nearly 40 diseases that were unknown a generation ago. In addition, during the last five years, WHO has verified more than 1100 epidemic events worldwide. (WHO, 2007b:x)

Becaause major parts of the public health response to infectious diseases are the same whether the origins of an incidents are natural, unintentional, or deliberate, as Dr. Raymond Lin of the Singapore National Public Health Laboratory noted at the workshop, "Preparedness for natu-

[9] See, for example, the discussions of advances in research in Section 2.1 and their potential applications for health, the environment, and economic growth. For a more general discussion, see NRC (2009b) and OECD (2009).

rally occurring infectious disease outbreaks equals preparedness for biothreat events" (Lin, 2010).

A critical area in which life sciences S&T is contributing to the operation of the BWC is thus in the development of systems for the surveillance, detection, and identification of diseases in human, animal, and plant communities. It also includes the development of vaccines and medical countermeasures to prevent and respond to outbreaks of human and animal diseases and the development of appropriate pesticides or rapid if not preemptive development of genetically resistant cultivars for plant diseases. This is a major example of how, over the years, the States Parties to the BWC have increasingly recognized the importance of using multiple means and methods to support the implementation of the treaty in addition to the regulatory aspects of disarmament and nonproliferation exemplified in Article IV. [10] This approach is commonly referred to as the "web of prevention."[11]

Because diseases do not recognize national borders, such systems greatly benefit from international cooperation. And because many emerging diseases arise in regions such as Southeast Asia, Africa, and Latin America (Jones et al., 2008), the ability to draw on global scientific capacity also contributes significantly to the field.

Diseases of concern are not limited to human illnesses; agricultural systems also remain vulnerable to devastating disease outbreaks (NRC, 2002). Vulnerabilities in agricultural systems exist because of both local-scale and global movement of people, animals, and goods, as well as the increasing prevalence of large-scale monoculture farming (Jeger, 2010). An agricultural disease outbreak can produce significant economic impacts and commercial implications even if the pathogen is present only in low numbers. For example, 53 countries banned the import of U.S. beef following the first detection in 2003 of bovine spongiform encephalopathy (BSE), or mad cow disease, in the United States, causing the beef industry estimated losses of several billion dollars in 2004 (CDC, 2004; Coffey et al., 2005). Although the BSE case was not due to a biological weapons attack and many markets gradually reopened, the potential economic

[10] Prevention for human, animal, or plant health, for example, is distinct from the range of other political, military, and technical measures that States Parties may take to prevent an intentional biological attack.

[11] The International Committee of the Red Cross coined the phrase as part of its 2004 initiative on "Biotechnology, Weapons, and Humanity"; more information is available at http://www.icrc.org/eng/resources/documents/misc/5vdj7s.htm. Also see Rappert and McLeish (2007).

consequences of an incident are clear.[12] Only limited plant and animal disease surveillance and identification systems currently exist (for example, monitoring of sentinel plants), and lack of funding has remained a challenge in this area.

3.2.2 Improving Disease Surveillance

International collaboration on the development of integrated and multidimensional disease surveillance systems provides clear benefits for understanding and monitoring human, animal, and plant diseases whether they are natural outbreaks, unintentional releases such as pathogen escape from a laboratory, or intentional exposures (Jeger, 2010; Lin, 2010). A variety of clinical and epidemiological monitoring tools can be used as part of surveillance systems, including testing relevant sentinel sites, screening blood samples from particular groups, or analyzing data from disease-specific Internet searches and Twitter postings to help estimate the prevalence of an infection (Lin, 2010). Communications systems are also important to rapidly share information about disease incidents.[13]

The program of annual meetings of experts and States Parties—the intersessional process—undertaken by the BWC States Parties in 2002 has provided the basis for the growing attention to the role that global health security plays in supporting the BWC regime. The annual meetings in 2004 and 2009 were devoted to global health topics, and the United Nations website for the meetings contains materials related to dozens

[12] An example from plant pathology would be Karnal bunt of wheat caused by *Tilletia indica*. The United States was free of this disease until it showed up on wheat in Arizona in 1996 and later in Texas and California. Nearly all countries that import wheat from the United States had and still have quarantine against introduction of this pathogen, whether on wheat for seed or food. Immediately, a $5 billion U.S. wheat export industry was in jeopardy as wheat-importing countries turned to Australia, Argentina, and Canada for their wheat. In response, the U.S. Department of Agriculture implemented a policy whereby wheat-producing states were surveyed and declared Karnal bunt free, state by state, for the export market, while wheat from states with the pathogen was dedicated for domestic use only. Karnal bunt is actually a minor disease of wheat, and the designation of *T indica* as a quarantined pathogen has been political and not based on science. Nevertheless, the vulnerability of the U.S. wheat industry remains (Bonde et al., 1997).

[13] An initiative from the nongovernmental community that preceded—and served as a model for—current intergovernmental efforts, the International Society for Infectious Diseases operates ProMed-mail, which provides reports on emerging infectious disease outbreaks online as well as through an email listserv and also operates region-specific notifications for areas such as Africa, the former Soviet Union, and Southeast Asia (http://www.promedmail.org/).

of presentations and other events.[14] The WHO, the World Organization for Animal Health (OIE), and the United Nations Food and Agriculture Organization (FAO) all made presentations at the 2009 meeting of experts. One of the outcomes from the meetings has been increasing connections between the BWC and the WHO, especially with regard to the implementation of the International Health Regulations (IHRs) adopted in 2005, because improved capacities to monitor and report disease outbreaks serve the goals of both regimes.[15]

OIE's participation in the intersessional meetings reflects increasing international attention to the connections between human and animal diseases. The WHO, OIE, and FAO are partners in the Global Early Warning and Response System (GLEWS), launched in 2006, which is

> a joint system that builds on the added value of combining and coordinating the alert and response mechanisms of OIE, FAO and WHO for the international community and stakeholders to assist in prediction, prevention and control of animal disease threats, including zoonoses, through sharing of information, epidemiological analysis and joint field missions to assess and control the outbreak, whenever needed. (http://www.glews.net/)

The growing emphasis on public health can be controversial. There continue to be concerns about the "securitization of health" by drawing

[14] See http://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument. In 2004, the focus was "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; and in 2009 it was enhancing international cooperation, assistance and exchange in biological sciences and technology for peaceful purposes, promoting capacity building in the fields of disease surveillance, detection, diagnosis, and containment of infectious diseases: (1) for States Parties in need of assistance, identifying requirements and requests for capacity enhancement; and (2) from States Parties in a position to do so, and international organizations, opportunities for providing assistance related to these fields."

[15] "The International Health Regulations (IHR) are an international legal instrument that is binding on 194 countries across the globe, including all the Member States of WHO. Their aim is to help the international community prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide. … The IHR, which entered into force on 15 June 2007, require countries to report certain disease outbreaks and public health events to WHO. Building on the unique experience of WHO in global disease surveillance, alert and response, the IHR define the rights and obligations of countries to report public health events, and establish a number of procedures that WHO must follow in its work to uphold global public health security. The IHR also require countries to strengthen their existing capacities for public health surveillance and response. WHO is working closely with countries and partners to provide technical guidance and support to mobilize the resources needed to implement the new rules in an effective and timely manner. Timely and open reporting of public health events will help make the world more secure" (WHO, What Are the IHR?, http://www.who.int/features/qa/39/en/index.html).

the WHO and the IHR into the realm of biosecurity (Kelle, 2006; Tucker, 2005).[16] On the other hand, participants in the meetings hosted by the BWC ISU and key States Parties to prepare for the Review Conference tended to emphasize the perceived benefits to viewing cooperation on disease surveillance via Article X (China, Canada, and BWC ISU, 2010; Indonesia, Norway, and BWC ISU, 2010), as do a number of national strategy documents (see, for example, White House, 2009a).

3.2.3 Laboratory Analysis and Response Capabilities

As discussed in Chapter 2, advances in technologies such as biosensors (Section 2.1.7), along with other forms of epidemiological monitoring (Jeger, 2010; Kurochkin, 2010; Lin, 2010; Resnick, 2010), help build the essential components of an effective public health system. In addition to clinical and epidemiological monitoring to detect a disease outbreak, laboratory analyses are a valuable part of the disease surveillance and response system to identify and characterize the pathogen in more detail (Lin, 2010; Murch, 2010). Particular genetic mutations of a pathogen may be associated with greater virulence or with antimicrobial drug resistance, for example. Genetic sequencing and other laboratory studies may help to identify particular changes to be monitored. Human, animal, and plant pathogens evolve as they spread, and scientific approaches can help trace the likely movement of pathogen strains over time and location. A closely related field, bioforensics, which uses scientific tools to help identify the origin of a particular pathogen and thus has the potential to support the investigation of natural disease outbreaks or potential bioweapons incidents as well as to contribute to the global network of national and international public health disease surveillance labs, is discussed in the next section.

The increased attention to global health security has included a significant expansion of laboratory capacity in many parts of the world, in part to support research and in part to enable identification of outbreaks close to the source. The increase in the number of laboratories working with highly dangerous pathogens has sparked concerns about safety and security. The 2007 *World Health Report* warned:

> As activities related to infectious disease surveillance and laboratory research have increased in recent years, so too has the potential for outbreaks associated with the accidental release of infectious agents. Breaches in biosafety measures are often responsible for these accidents. At the same time, opportunities for malicious releases of dangerous pathogens,

[16] A review of this debate in the context of the development of biosecurity as an issue may be found in Koblentz (2010).

> once unthinkable, have become a reality, as shown by the anthrax letters in the United States of America in 2001. (WHO, 2007b:xi)

The most recent edition of the WHO's Biosafety Manual, published in 2004, discusses biosecurity for the first time (WHO, 2004). The WHO's 2006 Biorisk Management: Laboratory Biosecurity Guidance provides guidance to member states for developing national approaches that can "strike a balance" between traditional biosafety and more recent security concerns (WHO, 2006:1).[17] And a 2010 report offers guidance on measures to address the risks of laboratory accidents or potential deliberate misuse "within the context of promoting and harnessing the power of the life sciences to improve health for all people" (WHO, 2010:1).

In 2008, the European Committee for Standardization (CEN) published its *International Laboratory Biorisk Management Standard*, which seeks "to set requirements necessary to control risks associated with the handling or storage and disposal of biological agents and toxins in laboratories and facilities" (CEN, 2008:8). The recent rapid growth of national and regional biosafety associations is intended to develop the capacity to implement and sustain high standards for laboratory safety and security.[18] In addition, a number of important initiatives focused specifically on security by national governments, regional organizations, and international partnerships are bringing substantial resources to bear to improve safety and security at laboratories around the world, along with more general public health capacity-building for surveillance and diagnosis.[19] Examples include the U.S. National Strategy for Countering Biological Threats (White House, 2009a) and the programs to implement it, the European Commission's CBRN Centres of Excellence, and the G8 Global Partnership Against the Spread of Weapons and Materials of Mass Destruction.[20]

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[17] The most recent edition of the *Biosafety in Microbiological and Biomedical Laboratories* from the U.S. National Institutes of Health, another widely used reference document, also added a discussion of laboratory biosecurity (CDC/NIH, 2007).

[18] Additional information may be found at the website of the International Federation of Biosafety Associations (IFBA) at http://www.internationalbiosafety.org/english/index.asp.

[19] The U.S. national strategy may be found at http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf. Information about the Centres of Excellence may be found at http://www.cbrn-coe.eu/. The 2011 report on the G8 Global Partnership may be found at http://www.g20-g8.com/g8-g20/g8/english/the-2011-summit/declarations-and-reports/appendices/report-on-the-g8-global-partnership-angainst-the.1353.html.

[20] For more information see, for example, the Biosecurity Engagement Program of the U.S. Department of State at http://www.bepstate.net/, the Centres of Excellence at http://www.cbrn-coe.eu/, and the G8 Global Partnership at http://www.canadainternational.gc.ca/g8/summit-sommet/2003/mass-destruction-massive.aspx?view=d.

Although disease monitoring and surveillance is critically important, a workshop participant eloquently noted that "surveillance without response is nothing but the quantification of misery." Immunological research to develop vaccines and medical countermeasures helps to provide a capability to respond to identified outbreaks, and some of the recent advances are discussed in Section 2.1.3. The field also benefits directly from collaborative international scientific research as shown in Figure 3.2. The sizes of the circles on the figure represent numbers of jointly authored scientific papers in the field of vaccine development, while the lines represent co-author linkages. Although the United States and Europe are heavily represented, the map indicates that countries like Brazil, South Africa, India, China, and Thailand show nodes of significant involvement as well.

In the area of animal diseases, a very recent global initiative may contribute to the research capacity to better understand some of these diseases. The Global Strategic Alliances for the Coordination of Research on the Major Infectious Diseases of Animals and Zoonoses (STAR-IDAZ) will include multiple partner counties and will be coordinated by the U.K. Department for Environment, Food and Rural Affairs (Defra) with the goal of improving information sharing, research coordination, and priority setting (http://www.star-idaz.net/).

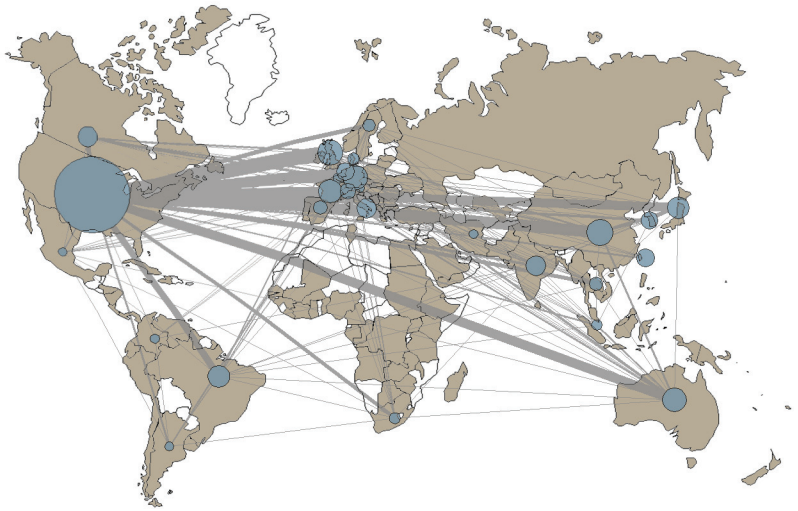

FIGURE 3.2 Patterns of international, multi-author journal publications in the field of vaccine development.
SOURCE: Ilchmann et al. (2011), reprinted with permission from the Harvard Sussex Program.

3.2.4 Discussion and Implications

The combination of tools including sensors, forensics and other laboratory investigations, epidemiological monitoring, and vaccine research—and its increasingly global distribution—contribute to the development of effective disease detection, investigation, and response systems. The specific tools and capabilities needed to investigate a disease outbreak will be scenario dependent, and it remains difficult to provide real-time awareness using surveillance networks. However, these multiple tools can provide a network of complementary support including general detection or rapid screening to flag a likely outbreak, specific diagnosis and more detailed characterization of the pathogen, and potential treatments that can be deployed to protect at-risk populations. Global travel and trade and the potential commercial as well as health implications of disease outbreaks highlight vulnerabilities in the system and also emphasize the important role of international cooperation in disease monitoring and response.

3.3 MICROBIAL FORENSICS: AN OPPORTUNITY TO TAKE ADVANTAGE OF GROWING INTERNATIONAL S&T CAPACITY TO SUPPORT THE BWC

One of the fundamental components of any investigation of alleged hostile use of biological agents, whether by states or non-state actors, will be scientific analysis to support efforts at attribution. Science may not offer definitive solutions for all scenarios, but it often plays a special role in supporting other aspects of an investigation. The investigation of the 2001 anthrax mailings in the United States highlighted the role of microbial forensics in support of pathogen identification and attribution and served as a driver for the development of new microbial forensics tools and approaches (Connell, 2010; NRC, 2011b).

