21st Century Borders/Synthetic Biology: *Focus on Responsibility and Governance*

Conference convened by the ISGP Dec. 4–7, 2012
at the Hilton El Conquistador, Tucson, Arizona

Institute on Science for Global Policy (ISGP)

21st Century Borders/Synthetic Biology: *Focus on Responsibility and Governance*

Conference convened by the ISGP in partnership with
the University of Arizona at the Hilton El Conquistador Hotel
Tucson, Arizona, U.S.
Dec. 4–7, 2012

An ongoing series of dialogues and critical debates
examining the role of science and technology
in advancing effective domestic and international policy decisions

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ISBN: 978-0-9803882-4-0

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Introduction

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Preface

The contents of this book were taken from material presented at an international conference convened by the Institute on Science for Global Policy (ISGP) on December 4–7, 2012, in cooperation with the University of Arizona at the El Conquistador Hotel and Resort in Tucson, Arizona. This ISGP conference was part of the ISGP program on 21st Century Borders (21CB) and focused on Synthetic Biology (SB).

The process underlying all ISGP conferences begins with the recognition that a scientific topic such as SB has emerged on the international stage with advances that promise immense opportunities to improve the human condition and also simultaneously challenge many cultural, ethical, and economic issues throughout societies worldwide. Decisions within societies concerning how to appropriately incorporate such transformational science into public and private sector policies rely on candid debates that highlight the credible options developed by scientific communities throughout the world. Since SB can potentially have significant impact across many different types of borders well beyond the geographical, it deserves attention from both domestic and international policy makers from a wide range of disciplines. ISGP conferences offer those rare environments where such critical debates can occur among credible scientists, influential policy makers, and societal stakeholders.

Based on extensive interviews conducted by the ISGP staff with an international group of subject-matter experts, the ISGP invited eight highly distinguished individuals with expertise in SB and the related aspects of the genomic revolution to prepare the three-page policy position papers to be debated at the Tucson conference. These eight policy position papers, together with the not-for-attribution summaries of the debates of each paper, are presented in this book. The areas of consensus and actionable next steps that were developed by all participants in the caucuses that followed the debates are also presented. The debate

summaries and caucus results were written by the ISGP staff and are based on contributions from the conference participants.

Current realities

While the material presented here is comprehensive