Contrary to the images from popular media, however, microbial forensics is in the early stages of development and faces substantial challenges that involve fundamental scientific questions. Dr. Randall Murch of the Virginia Polytechnic Institute and State University noted in his workshop presentation that many of the tools employed to investigate the anthrax strains are unique to that case and that only limited forensic systems have been worked out for other pathogens of interest. As a result, anthrax remains almost a unique case for which detailed forensics approaches are currently possible (Murch, 2010). Gaps in the development of microbial forensics that were identified during the discussions included a lack of common approaches and standards, as well as a lack of agreement on proper sample storage to prevent contamination.

Given the controversies likely to surround any investigation of alleged use, there could be substantial advantages to building capacity

in microbial forensics via international collaborations that engage the broader scientific community. The goal would be to create a shared technical understanding of the possibilities—and limitations—of the scientific basis for microbial forensic analysis. Because many of the challenges are also important questions for the life sciences and related disciplines more generally, these collaborations could engage the very best scientific talent across a range of fields. The diffusion of research capacity described in this chapter means that the effort could be genuinely international from the beginning. Such collaborations would complement work already being done by government agencies and scientists in a number of countries, and could build connections between this work and the contributions to be made by the wider scientific community. Examples of some of the science questions identified by Dr. Murch and carried into the workshop discussions include:

- How can systematics and genomics be reconciled to provide precise, consistent, and robust approaches to identifying and characterizing sources of microorganisms that can be used as biothreat agents?
- How could microbial systems be sampled to effectively address forensic questions?
- What are the "big leaps" in physico-chemical methodology and technology development that are needed for microbial forensics and what would be gained from them?
- What is the optimal and most adaptive combination of genomic and physico-chemical methods to achieve maximal forensic exploitation for current and future biothreat agents?
- What is the most robust statistical approach for defining and communicating certainty/uncertainty for microbial samples from known and questioned sources?
- What computational and bioinformatics tools are needed to support microbial forensics and what strategic approach could be developed to achieve them?
- What science has yet to be developed to distinguish among natural, deliberate, and unintentional outbreaks, and how can the time to doing so be reduced?

In addition to supporting investigations of alleged hostile uses of biological agents, advances in technology to support microbial forensics could be potentially applied to further the development of biosurveillance and detection systems. The challenge of building capacity for microbial forensics presents one opportunity to take advantage of life sciences research from around the world to support the work of the BWC.

3.4 DOING LIFE SCIENCES RESEARCH OUTSIDE TRADITIONAL INSTITUTIONS

The abundance of kits and commercial services now associated with modern life sciences research discussed in Section 3.1.2 above, coupled with excitement about the possibilities of discovery in rapidly advancing S&T, supports another important form of diffusion: enabling individuals and groups to do research outside traditional research institutions. In some cases these are trained scientists taking advantage of commercial kits and services, as well as the availability of secondhand equipment, to build their own laboratories and conduct experiments (Carlson, 2005). In other cases these are individuals who are undertaking research without having the detailed biological or mechanistic understanding previously required in the life sciences. Innovative approaches to engaging students in hands-on research early in their studies are another example. Although there are important differences among the cases, they are all frequently included in discussions of "amateur," "garage," or "do-it-yourself" (DIY) biology (Ledford, 2010; Penders, 2011).

3.4.1 Engaging Students: The International Genetically Engineered Machines (iGEM) Competition

The creation of registries of biological "parts" (sequences of DNA that can be combined in a straightforward manner to ultimately perform particular biological functions),[21] a key goal for one portion of the synthetic biology community, also raises the possibility that steps used in traditional genetic engineering and molecular biology are becoming more standardized and easier to accomplish. iGEM, which began at the Massachusetts Institute of Technology (MIT) in 2003, provides teams of undergraduate students with an assortment of standard parts to use to design new biological systems; the competition has recently added a division for high school teams.[22] The 2010 competition included 130 groups from more than 29 countries, including 5 teams from countries in Latin America and Africa. Projects in 2010 included the modification of biosynthetic pathways (Slovenia); the creation of a "Virus Construction Kit" of components for adeno-associated virus (AAV)-based viral gene therapy (Freiburg, Germany); and the creation of a bacterial diagnostic biosensor designed to respond as a population to a particular viral infection (WITS, South Africa). Reflecting the growing global participation, the 2011 competition will begin with

[21] The Registry of Standard Biological Parts, used by the iGEM competition, is available online, as "part of the Synthetic Biology community's efforts to make biology easier to engineer" (http://partsregistry.org/).

[22] More information is available on the iGem website at http://ung.igem.org.

regional competitions in Europe, Asia, and the Americas in October, followed by the Worldwide Championship in November at MIT.

3.4.2 DIY Bio

Just as the iGEM competition arises out of the synthetic biology community, much of the excitement within and around the amateur biology community has also come to be linked with the ability to manipulate DNA and with the synthetic biology goal of making biology easier to engineer.[23] The website Diybio.org (http://diybio.org/) lists local groups of amateur biologists in a variety of major cities, primarily in the United States and Europe, although groups are also listed in India and Singapore. These local groups may offer community lab space to help facilitate hands-on experiments (e.g., Genspace in New York [http://genspace.org/] or BioCurious in California [http://biocurious.org/]), or offer training to help people get started. Some DIY biologists also construct or purchase their own inexpensive versions of equipment for performing common laboratory tasks such as electrophoresis or thermal cycling, and information and videos are available online (Ledford, 2010). See, for example, Teklalabs (http://www.teklalabs.org/about/) and Singularity Hub (http://singularityhub.com/2010/08/03/making-the-modern-do-it-yourself-biology-laboratory-video/). It is not yet clear how widespread truly amateur biology has become, but it seems reasonable to expect that this trend will grow in the future. This underscores the need to understand how training and know-how are propagated and cultures of safety are developed in such noninstitutional environments. How does one identify and reach out to those who may operate unaware of (or indifferent to) government regulatory frameworks, which is the typical province of the BWC?

3.4.3 Discussion and Implications

Improving the understanding of and excitement for life sciences among the public can be seen as advantageous, because scientific research relies on public trust and public funding and because policies to address a range of issues require public engagement. It is obviously important from a safety and security as well as an educational standpoint that students and amateur/DIY biologists are able to safely conduct their experiments and that they are able to understand possible risks and ethical considerations.

[23] In the same manner that synthetic biologists have adopted electrical engineering and computer science terminology (referring to DNA as the "software" of life for example), some in the amateur biology community refer to themselves as "biohackers."

iGEM requires teams to answer safety-related questions about their proposed projects as part of their application for the competition, and judges are to consider the answers in assessing the proposals. The website includes references to various international, regional, and national policies and regulations related to biosafety. The potential for intentional misuse of research results is also addressed. The website includes references to the BWC as the key international legal agreement and to resources related to responsible conduct as well as national guidelines and regulations.[24] Dr. Piers Millet from the BWC's Implementation Support Unit serves as an iGEM judge and resource, and in 2010 a U.S.-French team received a special safety and security award for its development of screening software to identify whether DNA parts in the iGEM Standard Registry of Parts came from pathogens or toxins.[25]

According to its website, "One motivation for establishing DIYbio.org in advance of widespread amateur activity in the life sciences is to create a framework for best practices worldwide," including resources on biosafety and norms of ethics and practice (http://diybio.org/safety). In the United States, the American Association for the Advancement of Science is working with the Federal Bureau of Investigation (FBI) on a series of outreach activities to the amateur biology community. The meetings, which began in 2009, include researchers, FBI and other government officials, and members of the amateur biology community (AAAS, 2011). The FBI also has an active outreach program to U.S. iGEM teams.

Life sciences knowledge and research capacity continue to become more available to communities who operate outside of traditional settings. However, although commercial kits and services and other advances such as standardized DNA parts provide efficiencies and ease-of-use, when it comes to less highly trained practitioners, it is important to note that successful achievement of experimental goals generally relies on more than these products. Valuable knowledge and skills are also acquired through experience, and the importance of having these additional levels of knowledge increases with the complexity of the research projects undertaken.

[24] For example, the iGEM website contains a box suggesting that "as a participant in iGEM, there are three things you can do right now to help us secure our science:

- Include something in your project description and presentations that demonstrates that you have thought about how others could misuse your work
- Contribute to community discussions on what needs to go into a code against the use of our science for hostile purposes (see A Community Response)
- Look into what security provisions, such as laws and regulations, are already in place in your country (see Working within the Law)."

[25] More information is available at http://2010.igem.org/Security.

4

Integration of Multiple Disciplines in Life Sciences Research

Chapter 4 addresses the last of the overarching trends considered by the committee: the involvement of a variety of scientific and technical disciplines beyond biology in life sciences research. After a brief introduction to the diversity of fields now involved in the life sciences, the chapter focuses on the intersection of biology and chemistry, which may be particularly relevant for both the Biological Weapons Convention (BWC) and the Chemical Weapons Convention (CWC).

4.1 THE BREADTH OF RELEVANT FIELDS IN THE LIFE SCIENCES AND THE CONVERGENCE OF THE LIFE SCIENCES WITH OTHER DISCIPLINES

Life sciences research draws on the expertise not only of biologists but increasingly also on scientists from engineering, mathematics, computer science, chemistry, materials science, and many other disciplines. The importance of integrating contributions drawn from these multiple disciplines and applying them to life sciences challenges has been recognized in a variety of recent reports and articles (NRC, 2009b, 2010a, 2011c; Sharp et al., 2011), and was illustrated by many of the presentations during the Beijing workshop.

This integration of biology with other disciplines is an essential component of a vision of the life sciences articulated in the 2009 NRC report, *A New Biology for the 21st Century*.

> Biology is at a point of inflection. Years of research have generated detailed information about the components of the complex systems that characterize life—genes, cells, organisms, ecosystems—and this knowledge has begun to fuse into greater understanding of how all those components work together as systems. Powerful tools are allowing biologists to probe complex systems in ever-greater detail, from molecular events in individual cells to global biogeochemical cycles. Integration within biology and increasingly fruitful collaboration with physical, earth, and computational scientists, mathematicians, and engineers are making it possible to predict and control the activities of biological systems in ever greater detail. . . . [T]he life sciences have reached a point where a new level of inquiry is possible, a level that builds on the strengths of the traditional research establishment but provides a framework to draw on those strengths and focus them on large questions whose answers would provide many practical benefits. (NRC, 2009b:12-13)

The value of integration across disciplines to addressing challenges in biomedicine was also highlighted by President Obama in remarks to the 2009 Annual Meeting of the National Academy of Sciences.

> Because of recent progress—not just in biology, genetics and medicine, but also in physics, chemistry, computer science, and engineering—we have the potential to make enormous progress against diseases in the coming decades…. [w]e can harness the historic convergence between life sciences and physical sciences that's underway today; undertaking public projects—in the spirit of the Human Genome Project—to create data and capabilities that fuel discoveries in tens of thousands of laboratories; and identifying and overcoming scientific and bureaucratic barriers to rapidly translating scientific breakthroughs into diagnostics and therapeutics that serve patients. (White House, 2009b)

Although the concept of converging or integrating biology with other disciplines is not new and reflects approaches that many individual scientists are already taking, it remains challenging to clearly define. One definition was presented in a white paper on the topic issued by the Massachusetts Institute of Technology (MIT) in 2011 (Sharp et al., 2011). The authors state that convergence is not only the small area of intersection between fields, but also a new research model that represents "the merging of distinct technologies, processing disciplines, or devices into a unified whole that creates a host of new pathways and opportunities. It involves the coming together of different fields of study—particularly engineering, physical sciences, and life sciences—through collaboration among research groups and integration of approaches that were originally viewed as distinct and potentially contradictory" (Sharp et al., 2011:4) (see Figure 4.1).

Although the language used in describing this model varies somewhat from author to author, integration or convergence entails adapting

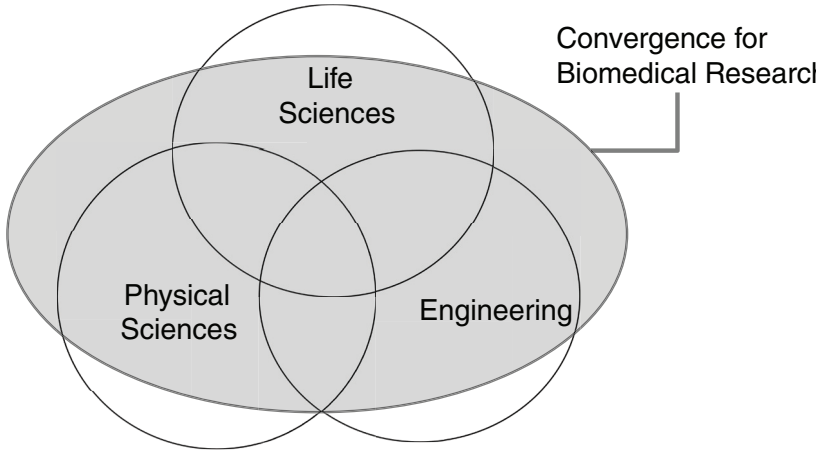

FIGURE 4.1 A diagram of the conceptual difference between intersection and convergence of biology, chemistry, and engineering.
SOURCE: Yamamoto (2011), reprinted and adapted with permission.

and applying the tools and conceptual, analytical, and technical "ways of looking" (NRC, 2010a) used by disciplines in the physical sciences and engineering to challenges in the biological sciences in order to bring new insight to problems. Reciprocally, approaches and understandings derived from the biological sciences are adapted and applied to address physical sciences questions (NRC, 2010a; Sharp et al., 2011). Although many of the existing scientific techniques cited in documents that emphasize the integration and convergence of multiple disciplines in the life sciences are familiar to the research community (e.g., genetic engineering, synthetic biology, etc.), there is a sense that the reduced costs and increasing availability of technology are making them more routine and are accelerating the pace at which research is progressing. As part of this paradigm, many scientists and engineers anticipate the development of new capabilities, techniques, and understandings that are not comfortably housed within conventional disciplines and that represent an expansion into new research areas.

4.2 EXAMPLES OF AREAS IN THE LIFE SCIENCES THAT REFLECT THE CONVERGENCE OF MULTIPLE DISCIPLINES

The Beijing workshop clearly reflected the multidisciplinary and integrative nature of modern life sciences research and highlighted the growing diversity of fields relevant to the future of the BWC. Although areas covered during the workshop are discussed in greater detail in Chapters

2 and 3, three brief examples are presented below to highlight the breadth of fields currently engaged in life sciences research and to illustrate the cross-cutting nature of this convergence trend:

1. *The importance of mathematical modeling to fields as diverse as systems biology and disease surveillance*. Quantitative models provide new tools for understanding interactions and relationships among biological entities and for predicting system behavior as the components or conditions are altered. As just one example, the E-cell project was launched in 1996 to create a virtual model of a minimal cell based on *Mycoplasma genitalium (*Tomita et al., 1999). As knowledge in fields like omics and systems biology has continued to advance, more complex cells and cellular pathways have been explored and modeled (http://www.e-cell.org). Modeling is also used to study and predict patterns of emerging infectious disease in populations (Lin, 2010). As described in Chapter 2, the range of complexity and variability in biological systems renders it challenging to reduce them to networks of mathematical equations and computer code. Even if such models are not yet capable of fully capturing or predicting all aspects of a particular system, however, the application of modeling tools derived from mathematical and computational sciences is helping to advance numerous life sciences research agendas.
2. *The integration of chemistry, materials science, and biology in order to design new biomaterials for use in targeted drug and gene delivery and in tissue engineering*. A wide range of active research is ongoing in this area, including the chemical design of materials that respond to physical changes like temperature or pH, conjugation of ligands onto new drug or gene carriers that interact with biological receptors to improve targeted uptake of nanoparticles into cells, and the design of polymer scaffolds that support the proliferation and development of cells for use in tissue regeneration (Ying, 2010). Many biological molecules of interest, from bioactive proteins and peptides to synthetic drugs to nucleic acids, have reduced environmental and physiological half-lives without protection provided by encapsulation, or have undesired side effects if administered non-selectively. As a result, the integration of multiple disciplines to create novel delivery systems and biomaterials is likely to continue as a significant area of interest in the life sciences.
3. *The field of synthetic biology, which seeks to combine perspectives from engineering and computer science with genetics and molecular biology in order to design new, purposely constructed biological components and systems*. Modular components composed of molecules such as

proteins are combined into devices that perform specific functions (for example, particular biological pathways), and these devices are in turn combined into larger systems. In this fashion, synthetic biologists seek to apply principles of engineering design drawn from areas such as electronic circuit construction to living systems. Although many challenges remain, the field integrates physical sciences and engineering approaches with those in the life sciences with the goal of ultimately creating novel biological applications.

These areas highlight just a few of the ways that knowledge from diverse fields such as mathematics, computational science, materials science, chemistry, and engineering are combined with advances in cellular and molecular biology to make important contributions across the life sciences.

4.3 THE CONVERGENCE OF CHEMISTRY AND BIOLOGY

Attention has increasingly been paid to the ways that chemistry and biology are converging and to the implications this convergence might have for the nonproliferation obligations for States Parties of the BWC and CWC. From their inception, the BWC and CWC have overlapped in their coverage of molecules that have biological effects. The text of the BWC and subsequent understandings established at five-year review conferences make clear that the treaty covers biological agents and toxins, whether natural or synthetic, whatever their origin or method of production, along with their components (United Nations, 2007, 2011). The CWC, meanwhile, covers "any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals…regardless of their origin or of their method of production" (OPCW, 2005). All biological molecules are fundamentally also chemicals, and studies of the action of chemicals that act on life processes to cause harm and the development of countermeasures against them draw on both the biological and chemical sciences.

The convergence between chemistry and biology and potential areas of overlap between the BWC and CWC include certain categories of molecules—such as biological toxins and biological regulators (bioregulators)—and developments that affect the mechanisms of production of chemical and biological substances. These themes are introduced briefly below, followed by a discussion of some of their potential implications.

4.3.1 Biological Toxins

A toxin is a poisonous substance produced by a biological organism and is generally a small molecule or a peptide or protein that causes harmful effects when it interacts with specific components of a living

system. Different toxins exhibit various mechanisms of action, and their severity and lethality also vary significantly. For example, several species of gastrointestinal bacteria produce and secrete enterotoxins, which generally act by altering ion permeability across the membranes of cells in the intestine and cause vomiting and diarrhea. Botulinum toxin produced by the bacterium *Clostridium botulinum*, on the other hand, interferes with release of the signaling molecule acetylcholine at junctions between nerve and muscle cells and causes paralysis. Toxins whose effects are particularly severe are generally highly regulated. Both saxitoxin, produced by certain types of marine plankton and bacteria and a cause of shellfish poisoning, and ricin, produced by the castor oil plant, are included on Schedule 1 of toxic chemicals under the CWC and thus are subject to declaration and verification protocols (OPCW, 2011a). Various toxins are also subject to national regulations such as those that apply in the United States under Department of Health and Human Services and Department of Agriculture select agent regulations.[1]

Many toxins are produced by microorganisms. The wealth of microbial diversity is still being explored, and techniques that allow the genomes of multiple microbial species to be sequenced without needing to individually isolate and culture each one are expected to continue rapidly expanding our knowledge of microbial systems. As new microbial species are identified and studied, it seems likely that new biological toxins also will be discovered. Although toxins are defined as substances having a harmful effect, it is important to note that they also play significant roles in basic and applied biological research for beneficial purposes. For example, studies using botulinum toxin have advanced basic science understanding of the process of neurotransmitter release, and the toxin has also been studied and employed extensively as a clinical treatment for diseases involving muscle spasms (Lim and Seet, 2010; Truong et al., 2009) and for esthetic purposes. Toxins or modified versions of toxins have also been tested as components of therapeutic agents directed against cancer or for improved tumor imaging (Engedal et al., 2011).

It should be noted that toxins are defined by their means of production or effect. There is no way to define them chemically—as discussed above,

[1] Select agents are defined by U.S. government regulations (Title 42, Code of Federal Regulations (CFR) Part 73 and 9 CFR 121), and laboratories working with materials on the list are subject to additional forms of registration, oversight, and other restrictions. The Select Agents and Toxins List currently includes botulinum toxin, ricin, saxitoxin, and several others (see http://www.selectagents.gov/select%20agents%20and%20toxins%20list.html). Other countries also have national policies that govern the safe handling, research, and transfer of pathogens and toxins, and these are supplemented by a number of regional and international efforts; a brief review may be found in *Responsible Research with Biological Select Agents and Toxins* (NRC, 2009c:64-67).

they range from small molecules to proteins. This is challenging from the perspectives of both definitions as well as detection methodologies.

4.4.2 Biological Regulators

Bioregulators are small molecules that modulate physiological function, for example by activating or inhibiting enzymes, binding to cellular receptors and activating signaling pathways, and influencing DNA regulation. These substances act as neurotransmitters and hormones and are frequently based on or derived from individual amino acids and small peptides. There are a large number of bioregulators, including, for example, the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate, biologically active peptides such as oxytocin, enkephalin, vasopressin, neuropeptide Y, and substance P, lipid-soluble steroid hormones such as cortisol, and protein hormones such as insulin.

Bioregulators affect multiple aspects of physiological systems in a variety of different ways—influencing metabolism and blood pressure, the immune and nervous systems, pain sensing, and many other processes. Some of the effects of oxytocin, for example, are discussed in Section 2.1.4. As a result of their wide-ranging effects, the low doses at which they act, their potentially rapid onset of action, and the fact that as normal components of physiological regulatory systems they would be less likely to trigger immune responses, bioregulators are potentially attractive targets to exploit. Discussions of the potential military, terrorist, or law enforcement uses of molecules such as biological regulators and their dual use implications have been recognized widely for a number of years (Bokan et al., 2002; Dando, 2002; Davison and Lewer, 2004; Kagan, 2006; Kelle et al., 2008; Nixdorff, 2010; NRC, 2005). However, their practical use may be limited by factors such as the need to better understand their effects, the need to encapsulate or otherwise render them suitable for aerosol delivery, and their short biological half-lives. As scientific knowledge advances on several of the fronts discussed in Chapter 2, however, these molecules may become more relevant. The ever-increasing understanding of biological systems may yield new knowledge of how bioregulators function and how they might be used to modulate system properties to desired ends. Advances in methods for producing or synthesizing peptides and proteins and for effectively delivering them (protecting them from degradation and assuring that they reach targeted cells or tissues) may also ultimately make these types of molecules easier to employ.

Advances in the understanding of bioregulators are not confined to humans and animals. Some of the most exciting advances in plant biology are in plant defense against insect pests and pathogens, such as the discovery of systemin, an 18-amino acid peptide in tomato and potato

(and probably in many other plant species), the first peptide hormone known in plants (Bergey et al., 1996; Pearce et al. 1991, 2001). Of further interest, this signaling pathway is analogous to the inflammatory response in animals to pathogens, whereby a polypeptide activates release of arachidonic acid, which leads to synthesis of prostaglandin.[2]

4.3.3 Advances in Techniques for Production: Chemical Synthesis of Biological Molecules and Biological Synthesis of Chemicals

Other authors have explored the increasing convergence between chemistry and biology with a focus on how S&T advances alter possible methods of production for molecules like toxins, regulators, and drugs. In particular, developments in S&T enable both chemical synthesis of biological molecules and biological synthesis of chemicals (Tucker, 2010, 2011b).

Although substances such as toxins and regulators are naturally produced by living organisms, advances in synthetic methods increasingly allow them to be made by chemical means. The genomes of viruses and small bacteria also have been synthetically created (Gibson et al., 2010; Wimmer et al., 2009). Both chemical synthesis using nucleotide building blocks (to assemble nucleic acids such as DNA and create synthetic genetic material) and chemical synthesis using amino acids (to assemble peptides and proteins) are becoming faster and easier, while the costs associated with the processes are decreasing (see Sections 2.1 and 2.2 for further discussion).

It is also feasible to use biological molecules and biological systems in the production of chemicals such as drugs. The use of molecular biology, genetics, and cell culture techniques to create recombinant bacteria and transgenic organisms capable of producing specific proteins and peptides is well known and has been exploited by the pharmaceutical industry

[2] When a Colorado potato beetle takes a bite from a leaf of potato or tomato, it induces a wound response that includes release of one or more protease inhibitors inimical to the digestion by the insect. Systemin is the protease-inhibitor-inducing factor, released from prosystemin upon wounding. Systemin then moves in nanomolar amounts to neighboring cells where it binds to a transmembrane receptor and leads to production of jasmonic acid (JA). JA, in turn, mediates long-distance signaling expressed as systemic production of the protease inhibitors and hence starvation of the leaf-chewing insects by inhibition of their digestive enzymes. Formation of more prosystemin is also induced by JA, thereby providing an amplification loop for the systemic defense response.

for many years in the production of "biologics."[3] As discussed in Section 2.1.5, advances in protein production in transgenic systems, including plants (sometimes referred to as "pharming"), continue to improve such efforts. As science advances, it is also increasingly possible to design metabolic pathways in biological systems that can produce additional types of chemical drugs. Research exploring terpenoid biosynthetic pathways, for example, enabled the metabolic engineering of yeast to produce the antimalarial drug precursor artemisinic acid (Ro et al., 2006), and research on the synthesis of alkaloid molecules is also being conducted (http://keaslinglab.lbl.gov).[4] Other groups are working to design bacteria capable of converting fatty acid molecules into hydrocarbons to develop biologically derived fuels (Schirmer et al., 2010; Service, 2008). Biological enzymes can also be used as components in organic chemistry syntheses to catalyze reactions (referred to as biocatalysis). The use of enzymes in such reactions is attractive because the specificity of enzymes improves the ability to conduct difficult syntheses that distinguish between closely similar chemicals, resulting in a better yield of the desired product and reduced need to separate out mixed impurities. Enzymes function in aqueous solutions and at physiological temperatures, allowing reactions to proceed at lower temperatures than might otherwise be required, although enzyme stability may be a concern for certain industrial applications. Enzymes are also degradable and are thus less environmentally toxic than some other chemicals for use in green chemical synthesis.

4.3.4 Discussion and Implications of the Convergence of Biology and Chemistry

Bioactive molecules such as bioregulators and biotoxins fall into a middle spectrum of agents ranging from classical chemical weapons (such as nerve gases) on one end to classical biological weapons (such as viruses and bacteria) on the other, and bioregulators in particular have been described as "prototypic nontraditional threat agents" (Kagan, 2006). As the life and chemical sciences continue to advance rapidly, this potential

[3] Biologics are medical products of biological origin and "can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources—human, animal, or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies…. In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized. Biological products, including those manufactured by biotechnology, tend to be heat sensitive and susceptible to microbial contamination" (http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133077.htm).

[4] Alkaloids are a large class of molecules generally synthesized in plants that includes drugs such as morphine.

mid-spectrum area of overlap between the BWC and CWC may continue to expand in several ways:

- Advancing knowledge will result in more molecules that fall within areas of overlap (such as toxins and regulators) being discovered and characterized;
- Ongoing research to understand the mechanisms of action of relevant biological molecules, their roles in physiological systems, and their regulation will generate improved understanding of how such molecules could be used;
- Advances will continue to be made in biological and chemical production technology, for example that make it easier to produce proteins, peptides, and drugs in transgenic animal and plant systems, in small-scale, cell culture bioreactors, and by chemical synthesis;
- Advances in delivery technology will continue to address limitations such as rapid degradation and need for targeted delivery to cells and tissues (including to the central nervous system), thus potentially rendering it more feasible to deliver agents such as bioregulators; and
- New research fields that exemplify scientific convergence, such as synthetic biology, will continue to develop.

The report of an advisory panel convened in 2011 by the Director General of the Organisation for the Prohibition of Chemical Weapons (OPCW) on future priorities for the CWC notes:

> This convergence calls for a closer interaction in the implementation of the [CWC] Convention, and the Biological Weapons Convention. Convergence in the sciences does not in itself lead to convergence of the regimes, but exchanges of experience and joint technical reviews could be helpful to understand how it affects the implementation of both treaties at the interface between chemistry and biology. That is particularly pertinent as there is an overlap between the two treaties with regard to the prohibition of toxin weapons. (OPCW, 2011b:20)

The convergence of scientific disciplines, including chemistry and biology, was highlighted at the international scientific workshop convened in 2006 prior to the Sixth BWC Review Conference (Royal Society, 2006b) and at the 2007 international scientific workshop convened by the International Union of Pure and Applied Chemistry (IUPAC) prior to the Second CWC Review Conference (Balali-Mood et al., 2008). This report draws attention to it again because it remains a significant feature of current research in the life sciences and chemistry. In April 2011 the Scientific Advisory Board of the OPCW recommended the establishment of a Tem-

porary Working Group to consider the implications of chemical-biological convergence for the CWC (OPCW, 2011c). Convergence is also expected to be a topic at a workshop to be convened by IUPAC in early 2012 to examine trends in S&T prior to the Third CWC Review Conference.

4.4 CHALLENGES AND OPPORTUNITIES RELATED TO THE INTEGRATION OF DISCIPLINES IN THE LIFE SCIENCES

For many years, discussions of relevant S&T areas for the BWC have involved more than the traditional microbial threat agents that were the focus of national offensive biological weapons programs prior to the treaty's entry into force in 1975. The increasing integration of the physical, engineering, and mathematical sciences with the biological sciences continues to expand the scope of these discussions. This continuing expansion of relevant areas of S&T may pose several challenges for the BWC and for the scientific community. As research in the life sciences draws increasingly on knowledge and techniques from other disciplines, the range of expertise necessary to track the state of scientific developments and to assess their potential implications also expands. The BWC has been making efforts to engage members of the life sciences community through its intersessional meetings and through presentations at scientific conferences.[5] These efforts are continuing to foster awareness of the BWC and of the norms and requirements it contains. Given the diversity of potentially relevant fields that are coming together to address challenges in the life sciences, expanding outreach to new scientific stakeholders who have not traditionally been part of the "life sciences" community may need to be considered.

Previous reports have noted the institutional, financial, and educational challenges associated with convergence between the life and physical sciences, including the structures of traditional academic departments, systems of incentives and promotion that may not sufficiently credit multi-author and collaborative projects, and the need for enhanced cross-disciplinary education as part of core training requirements (NRC, 2010a; Sharp et al., 2011). An additional challenge is the creation of ethical frameworks for responsible science that bridge communities that may be

[5] Intersessional topics including "improving national capabilities for disease surveillance, detection and diagnosis and public health systems" (2010), "enhancing international cooperation, assistance and exchange in biological sciences and technology for peaceful purposes" (2009), and "laboratory safety and security of pathogens and toxins" (2008) related directly to science. In addition to making presentations at meetings focused on biosafety, bioethics, and biosecurity, the BWC Implementation Support Unit has also participated in recent scientific community gatherings such as the 2010 International Genetically Engineered Machine Competition (iGEM) and the 2009 meeting of the International Association for Synthetic Biology (http://www.unog.ch/bwc/isu).

accustomed to discussing similar ethical themes in different ways, and have different cultural norms regarding the motivation for experiments, where they are published, and how they are evaluated (NRC, 2011a).[6] For example, in the case of synthetic biology, many practicing cell biologists and microbiologists focus on the end product ("it looks like what we already do") and not the engineers' emphasis on the fact that the process to get there was different. Similarly, a bioengineer may publish a paper on developing a reproducible scalable process to promote cell-based production of a compound. In contrast, traditional biology is usually focused on understanding "how it works," not "how do I use it to accomplish X?" Thus, even though responsible conduct across fields such as engineering and biology is likely to address common topics such as integrity, conflicts of interest, protection of propriety information, and decision-making consistent with public safety and welfare, the examples used to illustrate these concepts may differ.

Finally, the convergence of disciplines may pose challenges to the operation of regimes like the BWC and the CWC. New scientific developments might alter or expand the types of agents that could be of concern as biological or chemical weapons and/or might alter or expand the definitions of which molecules fall under the purview of both treaties. One possible role for the scientific community may be exploring and clarifying the technical issues surrounding these advances in chemistry and biology, to inform efforts to better define the nature and scope of the challenges they present. Ongoing scientific dialogue as well as the types of policy dialogues suggested by the OPCW advisory panel (OPCW, 2011b) might contribute to the consideration of the future challenges to both treaties posed by advances in S&T, including future threat agents and their methods of production.

Despite these potential challenges, the integration of diverse perspectives and the convergence of multiple disciplines in the life sciences remains an exciting trend. The model of convergence in the life sciences is one that may provide many creative new opportunities to address challenges across areas like health, energy, agriculture, and the environment.

[6] Information from a workshop organized by the U.S. National Academy of Engineering and the Woodrow Wilson Center on whether and how engineering ethics might inform the development of synthetic biology, for example, may be found at http://www.onlineethics.org/Topics/EmergingTech/TechEdu/SynBioWorkshop.aspx.

5

Monitoring and Assessing Trends in Science and Technology

The principal goal of the 2010 workshop was to draw on the expertise of the international scientific community to provide a broad, independent picture of the state of science and technology (S&T) research and development relevant to the Biological and Toxin Weapons Convention (BWC). In Chapters 2-4, the committee examined three key trends that emerged from the meeting: the rapid pace of developments, the increasing diffusion of research capacity and applications, and the integration of multiple disciplines that characterizes many areas of life sciences research. This chapter focuses on how the insights gained through processes like the workshop can be analyzed and applied.

Engaging a range of expertise within the scientific community, from academia, industry, and government, can contribute to efforts both to *monitor the state of science and technology* and to *assess the implications* of developments for the scope and operations of the BWC. Taking account of developments in S&T in ways that are useful to the BWC will require States Parties and experts in Geneva to have a reasonable grasp of the state of the science as it evolves, including a sense of the forces that drive different areas at different rates and the inevitable roadblocks that hamper progress. Input from experts from the broader scientific community, in conjunction with government technical experts, who often are also practicing scientists, may be particularly suited to the task of understanding these factors. Although there is a role for the scientific community in helping to assess the implications of S&T for the treaty, this is clearly also a matter for discussion among government technical experts, and

ultimately by States Parties when discussions surrounding S&T move into the realm of policy options and potential action.

This chapter has three major sections. The first section examines the forces mentioned above that broadly affect how S&T trends develop, including the differential impact of drivers such as commercial interests, some of the barriers to the distribution of scientific knowledge and capacity, and other factors that may present current roadblocks to progress. Tracking and analyzing the impact of these factors could be considered areas of potential interest for future monitoring of S&T trends. In the second section, the committee draws on the workshop results to highlight the relevance of S&T to the BWC's provisions. The final section discusses possible roles for the scientific community in contributing to future BWC discussions of S&T. The chapter ends with the committee's overall findings and conclusions.

5.1 DRIVERS AND ROADBLOCKS FOR S&T DEVELOPMENT

5.1.1 Drivers

The difficulty of attempting to predict future trends and developments is well recognized, and it was noted during the workshop that one should always prepare to be surprised. With this caveat in mind, the committee did not attempt to forecast the state of life sciences knowledge in the years ahead. However, the committee did discuss some of the common drivers of life sciences research, and these are illustrated with brief examples, below. S&T areas that are being pushed forward strongly by these drivers would be expected to continue to rapidly advance. The more general impetus for S&T advances arising from investments as part of broader national development strategies was discussed in Chapter 3 (see Section 3.1.2). Investments are important, but the amount of money invested is not necessarily a sign that one field will advance more rapidly than another. To date, for example, the substantial investments in systems and synthetic biology have yielded only limited commercial products.

Commercial markets are a powerful driver of life sciences research, in the healthcare and pharmaceutical industries as well as in sectors such as agriculture and energy. Several of the S&T areas discussed during the workshop appear to have commercial drivers for further development. These include diagnostic biosensors, advanced delivery technologies for controlled release and targeted delivery of biological molecules, protein production technology, and the potential applications derived from omics knowledge in areas such as personalized medicine. Fields such as synthetic biology, which likely have future medical applications, are also expected to have valuable applications in areas such as bioenergy and food production (Lee et al., 2008; NRC, 2009e). Developments in

neuroscience, particularly advances in the mind-machine interface, may clearly benefit patients with medical disabilities such as paralysis or loss of limbs. However, an interesting commercial driver in this field may also be the entertainment industry. The ability to remotely control computer interfaces and to produce sensations such as motion could be integrated into videogames to heighten the experience. The entertainment company Sony, for example, has reportedly filed a patent application for a device that emits ultrasound pulses to influence brain waves (Hogan and Fox, 2005). Many technologies that underpin and enable modern life sciences research, such as powerful computer networks and mobile and Internet-based communications systems, are broadly applicable far beyond the life sciences. Advances in these areas are driven by numerous markets and applications, appear to have moved forward especially rapidly, and would be expected to continue advancing.

Other areas of S&T lack strong commercial drivers and therefore rely on government investments to move forward. In at least some countries, government investments in defense-related research can be strong drivers for some areas of basic and applied research. The most dramatic case may be the United States' investments in biodefense; by one estimate, the government has spent $19 billion on research out of a total biodefense budget of $60 billion (Kaiser, 2011:1214).

Another arena where government and also philanthropic investments are critical is public health. Public health applications in general, including the development of new vaccines and antibiotics, typically exhibit market cost/benefit conditions that make them less attractive to the pharmaceutical industry absent government incentives. These challenges include the cost of R&D expenses compared to likely market size and profits and regulatory and liability issues, among others (Jarvis, 2008; Kieny et al., 2004; Smith et al., 2009). These same market challenges affect the development of vaccines and medical countermeasures against biothreat agents, because diseases of concern as potential bioweapons are often not endemic in the United States or Europe, the immune correlates of protection may not be well known, suitable nonhuman animal models may not exist, and there is no guarantee that a particular product would be needed given the hypothetical nature of a future bioweapons attack. Therefore, developing a licensable product with no clear end market may be challenging from both scientific and regulatory standpoints. As a result, incentives such as guaranteed government purchase orders or vouchers for priority regulatory review of another (usually more lucrative) company product have been used to help stimulate this field. Public health disease surveillance networks are another area with limited commercial markets but clear national and international benefits and that also rely on government and nonprofit investments.

Overall, areas of technology with strong commercial drivers seem likely to develop particularly rapidly, although the committee noted

that the optimum combination of variables for a particular commercial application may not be the same as that for a dedicated public health or biosecurity application. In these cases, government investments may be required to adapt technologies to meet the specific combinations of needed operating conditions. For areas that do not appear to have strong commercial market drivers, government investments may also be particularly important in advancing the field.

5.1.2 Roadblocks

Discussions of advances in science and technology can create the impression of a dynamic process characterized by uninterrupted progress, sometimes at daunting speed. As anyone engaged in research appreciates all too well, there can be many failures on the way to eventual success, and the path is not always predictable. Entire fields may face particular technical challenges that, until surmounted, represent significant roadblocks to progress. Once overcome, however, progress may be rapid (see Box 5.1 for some well-known examples). A number of current roadblocks were discussed in Chapter 2 and could be useful focal points for efforts to monitor areas of S&T relevant to the BWC. Other challenges may reside in the nature of how science is done or used, and as they change there can be impacts on how easily science is used and applied, whether for beneficial or malicious purposes. That is the subject of the next section.

5.1.2.1 The Process of Knowledge Creation and Barriers to Knowledge Transfer

From Data to Knowledge

As discussed in Chapter 2, advancing technologies within the omics fields, for example, generate large amounts of raw, discrete *data* (e.g., the results of nucleotide or amino acid sequencing, DNA and protein microarray results, nuclear magnetic resonance [NMR] and mass spectra, x-ray crystallographic images). These streams of data need to be managed, analyzed, and put in context in order to be converted to useful *information*. This process of converting data to information might include processing and representing data as graphs and charts to reveal patterns, for example. Because of the enormous volumes of data currently being generated, however, life scientists increasingly rely on information science (bioinformatics) and computer science expertise to create the databases, theories, and algorithms needed to analyze and transform these large data sets into information. A third and critical component is the organization, analysis, and conversion of biological information into *knowledge*, which involves a human dimension. This process of knowledge creation draws

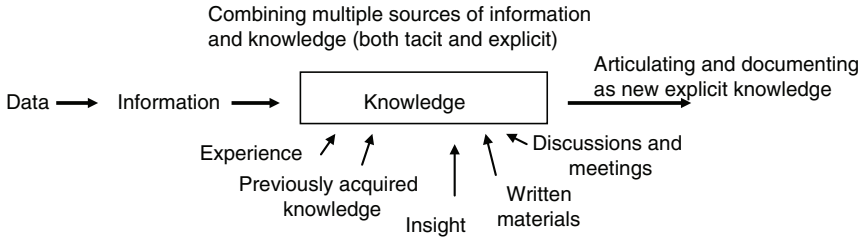

FIGURE 5.1 The process of knowledge creation.

on multiple pieces of information as well as previously acquired knowledge and experience to enable a scientist to interpret the information, give it meaning, and make it usable for a specific purpose.

Another distinction that can be drawn is between the two forms of knowledge referred to as "explicit" and "tacit." Explicit knowledge, which is frequently factual in nature, can be expressed in a relatively straightforward fashion and transmitted to another person. Tacit knowledge, on the other hand, resides within individuals, is based on experience and learning through doing, and is more difficult to convey. It has been stated that "practical knowledge has two dimensions—a visible, codified component that resembles the tip of an iceberg. The larger but crucial tacit component which lies submerged consists of values, procedures and tricks of the trade and cannot be easily documented or codified" (Rangachari, 2008).[1] Figure 5.1 depicts this process of conversion from data to information, incorporation of multiple sources of information and experience into tacit knowledge, and then externalization of that knowledge into new, explicit knowledge that can be communicated to others. The understanding and appreciation of the role of tacit knowledge draws on contributions from the social and behavioral sciences, particularly the field of science and technology studies (Hackett et al., 2007).

Scientific Communication and Tacit Knowledge

Scientists attempt to convert the knowledge they possess into explicit forms to be shared with others, for example through conference presentations and the publication of journal articles. Not all aspects of tacit knowledge are easy to express and convey explicitly, however, and scientific training still makes use of an interactive apprenticeship process that draws on personal interactions with advisors and other experts in com-

[1] In some cases, possessors of such tacit knowledge (either corporate or individuals) may not want to document or codify their knowledge, or in the case of the government employee, may be directed not to provide such information in a public report.

munities of practice to convey both forms of knowledge to new trainees. A large body of literature exists on the study of knowledge creation and conversion (Bathelt et al., 2004; Cross et al., 2001; Nonaka, 1994; Roberts, 2000), and it is not the committee's purpose to summarize the entire field here. However, the committee noted two points especially relevant to trends in S&T:

- *Data does not equal information does not equal knowledge*. There is a significant time and processing component in the conversion of data from scientific experiments to usable knowledge, as well as a human dimension to this transformation. Although modern life sciences are rapidly generating large amounts of data, these data do not immediately or directly advance understanding of biological processes or provide the ability to accomplish a specific task.
- *Challenges and bottlenecks can exist in the conversion process from data to knowledge*. The complexity of biological systems, complications in distinguishing data from background noise, and other similar factors, create significant challenges in developing algorithms and models that help convert data to usable information, a point also highlighted by the workshop presentations (Pitt, 2010a). The difficulty in rendering certain aspects of tacit knowledge explicit and conveying it to others can create a bottleneck in the second step of the pathway, that is, the conversion of information to knowledge.

The extent to which tacit knowledge as described in the second bullet might help to prevent the misuse of S&T is briefly discussed in the next section.

Tacit Knowledge as a Potential Roadblock to Misuse of Life Sciences Research

Several authors have highlighted the roles of tacit knowledge and of social and organizational factors in achieving research success, including the creation of biological weapons (Ben Ouagrham-Gormley and Vogel, 2010; Suk et al., 2011; Vogel, 2006). A subset of tacit knowledge, for example, deemed "intangible technology," is subject to export controls by a number of countries and international groups.[2]

It has also been suggested that tacit knowledge could serve as a roadblock to gaining weapons-relevant capabilities (Vogel, 2006). The study

[2] The relationship between tacit knowledge and intangible technology is somewhat complicated because for export control purposes—where the term "intangible technology" is most relevant for BWC implementation—intangible technology also includes documentation, plans, etc., that are not part of most understandings of tacit knowledge.

of the research that led to the chemical synthesis of polio virus DNA and use of this DNA to create viral polio particles (Cello et al., 2002), which drew the attention of the biosecurity community and aroused concerns that the method could be harnessed by persons seeking to create harmful viruses, concluded that it could not be duplicated because of the tacit knowledge required to prepare the virus. Understanding the influence of barriers beyond extrinsic scientific knowledge on success in bioweapons-related research emerged from historical studies of the Soviet biological weapons program, where different facilities had different outcomes that correlated with differences in organizational style and research culture (Ben Ouagrham-Gormley and Vogel, 2010). Similarly, a study of scientists in biotechnology and pharmaceutical companies suggested that teams of scientists contributing different types of human capital were important for success (Hess and Rothaermel, 2010). The authors observed that "star" scientists served as important sources of intellectual capital, including tacit and exploratory knowledge and networks of connectedness. However, the authors also reported that the importance of these star scientists decreased "as the knowledge associated with biotechnology was disseminated through the scientific community" (Hess and Rothaermel, 2010:10), suggesting that the significance of different types of tacit knowledge may change as S&T areas mature and develop.

Multiple factors appear to be important to the success of high-tech research, and thus "technology is much more than the sum of its material and informational aspects. Social contingencies and tacit knowledge, serendipity and unpredictability, institutional memory, and many other factors are essential to the successful design and deployment of any given technology" (Suk et al., 2011). Explicit forms of scientific information are now readily available through open access journal articles and databases, and individual and group communication and collaboration have been made easier by the Internet, social media platforms, and mobile devices. Furthermore, small communities of amateur biologists have been established around the world. As these new developments continue to shape the culture of science, consideration of the extent to which tacit biological knowledge and other factors continue to create roadblocks to the potential misuse of biology or creation of a biological weapon may be useful.

Both the business and online learning communities have studied ways to convey tacit knowledge effectively within organizations and to students online (Anderson, 2008; Cummings and Teng, 2003; Nonaka, 1994). Lessons drawn from these groups' experiences may help in assessing the significance of knowledge transfer barriers. If specific social media or other tools have proven particularly effective at conveying tacit knowledge or at integrating multiple streams of knowledge to tackle complex problems in the business or education communities, then monitoring whether these types of tools become commonly used within the scientific

community may provide a sense of when roadblocks related to scientific knowledge transfer are being overcome.

The increasing numbers and availability of kits and other tools to carry out laboratory procedures that were traditionally acquired as part of the hands-on learning described above (see Sections 3.1.2 on kits and services and 3.4 on how this is enabling the development of research communities outside traditional institutions) is a phenomenon that may affect the role of tacit knowledge. An increasing number of online resources provide step-by-step training, such as the *Journal of Visualized Experiments* (JoVE), which seeks to take

> advantage of video technology to capture and transmit the multiple facets and intricacies of life science research. Visualization greatly facilitates the understanding and efficient reproduction of both basic and complex experimental techniques, thereby addressing two of the biggest challenges faced by today's life science research community: i) low transparency and poor reproducibility of biological experiments and ii) time and labor-intensive nature of learning new experimental techniques. … Research progress and the translation of findings from the bench to clinical therapies relies on the rapid transfer of knowledge both within the research community and the general public. Written word and static picture-based traditional print journals are no longer sufficient to accurately transmit the intricacies of modern research. (JoVE website, http://www.jove.com/About.php?sectionid=-1)

This trend has led to discussions of the "de-skilling" of biology research (Mukunda et al., 2009; Schmidt, 2008; Tucker, 2011a). By permitting less skilled individuals to carry out more procedures, such materials and resources could reduce the importance of some forms of tacit knowledge and hence its role in limiting misuse. But there are also questions about the level of sophistication that could actually be achieved by practitioners without the deeper biological or mechanistic understanding that enables experienced researchers to respond to difficulties in the course of an experiment or effort to develop a weapons capability.[3]

The committee does not have an answer to the implications of the changes in the roadblocks provided by tacit knowledge to the potential misuses of life sciences research. The discussion is intended to highlight an area that could be the subject of future study and consideration as part of broader efforts to monitor S&T trends. It also notes the important role

[3] For an example of the possible difficulties, see the report from the Center for a New American Security on the efforts by Aum Shimrikyo to acquire both biological and chemical weapons capabilities (Danzig et al., 2011).

that understanding how to propagate norms about responsible conduct of science would play in the development of any response.

5.1.2.2 Overcoming Roadblocks: Serendipitous Discoveries and Those Enabled by Simultaneous Progress in Multiple Fields

Serendipity

Advances in technology that enable a deeper understanding of the processes and links between molecules, cells, organisms, and ecosystems have resulted in more detailed and thorough models of biological response and behavior than ever available before. However, these new technologies have also revealed a greater complexity within biological systems than previously known, and this complexity presents significant challenges to those modeling efforts. As a result, although our theoretical understanding has improved, the capacity to predict, *ab initio*, organism responses to changes in the molecular and biochemical structures within its cells remains largely out of reach. Biology remains at its core an empirical science and serendipitous discovery is still relatively common. A frequently cited example from an area of science with dual use potential is RNA interference (RNAi), whose initial discovery grew out of efforts by plant researchers to find ways to give petunias a deeper purple color (Chamberlin and Kwik Gronvall, 2007; Gilbert, 2010).

More and more researchers are crossing disciplinary and geographic boundaries and identifying new ways to tackle biological questions. It is probable that major advances in understanding and fine control of biological systems will be rapid relative to the past 5-10 years but one can expect that a number of them will come as surprises.

Parallel Tracks

Major leaps in scientific understanding and the emergence of new fields of research often occur because multiple, parallel technologies have advanced concurrently to a stage where they can be drawn upon to create something new. For example, early efforts in synthetic biology drew upon x-ray crystallography; DNA sequencing and recombination techniques; the development of sensitive, small-scale analytical methods; and advances in modeling techniques and computing power. Today, there is a general sense within the life sciences community that many parallel tracks and fields of research are developing simultaneously. When advances in multiple fields reach a stage where they can be successfully combined to build upon each other, there will be the potential for the emergence of new fields of discovery and the development of new, powerful techniques for

manipulating and understanding biological systems. As just one possible example, combining the development of an aerosol delivery system able to effectively cross the blood brain barrier and deliver controlled quantities of a biologically active peptide drug to specific, targeted cells; more precise physiological understanding of how regulatory molecules affect the central nervous system and how such effects can be controlled; and cost-effective and scalable production of both the peptide and the delivery vector would significantly expand options for using peptide bioregulators to influence human systems. The emergence of new fields and new advances building on parallel developments will likely occur most often around applications and issues that are affected by the drivers described above, i.e., those that have strong economic and public health impacts, although they may also appear in other areas. The pace of research today suggests that new developments will be swept up very quickly into the general practice of biology and related fields.

5.1.3 Discussion and Implications

Certain scientific and technical roadblocks may impede future progress, but when they are overcome they will enable particularly rapid development to follow. Two examples from 20th-century life sciences are presented in Box 5.1.

The workshop and committee discussions highlighted several current roadblocks in the life sciences that could be subjects for future monitoring and assessments of S&T trends. These include:

- Advances in mathematical and computational modeling that are able to better account for biological complexity and to render the models more accurately predictive of biological behavior. To achieve this goal, sophisticated mathematics may be required to more accurately express biological systems as equations, given that biological systems do not always behave in precisely defined ways but instead exhibit variability and ranges of responses. In addition, increased computational power may be required to simultaneously solve the very large numbers of equations needed to describe a biological system.
- Developments in the understanding of immunology and the relationships of the immune system with other biological systems that would allow for controlled and predictive immune system modulation.
- The design and creation of more and more complex synthetic biological pathways.
- The development of more effective methods of targeted and controlled delivery, able to deliver high levels of a protein or drug

BOX 5.1
Overcoming Scientific Roadblocks: PCR and Penicillin

The dramatic explosion of research and application that can follow from overcoming a scientific roadblock is demonstrated by two well-known examples from 20th-century life sciences.

Polymerase Chain Reaction (PCR)

Scientists knew that the primary genetic material of life was encoded in DNA but were limited in their abilities to analyze and manipulate specific genes because any particular sample contained such a small quantity mixed among other genetic material. In the 1980s, Dr. Kary Mullis described a technique to amplify a specific DNA sequence multiple fold. PCR exploits key aspects of DNA replication: double-stranded pieces of DNA are separated at high temperature; short DNA primers flanking and complementary to the target DNA sequence are annealed at lower temperature; and the enzyme DNA polymerase synthesizes new DNA to copy the target sequence. These cycles of heating and cooling are repeated, doubling the amount of target DNA each time. Starting from a single DNA copy, 32 cycles of PCR will yield more than 1 million copies of the target sequence. This technique revolutionized molecular biology and paved the way for a subsequent explosion in genetic research. The ability to amplify individual DNA sequences greatly expanded the ability to detect and analyze gene mutations, to associate genetic changes with particular diseases, and to enable medical diagnosis and genetic screening. PCR is one of the fundamental techniques that underpin modern biotechnology.

Penicillin

In 1928, Alexander Fleming at St. Mary's Hospital in London identified a mold from the genus Penicillium on a culture plate of Staphylococcus bacteria he had left on a lab bench. A substance released by the mold had killed the bacteria, leaving a plaque—he subsequently named this substance penicillin and tested its efficacy against various types of bacteria. Early studies on the potential disease-fighting properties of penicillin were severely hampered by difficulty isolating and producing it. In the late 1930s, Ernst Chain, Howard Florey, and Norman Heatley at the University of Oxford became interested in penicillin, studying its chemistry and working in collaboration with Andrew Moyer of the U.S. Department of Agriculture's (USDA's) Northern Regional Research Laboratory to significantly improve the ability to purify and produce it in larger quantities. The subsequent medical studies this enabled established penicillin as a "miracle drug" that dramatically improved treatment for bacterial diseases and started the age of antibiotic therapeutics. The discovery of penicillin also highlights the long-standing interdisciplinary nature of life sciences research—the combination of Fleming's biological observations with the Oxford and USDA researchers' chemical and production work, as well as the determination by Dorothy Hodgkin of penicillin's molecular structure using x-ray crystallography, brought penicillin to the point that it could feasibly be tested and used clinically and helped facilitate the development of new antibiotics.

to a target cell or to express high levels of a gene within that cell, while minimizing destruction of the delivery vector and its drug or gene payload within the body and minimizing its uptake into non-specific cells and tissues.
- More accurate and detailed understanding of the nervous system and its relationship to other physiological systems, as well as mechanisms to effectively deliver a range of biologically relevant molecules to targeted nervous system cells.
- The development of real-time biosensors that can rapidly distinguish signal from noise for multiple substances under real-world conditions in small size and at reasonable cost.

The committee presents the research areas above as examples of significant current challenges based on the workshop discussions. If or when life sciences achieve one or more of these goals, further rapid developments in the field may follow. Continued tracking of trends and developments in S&T to identify when key scientific roadblocks have been overcome may be particularly helpful, and the scientific community can play a useful role in monitoring the state of the science in relevant areas.

In addition to these S&T challenges, the availability of web-based technologies can enable the transfer of tacit knowledge through the creation of formal or informal learning communities or from individual to individual. These technologies are used to reduce the barriers to S&T knowledge for responsible, educational purposes, but they may also potentially be used to provide access to tacit knowledge that acts as a barrier to misuse. This is an area that would benefit from more in-depth analysis to gain a more nuanced understanding of the developments and trends.

5.2 THE RELEVANCE OF S&T TO THE BWC: LOOKING BEYOND ARTICLE I

One of the primary themes to emerge from the workshop is the continuing relevance of S&T to the BWC. This relevance extends beyond concerns over the misuse of microbiology for the creation of pathogen weapons to include multiple areas of the life sciences and intersecting disciplines. The impact of the advances in S&T also affect the implementation of the treaty.

5.2.1 Article I: S&T and the Scope of the BWC

Many areas of S&T discussed at the workshop are potentially relevant to both the BWC's scope and its implementation. Perhaps the most com-

mon motivation for regularly reviewing advances in S&T is to determine whether any new developments appear to fall outside of the current scope of the treaty, as articulated in Article I, which prohibits States Parties from undertaking to "develop, produce, stockpile or otherwise acquire or retain" both biological agents and their means of delivery "whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes" (United Nations, 2011). This has been an issue from the treaty's earliest days; the treaty's entry into force in 1975 coincided with the development of the technology to create recombinant DNA (rDNA). Among the concerns raised at the time was that "the technology might deliberately or inadvertently be used to create organisms with increased virulence or novel characteristics" (NRC, 2004:30). The First Review Conference in 1981 agreed that the prohibitions in Article I covered recent developments in S&T, including efforts to genetically engineer biological warfare agents (Sims, 1988). Subsequent review conferences reaffirmed the comprehensive coverage provided by Article I:

> The Second, Third and Fourth Review Conferences, conscious of apprehensions arising from relevant scientific and technological developments, inter alia, in the fields of microbiology, genetic engineering and biotechnology, and the possibilities of their use for purposes inconsistent with the objectives and the provisions of the Convention, reaffirmed that the undertaking given by the States Parties in Article I applies to all such developments. The Fourth Review Conference supplemented the list of scientific and technological developments with molecular biology… and any applications resulting from genome studies [IV.I.6, III.I.3, II.I.4] (United Nations, 2007:4).

The report of the 2006 workshop at the Royal Society, which looked at trends in the early part of the decade, noted that the misapplication of any of the S&T developments it discussed would be covered by the general-purpose nature of the Article I prohibitions (Royal Society, 2006b). For example, the malign creation of a pathogen entirely through chemical synthetic techniques, the use of understandings gained through computer modeling and systems biology to manipulate biological pathways for harm, or the delivery as a bioweapon of DNA encoding a pathogen toxin so that the resulting toxin protein is produced within a host's own cells, could all be addressed by the Article I prohibitions on agents of types and quantities having no peaceful purpose "whatever their origin or mechanism of production." Similarly, the misuse of materials science to encapsulate drugs and genes into bioweapons consisting of nanoparticles or "artificial viruses" for improved biological targeting and uptake could be covered through the inclusion of delivery systems as part of the treaty's prohibitions. "The Sixth Review Conference reaffirmed that

Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention [VI.I.2]" (United Nations, 2007:5).

5.2.2 S&T and Implementation of the BWC

S&T developments are also relevant to the BWC beyond the issue of scope and the general prohibitions contained in Article I. S&T developments lend themselves particularly well to supporting articles that address States Parties' implementation of BWC provisions (such as Article IV) and that emphasize international collaboration (such as Articles V and X). Table 5.1 sets out selected ways that developments in the life sciences might be relevant to the provisions of the BWC.

5.3 ROLE OF THE SCIENTIFIC COMMUNITY

The potential dual use nature of multiple areas of life sciences research, coupled with the rapid progress in the fields described in Chapters 2 through 4, underscore the need for the scientific community to be aware of the legal prohibitions enshrined in the BWC and translated into domestic criminal legislation.[4] Scientists also need to be engaged in helping policy makers understand the ways that scientific advances might affect such agreements. The role of the scientific community in providing factual information about S&T developments and in contributing to stakeholder discussions about their potential implications for international security in general and weapons of mass destruction in particular has been recognized for many years.[5] As discussed in Chapter 1, international scientific organizations have been contributing to the BWC and the Chemical Weapons Convention (CWC) for almost a decade. Although it was not part of the formal mandate for the project, in anticipation of the likely discussions at the Seventh Review Conference, the workshop included consideration of the contributions of the scientific community to the BWC.

[4] Article IV requires States Parties to enact measures to prohibit and prevent—therefore it is implicit on States Parties not only to enact domestic law, but also to undertake other measures to ensure its citizens (including the scientific community) do not violate the basic prohibitions of the BWC (a cooperative activity between the governments and the scientific communities).

[5] Pioneering nuclear physicists, for example, recognized the potential implications of their research and were involved in promoting nonproliferation. This and other examples are discussed in Finney and Slaus (2010).

TABLE 5.1 Relevance of Trends in Science and Technology to the BWC: An Article-byArticle Summary

BWC Article	Relationship to Selected S&T Developments
I. Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain: (1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; (2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.	The general prohibitions embodied in Article I apply to the misapplication of any of the S&T developments discussed at the workshop. This includes the use of synthetic techniques (e.g., chemical synthesis of nucleic acids and synthetic biology) as well as materials science and nanoscience technologies that could be used to develop targeted toxin and gene delivery systems.
II. Each State Party to this Convention undertakes to destroy, or to divert to peaceful purposes, as soon as possible but not later than nine months after entry into force of the Convention, all agents, toxins, weapons, equipment and means of delivery specified in Article I of the Convention, which are in its possession or under its jurisdiction or control. In implementing the provisions of this article all necessary safety precautions shall be observed to protect populations and the environment.	If destruction were ever needed, S&T advances in areas such as detection and surveillance technologies such as biosensors could also help States Parties monitor the process. Advances in vaccine and medical countermeasures development have the potential to contribute to appropriate safety precautions during destruction.
III. Each State Party to this Convention undertakes not to transfer to any recipient whatsoever, directly or indirectly, and not in any way to assist, encourage, or induce any State, group of States or international organizations to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or means of delivery specified in Article I of this Convention.	Norms of responsible conduct within the scientific community can assist in establishing an environment that does not support misuse. The importance of enabling technologies and services in the life sciences and a partnership with the industries that supply the research community also contribute, for example in developing ways to evaluate gene synthesis requests against pathogen sequences.[a] The research community and industry can also be partners with the policy and legal communities in striking the appropriate balance between regulation and scientific progress.

continues

TABLE 5.1 Continued

BWC Article	Relationship to Selected S&T Developments
IV. Each State Party to this Convention shall, in accordance with its constitutional processes, take any necessary measures to prohibit and prevent the 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.	Clarifications with regard to the coverage of advances in S&T under Article I could require additional legislative or regulatory steps by the States Parties under Article IV to embed them into national laws and regulations. The increased power of and access to S&T could make it easier (subject to all the roadblocks discussed earlier) for terrorist and other non-state groups to develop and produce biological weapons, and thus trends in S&T are changing states' ability to counter/prevent/respond to bioterrorism. Awareness within the S&T community of the broad set of ethical norms and legal obligations that prohibit misuse, along with engagement in relevant discussions, is valuable in supporting the treaty.
V. The States Parties to this Convention undertake to consult one another and to cooperate in solving any problems which may arise in relation to the objective of, or in the application of the provisions of, the Convention. Consultation and Cooperation pursuant to this article may also be undertaken through appropriate international procedures within the framework of the United Nations and in accordance with its Charter.	S&T developments can help support States Parties' national efforts to implement the provisions of the BWC. In particular, developments in biosensors, plant and animal disease surveillance systems, and microbial forensics could contribute to monitoring and investigating potential instances of the development, acquisition, or use of a biological agent. International collaborations that help support other aspects of BWC implementation—global cooperation in scientific research, in systems for disease surveillance and identification, and in development and manufacture of vaccines and medical therapeutics—also foster transparency and contribute to the creation of conditions under which any concerns about possible risks can be discussed in a cooperative manner.

TABLE 5.1 Continued

BWC Article	Relationship to Selected S&T Developments
VI. (1) Any State Party to this convention which finds that any other State Party is acting in breach of obligations deriving from the provisions of the Convention may lodge a complaint with the Security Council of the United Nations. Such a complaint should include all possible evidence confirming its validity, as well as a request for its consideration by the Security Council. (2) Each State Party to this Convention undertakes to cooperate in carrying out any investigation which the Security Council may initiate, in accordance with the provisions of the Charter of the United Nations, on the basis of the complaint received by the Council. The Security Council shall inform the States Parties to the Convention of the results of the investigation.	S&T can contribute to investigations of instances of alleged misuse of biological materials. Genomics and other "omics" fields provide information that can help characterize a potential agent. Creating international capacity in the field of microbial forensics, which is built on these areas of sciences, may also help identify the origins of a microbial pathogen, and this is one area of particular relevance to the BWC. Other detection and surveillance systems (e.g., biosensors, disease surveillance networks) may also help provide evidence of the occurrence of an event and assist in determining whether it is likely to be a natural outbreak, an accidental release, or an intentional act.
VII. Each State Party to this Convention undertakes to provide or support assistance, in accordance with the United Nations Charter, to any Party to the Convention which so requests, if the Security Council decides that such Party has been exposed to danger as a result of violation of the Convention.	S&T can contribute to the provision of assistance through the sharing of scientific information and capabilities in areas like microbial forensics, disease surveillance, vaccine development, improved treatments and prophylaxis, as well as other advances that improve biodefense and domestic response capabilities.
IX. Each State Party to this Convention affirms the recognized objective of effective prohibition of chemical weapons and, to this end, undertakes to continue negotiations in good faith with a view to reaching early agreement on effective measures for the prohibition of their development, production and stockpiling and for their destruction, and on appropriate measures concerning equipment and means of delivery specifically designed for the production or use of chemical agents for weapons purposes.	The use of chemical techniques to synthesize biological molecules and the use of engineered biological systems to produce chemicals highlight areas of convergence between chemistry and biology and the value of dialogue between the BWC and Chemical Weapons Convention (CWC). S&T developments discussed during the workshop (e.g., sensors, countermeasures) can also contribute to addressing potential chemical weapons threats.

continues

TABLE 5.1 Continued

BWC Article	Relationship to Selected S&T Developments
X. (1) The States Parties to this Convention undertake to facilitate, and have the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. Parties to the Convention in a position to do so shall also cooperate in contributing individually or together with other States or international organizations to the further development and application of scientific discoveries in the field of bacteriology (biology) for prevention of disease, or for other peaceful purposes. (2) This Convention shall be implemented in a manner designed to avoid hampering the economic or technological development of States Partie s to the Convention or international cooperation in the field of peaceful bacteriological (biological) activities, including the international exchange of bacteriological (biological) and toxins and equipment for the processing, use or production of bacteriological (biological) agents and toxins for peaceful purposes in accordance with the provisions of the Convention.	S&T developments contribute directly to the effective use of science for peaceful and beneficial purposes. Enabling technologies such as the Internet enhance scientific collaboration and information sharing. Cooperative efforts in areas like genome sequencing, understanding human variation, vaccine development, and disease surveillance all support the goals expressed in Article X. The scientific community can also support national and international efforts by fostering a culture of awareness, self-governance, and responsible conduct and by engaging in stakeholder discussions to achieve security goals while not unduly restricting legitimate and beneficial research. The growing S&T capacity in many parts of the world can also enable more States Parties to participate actively in the implementation of the convention.

[a] In recent years the five largest (the International Gene Synthesis Consortium (IGSC), http://www.genesynthesisconsortium.org/Home.html) and a number of smaller gene synthesis companies (the International Association Synthetic Biology (IASB), http://www.ia-sb.eu/go/synthetic-biology/) have created consortia to promote adherence to different voluntary protocols to screen orders (IGSC's emphasis) and vet customers (IASB's) to check that transactions are legitimate. An account of this and other approaches to self-governance may be found in Smithson (2010).
SOURCE: United Nations (2011) for text of the BWC Articles.

5.3.1 Promoting Norms of Responsible Conduct within the Scientific Community

The BWC is a formal international legal agreement, but it is also an expression of an international norm. As Ambassador Masood Khan, the chair of the BWC's Sixth Review Conference, told the United Nations:

> The BWC has had marked success in defining a clear and unambiguous global norm, completely prohibiting the acquisition and use of biological and toxin weapons under any circumstances. The preamble to the Convention so forcefully states: the use of disease as a weapon would be "repugnant to the conscience of mankind." It captures the solemn undertaking of the states parties "never in any circumstances to develop, produce, stockpile or otherwise acquire or retain" such weapons. With 155 states parties, the treaty is not universal, but no country dares argue that biological weapons can ever have a legitimate role in national defense. Such is the force of the treaty." (Khan, 2006)

Thus, in addition to any obligations that may fall on scientists through the legal requirements of national laws to implement the Convention, the BWC also suggests responsibilities on the part of the scientific community to help mitigate the risks that their discoveries could be misused. Two of the intersessional meetings—2005 and 2008—dealt with topics that reflect on promoting awareness and a sense of responsibility among scientists.[6] Both meetings also served as major vehicles for engaging the scientific community; a number of international scientific organizations held events to prepare for and took part in the intersessional meetings themselves (NRC, 2009a, 2011a). This engagement helps encourage scientists to take part in other activities that assist with the BWC's implementation, such as helping States Parties understand current developments in science. Efforts to engage the scientific community by emphasizing responsibilities in addition to legal requirements may also benefit from larger discussions currently taking place in various international settings about science ethics, the social responsibility of science, and specific issues related to research integrity.[7]

5.3.2 Monitoring and Assessing Scientific Developments

The preparations for the Seventh Review Conference have highlighted the potential for adopting a more systematic process to monitoring and assessing developments in S&T (see, for example, China, Canada, and BWC ISU [2010] and Indonesia, Norway, and BWC ISU [2011]). A project

[6] The topic in 2005 was "content, promulgation, and adoption of codes of conduct for scientists," and the topic in 2008 was "oversight, education, awareness raising, and adoption and/or development of codes of conduct with the aim of preventing misuse in the context of advances in bioscience and biotechnology research with the potential of use for purposes prohibited by the convention" (Bansak, 2011).

[7] Two examples of efforts that include some consideration of security issues are the 2nd World Congress on Research Integrity (http://www.wcri2010.org/index.asp) and the 2010 Draft Report on Science Ethics from the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (http://unesdoc.unesco.org/images/0018/001884/188498e.pdf).

of the Harvard Sussex Program on Chemical and Biological Weapons, "Examining the role of Science and Technology reviews in the Biological Weapons Convention," is currently assembling an extensive list of options for taking account of S&T in the BWC's future program.[8] A detailed explanation and analysis of these options is expected to be available in the autumn of 2011 (McLeish and Revill, 2011). The committee has not attempted to duplicate the list of possible options here, but offers some general thoughts on processes that might be employed.

5.3.2.1 Employing a Formal Scientific Advisory Mechanism

As biology and chemistry increasingly interact across life sciences research, some BWC States Parties have suggested that the experiences of the CWC provide useful lessons for how the BWC could address S&T trends (China, Canada, and BWC ISU, 2010; Indonesia, Norway, and BWC ISU, 2011). The CWC includes a formal Scientific Advisory Board (SAB) appointed by the Director General of the Organization for the Prevention of Chemical Weapons (OPCW), with mechanisms for appointments, member rotation, geographical balance, and formal tasking. Substantive work within the CWC SAB is carried out at its regular meetings and also through Temporary Working Groups with formal reporting processes. Much of the SAB's work is in developing improved verification procedures and providing S&T advice and guidance related to treaty implementation. However, such a SAB mechanism also needs institutional support (i.e., by the CWC Technical Secretariat) and has the potential to become politicized. The SAB was never intended to be the only source for reviews of S&T developments, and OPCW has found it valuable to receive input on developments in S&T from the wider scientific community. The relationship of OPCW with the International Union of Pure and Applied Chemistry described in Chapter 1, which has twice convened workshops on relevant developments in the chemical sciences and technology, reflects this broader engagement.

5.3.2.2 Making Use of Flexible Mechanisms to Address S&T

The current approach for BWC review conferences is to rely on contributions from States Parties and from experts within the relevant scientific and technical communities in a more ad hoc fashion. This approach is more flexible than appointing a formal advisory board and might more easily draw on the specific experts needed to review individual areas of

[8] Further information about the project is available at http://hsp.sussex.ac.uk/sandtreviews/.

science or to answer particular scientific questions posed by the States Parties to the BWC. Another option under consideration for a future intersessional process is to create working groups or experts meetings that could be established as semi-formal arrangements between the BWC and external organizations, such as the IAP and scientific unions. The workshops in 2006 and 2010 have demonstrated the interest of these groups in the BWC and their willingness to contribute. Such groups offer potential advantages because they:

- Bring a reputation for scientific quality and independence to the discussions and provide "champions" who can act at the interface between S&T and policy communities.
- Provide access to scientists working at the cutting edge, as well as to educators, science historians, and publishers, all of whom can contribute to understanding developments.
- Provide access to scientific meetings, symposia, and journals as windows on the research community and also some access to industry.

The groups are also currently limited by budgetary constraints, minimal support staff, and organizational agendas and priorities that do not necessarily include the BWC. All four of the workshops described in Chapter 1 experienced difficulty in finding funding and staff support in time to complete their contributions to the review conference process. A somewhat more regular process for engaging the scientific community would require the provision of resources but could help ensure useful and timely contributions.

5.3.2.3 Advising Activities

Whatever sort of mechanism is selected would depend on how the States Parties define their objectives for reviewing S&T areas and the desired outcomes of the process. These decisions will impact both the types of activities that are undertaken and the timing of activities in order to most effectively meet the objectives:

- *Broad Reviews of S&T Trends*
  At present, assessments of S&T relevant to the BWC are undertaken every five years as part of the regular review conference process. The workshops held in 2006 and 2010 reflect independent contributions from the scientific community to this process; individual States Parties and the BWC Implementation Support Unit also submit contributions on S&T. These types of workshops and contributions can provide a very broad-based overview of the state

of life sciences but are not able to delve into great detail in any one area. It has been suggested that more frequent assessments are needed, but whether they are comprehensive or focus on one or more topics of particular interest will have to be discussed and debated.

- *Focused Assessments of Specific Areas of S&T*
  States Parties may be interested in specific areas of S&T, such as synthetic biology or microbial forensics. Activities that bring together experts in more specific fields could address developments, needs, opportunities, and implications in greater detail, or could help inform States Parties based on specific questions. New topics could be chosen yearly or on some other timeframe. Activities could include workshops, papers, and briefings of expert scientists with government technical experts or with States Parties, or other options.

Another question for States Parties to consider is how they wish to be informed about relevant S&T. As the 2006 and 2010 workshops demonstrated, scientists sometimes disagree about the state of a particular line of research, how feasible certain tasks or developments may be to accomplish, and certainly about what the potential implications of advances might be for the BWC or security more generally.[9] A broad consensus may mask considerable complexity in scientific interactions. This complexity and disagreement is essential for understanding the pace and prospects for S&T developments. For policy makers, however, the messages on S&T implications may need to be presented in less complicated or more easily digestible form. This suggests an important role for government technical experts in bridging the gap between scientists from academia and industry and diplomats. The four workshops for the CWC and BWC on S&T have included technical experts for this reason and for the assistance they provide to researchers in understanding the potential implications of their work.

5.4 SUMMING UP: THE COMMITTEE'S FINDINGS AND CONCLUSIONS

Discussions of a wide range of scientific and technological developments, along with their implications, are found throughout the report. This section brings together the threads of these discussions to present the committee's overall findings and conclusions. Because of the diversity of

[9] An example is the debate over the past decade about the risks posed by the publication of various research results. Some early examples of "contentious research" (Epstein, 2001) are discussed in a report from the National Research Council (2004).

research in the life sciences, the report does not cover all areas of S&T in depth. Rather, the report seeks to provide an overview of developments that the committee believes are potentially relevant to the future of the BWC, identify areas that suggest useful opportunities for further exploration and analysis, and discuss options for continued monitoring and assessing. The report is organized around three trends commonly noted in discussions of S&T: the rapid pace of life sciences developments, the increasing diffusion of research capacity, and the integration of additional disciplines beyond biology in current life sciences research.

Pace of S&T Developments

As was clear from the workshop presentations and discussions, life sciences research continues to advance rapidly and is expected to do so for the foreseeable future. Research in areas such as omics, systems biology, immunology, neuroscience, and many other fields is improving the understanding of complex biological processes. At the same time, the power and availability of many of the enabling technologies that support life sciences research continue to grow.

Diffusion of Research Capacity

The workshop highlighted global research capacity and the growing number of international collaborations in S&T. Examples in areas such as disease surveillance and microbial forensics provide clear illustrations of how international collaboration can support the BWC's goals. The engagement of students in hands-on research through efforts like the International Genetically Engineered Machine competition (iGEM) and the expanding interest in do-it-yourself biology represent yet other forms of this diffusion. The report considers several factors that may enhance or impede developments in relevant areas of S&T and the continuing spread of research capacity, while noting the value of efforts to continue assessing and understanding the implications of these for the BWC.

Integration of Life Sciences with Other Disciplines

Life sciences research draws on the expertise not only of biologists but increasingly also on scientists from multiple disciplines in the physical sciences, engineering, and computational sciences. As a result, efforts to monitor and assess S&T developments draw on a growing range of expertise. The scientific community may have roles to play as part of this process, for example by exploring and clarifying scientific issues in areas of overlap between chemistry and biology that might have potential implications for the BWC and CWC.

The committee reached the following nine findings:

Finding I: The committee did not identify any discoveries that fundamentally altered the nature of life sciences research since 2006. However, advances in S&T on many fronts have increased our overall understanding and exploitation of biological systems, despite their daunting complexity.

Finding II: There has been particularly rapid progress in the power of, and access to, enabling technologies, especially those depending upon increased computing power. These include high throughput laboratory technologies and computational and communication resources. This has the following consequences:

- **Collaborations between individual investigators, global networks of researchers, and the formation of "virtual laboratories" are growing trends in the life sciences.**
- **Increasing access to sophisticated reagents such as standardized DNA "parts" and easy-to-use commercial kits and services has placed some hitherto advanced technologies within the reach of less highly trained practitioners, and has expanded the global spread of life sciences research and its industrial applications.**
- **Although first class research continues to rely heavily upon tacit knowledge, the availability of web-based technologies is facilitating the transfer of tacit knowledge through the creation of worldwide formal or informal learning communities or partnerships.**
- **These technologies reduce the barriers to the spread of S&T knowledge for responsible, educational purposes, thus creating more favorable conditions for international cooperation in the peaceful application of the life sciences.**
- **At the same time, we must recognize that these same barriers also serve as impediments to misuse. This is an area that would benefit from more in-depth analysis to gain a more nuanced understanding of the developments and trends and their impact on the norm against biological weapons.**

Finding III: Multiple disciplines, including the life, chemical, physical, mathematical, computational, and engineering sciences, are converging. This trend will continue and is relevant to the BWC as well as the CWC. The impact of this convergence on the existing arms control system must be better understood in order to draw conclusions about whether adaptations in the application of the existing regimes may be required, and if so, what they should be.

Finding IV: The field of bioreactor research and the use of transgenic organisms to produce commercially or medically important proteins have seen impressive advances. These have reduced the time needed to produce proteins and have the potential to affect the scale of the facilities required. This has obvious implications for the BWC, for example with regard to the measures States Parties need to take to implement the BWC and to prevent the use of biological or toxin agents for hostile purposes.

Finding V: The development of microbial forensics illustrates one way that life sciences research from around the world can support the BWC and create better tools to investigate and discriminate between natural and deliberate disease outbreaks.

Finding VI: Notable technical advances have been made at the level of individual-use biosensor detector systems, although there are limitations to what can be achieved given that sensor development must balance factors such as specificity, sensitivity, range of target molecules analyzed, and type of use.

Finding VII: The combination of approaches including improved biosensors, epidemiological monitoring, vaccine research, forensics, and other laboratory investigations can contribute to effective disease detection, investigation, and response systems worldwide.

Finding VIII: These advances underscore the potential for more States Parties to contribute to the implementation of the BWC, for example by expanding their global public health and disease surveillance capabilities, or by playing leadership roles in capacity building in their regions.

Finding IX: Certain scientific and technical roadblocks (e.g., drug delivery technologies) impede future progress, but once overcome, would presage a phase of rapid development. The international scientific community can play a useful role in tracking trends and developments in S&T. Its continued engagement with the BWC is essential to identifying these key scientific hurdles and when they have been overcome.

Many of the committee's findings about developments in S&T will not surprise those who follow trends in research that are potentially relevant to the BWC. Taken together, they represent the S&T reality in which the convention is now operating and the challenges and opportunities

this reality poses for the Seventh Review Conference. They also lead the committee to four general conclusions

Conclusion 1: None of the trends surveyed for this report currently falls outside the scope of Article I. The language of the treaty, as reinforced by the common understandings reached in prior review conferences, provides a degree of flexibility that has so far allowed it to adapt to progress in the life sciences and related scientific fields. The committee recognizes, however, that as new developments arise, including in fields of research that this report did not assess in depth, there may be surprise discoveries; hence, continued monitoring of advances in the life sciences and evaluation of their relevance for the BWC will be important.

Conclusion 2: Beyond the question of whether these trends pose fundamental challenges to the scope of the treaty, every major article of the treaty will be affected by the developments surveyed. The trends may pose challenges to the implementation of some aspects, but they also offer important opportunities to support the operation of the convention.

Conclusion 3: The three broad trends that provided the organization of the report—the increasing pace, diffusion, and convergence of S&T—will continue for the foreseeable future. The diversity of the fields potentially relevant to the BWC and the potential for surprise discoveries make efforts to predict developments problematic. Within these trends, however, particular fields will be affected in important ways by factors such as commercial interests that drive developments at different rates, as well as roadblocks that impede progress. Gaining a deeper understanding of the drivers and roadblocks would provide a more meaningful picture of how and when continuing S&T developments are likely to affect the convention.

Conclusion 4: There are potential roles for the scientific community in helping to monitor trends in S&T and to assess their implications for the BWC, and there are a number of mechanisms by which input and advice could be provided. The most effective starting point for the Seventh Review Conference, therefore, would be to address the functions that such advice and analysis will serve for the future operation of the convention, including increasing the capacity of States Parties to participate fully in its implementation.

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Appendix A

Committee Member Biographies

Roderick J. Flower, Ph.D., D.Sc., FMedSci, FBPharmacolS, FRS (*Chair*) is professor of biochemical pharmacology at the William Harvey Research lnstitute, Barts, and The London School of Medicine and Dentistry. Dr. Flower received his postgraduate training at the Department of Pharmacology in the Royal College of Surgeons of England under the supervision of Sir John Vane. He moved with Vane when the latter became research and development (R&D) director at the Wellcome Foundation in Kent and worked there as part of his prostaglandin research team until 1984. Dr. Flower then served as chair of pharmacology at the University of Bath, where he also served as head of the School of Pharmacy and Pharmacology (1987-1989). ln 1989, he moved to the medical college of St. Bartholomew's Hospital, where he became a director and founding member of the William Harvey Research lnstitute and started a new Department of Biochemical Pharmacology. He served as head of the institute (1998-2002) and was also Wellcome Principal Research Fellow (1994-2007). His main interests are the mechanism of action of anti-inflammatory drugs including Cox inhibitors and glucocorticoid steroids. Dr. Flower has published more than 300 peer-reviewed research papers and holds several patents. He has trained numerous Ph.D. students, hosted many researchers from overseas in his group, and made important contributions to undergraduate teaching. He has served on several editorial and scientific boards and was president of the British Pharmacological Society (2000-2003). Dr. Flower's honors include the Thomas Woodcock Physiology Prize (University of Sheffield, 1972), British Pharmacological Society's Sandoz Prize (1978), Gaddum Memorial Lecture and Medal of The British

Pharmacological Society (1986), Fellow of the Academy of Medical Sciences (1999), Fellow of Academia Europeae (2001), William Withering Medal of the Royal College of Physicians (2003), Lifetime Achievement Award of the lnternational Society of lnflammation Associations (2005), and Bayliss-starling Prize Lecture of the Physiological Society (2006). He was elected a Fellow of the Royal Society in 2003. Dr. Flower served on the NRC Committee for the lnternational Outreach Activities on Biosecurity: A Workshop on Building Bridges Between the Scientific and Policy Communities and also on the organizing committee for a 2006 Royal Society-lAP-ICSU workshop on developments in the life sciences and potential implications for the Biological and Toxin Weapons Convention.

Hernan Chaimovich, Ph.D. is a professor in the Department of Biochemistry of the lnstitute of Chemistry, Universidade de São Paulo, Brazil, and superintendent general of the Butantan Foundation. He received a degree in biochemistry from the Universidad de Chile, worked with Osvaldo Cori in apyrase enzymology, and spent 2.5 years in the United States working under the supervision of C. A. Bunton (University of California, Santa Barbara) and F. H. Westheimer (Harvard University) in physical organic chemistry. He returned to Chile as an assistant professor of biochemistry and moved to Brazil in 1969, first as a FAPESP fellow in the Department of Physiology at the Faculty of Medicine, Universidade de São Paulo (USP) and later in the Department of Biochemistry of the lnstitute of Chemistry, USP, where he became a full professor in 1985. Dr. Chaimovich's research is in interfacial effects on chemical and biological reactivity using micelles and vesicles as models. The contributions of his group, including theoretical and experimental studies of the effect of micelles and vesicles on a number of chemical reactions, have contributed to dissect the effect of these aggregates on chemical reactivity. Dr. Chaimovich is a co-chair of the lnterAmerican Network of Academies of Sciences (IANAS) and is a full member of the Brazilian Academy of Sciences and the Academy of Sciences of Latin America (ACAL). He is also a fellow of the Third World Academy of Sciences (TWAS) and of the American Association for the Advancement of Science (AAAS), being a corresponding member of the Chilean Academy of Sciences. He has received several prizes, including the Grand-Cross of the National Order of Scientific and Technological Merit, the highest scientific distinction conceded by the Brazilian government. Dr. Chaimovich has also recently served as vice-president for external relations for the lnternational Council for Science (ICSU) and has encouraged its unions to become engaged in biosecurity issues.

Nancy D. Connell, Ph.D. is a professor of infectious disease at the University of Medicine and Dentistry of New Jersey (UMDNJ)-New Jersey Medi-

cal School and director of the UMDNJ Center for BioDefense and the Biosafety Level 3 Facility of UMDNJ's Center for the Study of Emerging and Re-emerging Pathogens. She chairs the university's Institutional Biosafety Committee, and she has worked with several international programs on dual use issues. She is past chair of the National Institutes of Health's Center for Scientific Review Study Section HIBP (Host Interactions with Bacterial Pathogens), which reviews bacterial-pathogenesis submissions to the National Institute of Allergy and Infectious Diseases. She is current chair of the F13 Infectious Diseases and Microbiology Fellowship Panel. Dr. Connell's involvement in biological weapons control began in 1984, when she was chair of the Committee on the Military Use of Biological Research, a subcommittee of the Council for Responsible Genetics, based in Cambridge, Massachusetts. Dr. Connell received her Ph.D. in microbial genetics from Harvard University. Her major research focus is in bacterial antibiotic drug discovery.

Andrzej Górski, M.D., Ph.D. is professor of medicine and immunology at the Medical University of Warsaw and vice president of the Polish Academy of Sciences. He is board certified in internal medicine with a subspecialty certification in clinical immunology. Dr. Górski received his M.D. (1970) and Ph.D. (1973) degrees from the Medical University of Warsaw and was a Fulbright Scholar at the Sloan-Kettering Institute for Cancer Research, USA. He has been a visiting professor at Adelaide Children's Hospital, Australia, the Weizmann Institute of Science, Israel, the University of London United Medical and Dental Schools of Guy's and St. Thomas's Hospitals, England, and the Universidad Autonoma, Madrid, Spain. Dr. Górski served as prorector for scientific affairs & international cooperation (1993-1996) and as rector (1996-1999) of the Medical University of Warsaw. From 1999-2007 he was also director of the L. Hirszfeld Institute of Immunology and Experimental Therapy at the Polish Academy of Sciences. Dr. Górski has authored more than 100 scientific publications, serves as the editor in chief of *Archivum Immunologiae et Therapiae Experimentalis*, and has served as a member of the editorial board of *Science & Engineering Ethics*. His awards include the Meller Award for excellence in cancer research from Sloan-Kettering Institute, the ICRETT Award and the Yamagiwa-Yoshida Award from the International Union Against Cancer, the J. Sniadecki Memorial Award from the Polish Academy of Sciences (the highest award in medical sciences in Poland), and the Gloria Medicinae awarded by the Polish Medical Association. In addition, Dr. Górski is a member of the Committee for Ethics in Science at the Polish Academy of Sciences, a member of the Committee for Ethics in Science at the Ministry of Science, Head of the Bioethics Committee, Ministry of Health, and represents Poland in the Forum of National Ethics Committees to the European Commission.

Li Huang, Ph.D. received his Ph.D. in the Department of Microbiology at the University of Guelph, Ontario, Canada, in 1988. He was a postdoctoral fellow in the Department of Biochemistry of the School of Hygiene and Public Health at the Johns Hopkins University, Maryland, from 1988 to 1993. He became assistant professor in the Department of Biology at Pomona College, California, in 1993 before joining the faculty in the Institute of Microbiology, Chinese Academy of Sciences, in 1996. He was appointed to full professorship in 1998 and is now director-general of the Institute of Microbiology, Chinese Academy of Sciences. Dr. Huang's scientific work concerns the isolation and biotechnological exploitation of microorganisms and their genes from various environments. He has also been working on biosecurity-related issues since 2001, and he is currently a member of the Biosecurity Working Group of the InterAcademy Panel (IAP).

Maxwell Otim Onapa, Ph.D., M.Sc. is the deputy executive secretary of the Uganda National Council for Science and Technology (UNCST), where he has been stationed since 2006. His responsibilities include providing leadership and technical support in the design, development, and implementation of programs and projects. He also served as chair of the Uganda National Academy of Sciences' Committee on Assessing the Current State of Knowledge Pertaining to the Meaning and Scope of Biosafety and Biosecurity in the Context of Uganda, which published the report, *The Scope of Biosafety and Biosecurity in Uganda: Policy Recommendations for the Control of Associated Risks* (2010). Previously, Dr. Otim Onapa worked at the National Agricultural Research Organisation (NARO) as a research officer, infectious disease, Livestock Health Research Institute (2000-2006) and as a research assistant (1994-1999). From 1992 to 1994, he had worked as a veterinary research officer, microbiology, Animal Health Research Centre, Entebbe. Academically, Dr. Otim Onapa has a Ph.D. from the Royal Veterinary and Agricultural University, Copenhagen; an M.Sc. (Tropical Veterinary Epidemiology) from the Free University of Berlin/ Addis Ababa University; and a Bachelor of Veterinary Medicine (BVM) from Makerere University, Uganda. Dr. Otim Onapa has published widely and has had additional professional training in various areas including strategic management, molecular diagnostic polymerase chain reaction training, laboratory diagnosis of avian influenza, among others. He has also presented as a member of papers on biosafety and biosecurity in different international forums.

M. Iqbal Parker, Ph.D. received his B.Sc. in biochemistry and microbiology in 1974, his B.Sc. (Honors) in 1975, and his Ph.D. in biochemistry in 1979 from the University of Cape Town. Dr. Parker is currently director of the Cape Town component of the International Center for Genetic Engi-

neering and Biotechnology (ICGEB), professor in medical biochemistry at the University of Cape Town, and director of the South African Medical Research Council's Oesophageal Cancer Research Group based at the University of Cape Town. Before taking up the post with the ICGEB, he was director of the School of Biomedical Sciences and head of the Division of Medical Biochemistry at the University of Cape Town and subsequently, the deputy dean for research in the Health Science Faculty. Dr. Parker is past-president of the South African Society for Biochemistry and Molecular Biology and was a key member in founding of the Federation African Societies on Biochemistry and Molecular Biology and is currently its treasurer. He has been elected onto the IUBMB Executive Committee on Symposia and also the Chair of the Wood-Whelan Fellowship Committee. He is a founding member, current secretary general, and chair of the Biosafety Committee of the South African Academy of Sciences.

Andrew Pitt, D. Phil. is chair of Pharmaceutical Chemistry and Chemical Biology, School of Health and Life Sciences at Ashton University in Birmingham, United Kingdom. Until 2011 he was reader and director of the Sir Henry Wellcome Functional Genomics Facility (SHWFGF) at the University of Glasgow. He also served as director of the Doctoral Training Centre in Proteomics and as managing director of the RASOR Interdisciplinary Research Collaboration in Proteomic Technologies, which brings together engineers, physical scientists, and biologists across the Universities of Glasgow, Dundee, Edinburgh, and Strathclyde. Dr. Pitt's multidisciplinary research involves proteomics, protein science, post-genomics technologies, biochemistry, biomolecular analysis, and systems and synthetic biology. His research focuses particularly on the generation of new technologies for modern protein research, biomarker discovery and identification, complex biochemical pathways and molecular networks, integration and modeling for systems biology, and clinical applications of proteomics. He is a member of the Royal Society Standing Committee on Scientific Aspects of International Security (2007-present), a member of the Executive Board of the British Society for Proteome Research (2007-present), and a member of the editorial board of the *Journal of Proteomics*.

Ralf Trapp, Ph.D. is an independent consultant who has worked and published extensively in the fields of chemical and biological weapons disarmament and nonproliferation. His research includes the impact of advances in science and technology on the regimes pertaining to chemical and biological weapons, national implementation measures for the Chemical Weapons Convention and the Biological Weapons Convention (such as legislation, regulations, training, enforcement, self-regulation in industry and academia, oversight, and education), and other aspects of preparedness and consequence management. He formerly served as

secretary of the Scientific Advisory Board of the Organization for the Prohibition of Chemical Weapons (1998-2006), which administers the Chemical Weapons Convention. He also served as legal coordinator (consultant) for the European Union Joint Action in Support of the Biological and Toxin Weapons Convention (2007-2008), which was executed by the Bio-Weapons Prevention Project, Geneva, Switzerland. Dr Trapp is an external member of the Academy of Sciences of Bologna and a fellow of the International Union of Pure and Applied Chemistry (IUPAC). He received his Dr. rer. nat. (Ph.D.) from the Technical University "Carl Schorlemmer" Leuna-Merseburg (former German Democratic Republic) in 1978 and Dr. sc. nat. from the GDR Academy of Sciences, Leipzig, in 1986.

Lloyd Whitman, Ph.D., M.S. joined the Center for Nanoscale Science and Technology at the National Institute of Standards and Technology (NIST) as the deputy director in April 2008. He received a B.S. in physics from Brown University (with honors, magna cum laude) and M.S. and Ph.D. degrees in physics from Cornell University. After a National Research Council Postdoctoral Research Fellowship at NIST, he joined the research staff at the Naval Research Laboratory (NRL). At NRL, Dr. Whitman was most recently the head of the Surface Nanoscience and Sensor Technology Section, a multidisciplinary research group working at the nexus of nanoscience, biotechnology, and microsystems. He led a diverse portfolio of research studying semiconductor, organic, and biomolecular nanostructures, their use in novel functional surfaces, and their integration into advanced sensor systems for national security applications. In addition to leading research at NRL, Dr. Whitman served as a science advisor to the Special Assistant to the Secretary of Defense for Chemical and Biological Defense and Chemical Demilitarization Programs. In this capacity, he represented the Department of Defense on the National Science and Technology Council, Committee on Technology Subcommittee on Nanoscale Science, Engineering and Technology. Dr. Whitman has more than 140 publications and patent applications in the areas of nanoscience and sensor technology, and numerous media citations and awards, including the Navy Meritorious Civilian Service Award.

Appendix B

National and International Scientific Organizations Relevant to the BWC

THE CONVENING ORGANIZATIONS FOR THE WORKSHOP

IAP—the Global Network of Science Academies (formerly the Inter-Academy Panel on International Issues), founded in 1993, is a global network of 104 science academies in partnership designed "to help its members develop the tools they need to participate effectively in science policy discussions and decision making." The current co-chairs are Canada and the African Academy of Sciences. More information about IAP can be found on its website at http://www.interacademies.net/. The IAP executive council established a Biosecurity Working Group (BWG) in 2004 to coordinate its activities; its current members are the academies of China, Cuba, Nigeria, Poland (chair), the United Kingdom, and the United States.

The **International Union of Biochemistry and Molecular Biology** (IUBMB), founded in 1955, unites biochemists and molecular biologists in 66 countries that belong to the Union as Adhering or Associate Adhering Bodies, representing biochemical societies, national research councils, or academies of sciences. The Union is devoted to promoting research and education in biochemistry and molecular biology throughout the world and gives particular attention to areas where the subject is still in its early development. It achieves this in several ways. For example, every three years the Union sponsors an International Congress of Biochemistry and Molecular Biology; co-sponsorship of these Congresses by regional organizations of biochemistry and molecular biology is an increasing trend. These Congresses are major international meetings where current

research in all fields of biochemistry and molecular biology is considered. Thousands of individual research projects are presented in poster sessions, and leading investigators from many nations survey their fields and describe their own research in symposia and plenary lectures. Since 1992 IUBMB has also sponsored IUBMB Conferences and Special Meetings, held in the years between the International Congresses. Further information is available online at http://www.iubmb.org.

The **International Union of Microbiological Societies** (IUMS) is one of the 29 Scientific Unions of the International Council for Science (ICSU). It was founded in 1927 as the International Society of Microbiology, and became the International Association of Microbiological Societies affiliated to the International Union of Biological Sciences (IUBS) as a division in 1967. It acquired independence in 1980 and became a Union Member of ICSU in 1982. IUMS currently has 113 member societies and 14 associate members representing more than 100 countries. Members are national societies and associations for microbiologists, and associate members are other institutions with an interest in microbiological and connected sciences. IUMS's objectives are to promote the study of microbiological sciences internationally; initiate, facilitate, and coordinate research and other scientific activities that involve international cooperation; ensure the discussion and dissemination of the results of international conferences, symposia, and meetings and assist in the publication of their reports; represent microbiological sciences in ICSU; and maintain contact with other international organizations. Further information is available online at http://www.iums.org.

The **Chinese Academy of Sciences** (CAS) was founded in Beijing on November 1, 1949. As the nation's highest academic institution in natural sciences, supreme scientific and technological advisory body, and national comprehensive research and development center in natural sciences and high technologies, it consists of the academic divisions and various subordinate institutions. It currently has 694 members. At present, there are six academic divisions, functioning as the national scientific think-tank, providing advisory and appraisal services on issues stemming from the national economy, social development, and science and technology progress. Today's CAS has 12 branch offices, 117 institutes with legal entity, more than 100 national key laboratories and national engineering research centers, and about 1,000 field stations throughout the country. CAS has made a series of major scientific breakthroughs in basic and cutting-edge research, bio-medical sciences, strategic high-technology, and research on sustainable development, thus making important contributions to China's economic development, social progress and national security. In 2009, the Science & Technology in China: A Roadmap to 2050 series outlined major

scientific issues and critical technical problems in China's modernization process, and made suggestions on how to resolve them, ensuring the contribution of science and technology in realizing China's modernization goals by 2050. CAS also attaches great importance to international cooperation and exchanges, reinforcing strategic partnerships with key research institutions through high-level exchange visits and organizing high-level strategic fora and academic symposia on frontier research. Further information is available online at http://english.cas.cn/.

Information about the **U.S. National Research Council and National Academy of Sciences** is available in the front matter of the report.

OTHER INTERNATIONAL SCIENTIFIC ORGANIZATIONS

The **International Union of Pure and Applied Chemistry** (IUPAC) serves to advance the worldwide aspects of the chemical sciences and to contribute to the application of chemistry in the service of humankind. As a scientific, international, nongovernmental, and objective body, IUPAC can address many global issues involving the chemical sciences.

IUPAC was formed in 1919 by chemists from industry and academia. Over nearly nine decades, IUPAC has succeeded in fostering worldwide communications in the chemical sciences and in uniting academic, industrial, and public-sector chemistry in a common language. IUPAC has long been recognized as the world authority on chemical nomenclature, terminology, standardized methods for measurement, atomic weights, and many other critically evaluated data. IUPAC continues to sponsor major international meetings that range from specialized scientific symposia to CHEMRAWN (CHEMical Research Applied to World Needs) meetings with societal impact. During the Cold War, IUPAC became an important instrument for maintaining technical dialogue among scientists throughout the world.

IUPAC is an association of bodies, National Adhering Organizations, which represent the chemists of different member countries. There are 45 National Adhering Organizations, and 20 other countries are also linked to IUPAC in the status of Associate National Adhering Organizations. Almost 1,000 chemists throughout the world are engaged on a voluntary basis in the scientific work of IUPAC, primarily through projects, which are components of eight divisions and several other committees. Further information is available online at http://www.iupac.org.

The **International Council for Science** (ICSU), founded in 1931, is a nongovernmental organization representing a global membership that includes both national scientific bodies (111 members) and international scientific unions (29 members). As its website notes: "Because of its broad

and diverse membership, the Council is increasingly called upon to speak on behalf of the global scientific community and to act as an advisor in matters ranging from ethics to the environment." Approximately a dozen of ICSU's unions can be considered to be part of the "life sciences"—reflecting the breadth and fragmentation of the field, unlike the single unions for physics and chemistry. ICSU also has a standing Committee on Freedom and Responsibility in the Conduct of Science. Further information may be found online at http://www.icsu.org.

Appendix C

Workshop Agenda and Participants

AGENDA

Sunday, October 31

6:00 PM Reception and Welcome Remarks from Sponsoring Organizations

— *Rod Flower,* Chair, Committee on Trends in Science and Technology Relevant to the Biological Weapons Convention: An International Workshop
— *Lei Zhang*, Chinese Academy of Sciences
— *Andrzej Górski*, Chair, IAP Biosecurity Working Group
— *Iqbal Parker*, International Union of Biochemistry and Molecular Biology
— *Stephen Lerner*, International Union of Microbiological Societies
— *Meg Flanagan*, Defense Threat Reduction Agency
— *Lorna Miller*, U.K. Global Partnership Programme
— *Christopher Park*, U.S. Department of State

Monday, November 1

9:00 AM **Plenary Session 1:** Introduction to the Themes, Goals, and Context of the Workshop
Chair: *Andrzej Gorski, Polish Academy of Sciences, Poland*

Welcome Address: *Tao Xu, Director-General, Institute of Biophysics, Chinese Academy of Sciences*

1. Aims and Objectives of the Meeting—*Roderick Flower, Queen Mary University of London, UK*
2. The Biological Weapons Convention: A Brief Overview—*Piers Millet, BWC Implementation Support Unit, United Nations, Switzerland*
3. Introduction to Framework for Evaluating New Science and Technology—*Ralf Trapp, CBW Consultant, France*
4. Perspective from the Chinese Academy of Sciences—*Li Huang, Institute of Microbiology, Chinese Academy of Sciences, China*
5. Discussion

10:45 AM **Plenary Session 2:** Developments in Design, Fabrication, and Production (A)
Chair: *Iqbal Parker, University of Cape Town, South Africa*

1. Bioinformatics and Computational Tools—*Etienne de Villiers, International Livestock Research Institute, Kenya*
2. Systems Biology: Relevance to the Biological and Toxins Weapons Convention—*Andrew Pitt, University of Glasgow, UK*
3. Emerging Trends in Synthetic Biology—*Pawan Dhar, University of Kerala, India*
4. Discussion

1:15 PM **Plenary Session 3:** Developments in Design, Fabrication, and Production (B)
Chair: *Andrew Pitt, University of Glasgow, UK*

1. Bioreactors and Transgenic Animals—*Ryszard Słomski, Pozna—University of Life Sciences, Poland*
2. Transgenic Plants and Recombinant Pharmaceuticals—*Julian Ma, St. Georges University of London, UK*
3. Neuroscience Developments—*James Eberwine, University of Pennsylvania School of Medicine, USA*
4. Discussion

3:00 PM **Plenary Session 4:** Dispersal and Delivery
Chair: *Ralf Trapp, CBW Consultant, France*

1. Aerosols and Aerobiology—*Chad Roy, Tulane National Primate Research Center, USA*

2. Nanostructured Delivery Systems for Drugs, Proteins and Cells—*Jackie Ying, Institute of Bioengineering and Nanotechnology, Singapore*
3. Commentary: Implications Stemming from Advances in Dual-Use Targeted Delivery Systems—*Kathryn Nixdorff, Darmstadt University of Science and Technology, Germany*
4. Discussion

4:15 PM **Breakout Discussion Sessions**

7:30 PM **Special Event:** "Strengthening the culture of responsibility with respect to dual use research and biosecurity" (video-teleconference). Organized by NIH/NSABB and the Chinese Academy of Sciences, in cooperation with the IAP, IUMS, IUBMB, and NAS.

Tuesday, November 2

9:00 AM **Plenary Session 5:** Summary from Day 1
Chair: *Maxwell Otim Onapa, Uganda National Council for Science and Technology, Uganda*

1. Presentations from Rapporteurs of Day 1 Breakout Sessions
2. Discussion

9:30 AM **Plenary Session 6:** Detection, Identification, and Monitoring
Chair: *Lloyd Whitman, National Institute of Standards and Technology, USA*

1. Postgenomic Technologies—*Andrew Pitt, University of Glasgow, UK*
2. Exploring an International Microbial Forensics Capability to Support Attribution and Advance Global Biosecurity—*Randall Murch, Virginia Polytechnic Institute and State University, USA*
3. Biosensors Overview—*Gary Resnick, Los Alamos National Laboratory, USA*
4. Biosensor Development—*Ilya Kurochkin, M.V. Lomonosov Moscow State University, Russia*
5. Remarks: Brief Summary of the Science used by the FBI in the Anthrax Attacks Case of 2001—*Nancy Connell, University of Medicine and Dentistry of New Jersey, USA*
6. Discussion

11:15 AM **Plenary Session 7:** Defense and Countermeasures
Chair: *Anwar Nasim, COMSTECH, Pakistan*
1. Vaccines and Medical Countermeasures—*Nancy Connell, University of Medicine and Dentistry of New Jersey, USA*
2. Monitoring and Molecular Diagnosis of Emerging Infectious Diseases—*Raymond Lin, National Public Health Laboratory, Singapore*
3. Agricultural Biosecurity: Threats to Crop Production—*Michael Jeger, Imperial College London, UK*
4. Discussion

1:45 PM **Breakout Discussion Sessions**

4:15 PM **Plenary Session 8:** Communication
Chair: *Hernan Chaimovich, Fundação Butantan, Brazil*
1. How the Internet Has Changed Scientific Interchanges—*James Meadway, The Royal Society, UK*
2. Influence of Technology on Scientific Collaboration: Indonesia Experience—*Herawati Sudoyo, Eijkman Institute for Molecular Biology, Indonesia*
3. Biological Risks—Future Trends: Conveying the Concept of Risk—*Terence Taylor, International Council for the Life Sciences, USA*
4. Discussion

Wednesday, November 3

9:00 AM **Plenary Session 9:** Summary from Day 2
Chair: *Li Huang, Institute of Microbiology, Chinese Academy of Sciences, China*
1. Presentations from Rapporteurs of Day 2 Breakout Sessions
2. Discussion of Days 1 and 2

10:30 AM **Plenary Session 10:** Workshop Conclusions
Chair: *Roderick Flower, Queen Mary University of London, UK*
1. Facilitated Discussion: Improving Scientific Input into the BWC
2. Discussion of Workshop Findings and Conclusions
3. Next Steps

12:00 PM Meeting Adjournment

PARTICIPANT LIST

Katherine Bowman
Board on Life Sciences
The U.S. National Academies

Göran Bucht
Swedish Defense Research Establishment

Hernan Chaimovich
Fundação Butantan
University of São Paulo

Teck-Mean Chua
Asia Pacific Biosafety Association

Nancy Connell
Department of Medicine
University of Medicine and Dentistry of New Jersey

Neil Davison
Security and Diplomacy
The Royal Society

Etienne De Villiers
International Livestock Research Institute

Pawan Dhar
Centre for Systems and Synthetic Biology
University of Kerala

Gang Dong
Chinese Academy of Military Medical Sciences

Qi Dong
Division of International Organization Bureau of International Cooperation
Chinese Academy of Sciences

Cris dos Remedios
International Union for Pure & Applied Biophysics
University of Sydney

James Eberwine
Department of Pharmacology
University of Pennsylvania School of Medicine

Gerald Epstein
Center for Science, Technology, and Security Policy
American Association for the Advancement of Science

Meg Flanagan
U.S. Defense Threat Reduction Agency

Rod Flower
St. Barts and The London School of Medicine
Queen Mary University of London

David R. Franz
Midwest Research Institute

David Friedman
Institute for National Security Studies
Tel-Aviv University

Katsuhisa Furukawa
Japan Science and Technology Agency

Andrzej Gorski
Polish Academy of Sciences

Anfeng Guo
Visiting Fellow, Princeton University
Beijing Science Technology and Security Center

Li Huang
Institute of Microbiology
Chinese Academy of Sciences

Kathryn Hughes
Board on Chemical Sciences and Technology
The U.S. National Academies

Jo L. Husbands
Board on Life Sciences
The U.S. National Academies

Saied Jaradat
Princess Haya Biotechnology Center

Michael J. Jeger
Imperial College London

Serhiy Komisarenko
National Biosafety and Biosecurity Commission
Academy of Sciences of Ukraine

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Weapons of Mass Destruction Branch
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Vilnius University

Stephen Lerner
International Union of Microbiological Societies
Wayne State University School of Medicine

Ming Li
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Chinese Academy of Sciences

Zhenjun Li
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Raymond Lin
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Shu Liu
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Yidong Liu
Institute for the History of Natural Science
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Julian Ma
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Irma Makalinao
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University of the Philippines Manila

Robert Mathews
NBC Arms Control Unit
Defence Science and Technology Organisation

James Meadway
The Royal Society

Sue Meek
Australian Academy of Science

Lorna Miller
Defence Science and Technology Laboratory

Piers Millett
BWC Implementation Support Unit
United Nations

Randall Murch
Virginia Polytechnic Institute and State University

Anwar Nasim
OIC Standing Committee on Scientific and Technological Cooperation (COMSTECH)

Kathryn Nixdorff
Darmstadt University of Technology

Godwin Haruna Ogbadu
Sheda Science and Technology Complex

Maxwell Otim Onapa
Uganda National Council for Science and Technology

Christopher Park
Bureau of International Security and Nonproliferation
U.S. Department of State

M. Iqbal Parker
International Centre for Genetic Engineering and Biotechnology
University of Cape Town

Graham Pearson
Department of Peace Studies
University of Bradford

Lei Pei
Organisation for International Dialogue & Conflict Management

Andrew Pitt
University of Glasgow

Yerlan Ramankulov
National Center for Biotechnology of the Republic of Kazakhstan

I. Gary Resnick
Bioscience Division
Los Alamos National Laboratory

James Revill
Science and Technology Policy Research
University of Sussex

Chad Roy
Tulane National Primate Research Center
Tulane University School of Medicine

Benjamin Rusek
Committee on International Security and Arms Control
The U.S. National Academies

Nariyoshi Shinomiya
Department of Integrative Physiology and Bio-Nano Medicine
National Defense Medical College of Japan

Aleksandr Simonian
Biosensing/CBET
National Science Foundation

Ryszard Slomski
Department of Biochemistry and Biotechnology
Poznan University of Life Sciences

James Stack
Kansas State University
Great Plains Diagnostic Network

Colonel Ben Steyn
Chemical and Biological Defence Advisor
South African Military Health Service

Herawati Sudoyo
Eijkman Institute for Molecular Biology

Leiv Sydnes
Department of Chemistry
University of Bergen

Marlena Szalata
Department of Biochemistry and Biotechnology
Poznan University of Life Sciences

Terence Taylor
International Council for the Life Sciences

Ralf Trapp
Consultant, CBW Arms Control and Disarmament

Jinglin Wang
Institute of Microbiology and Epidemiology
Chinese Academy of Military Medical Sciences

Lei Wang
Chinese Academy of Military Medical Sciences

Li Wang
Chinese Academy of Military Medical Sciences

Lloyd Whitman
Center for Nanoscale Science and Technology
National Institute of Standards and Technology (NIST)

Angela Woodward
Verification Research, Training and Information Centre (VERTIC)

Jackie Ying
Institute of Bioengineering and Nanotechnology

Zhiming Yuan
Wuhan Institute of Virology
Chinese Academy of Sciences

Lei Zhang
Institute of Biophysics
Chinese Academy of Sciences

Xiushan Zhang
Chinese Academy of Military Medical Sciences

Lianhui Zhu
Chinese Academy of Military Medical Sciences

Enlin Zhu
Plant Protection and Plant Quarantine Division
Ministry of Agriculture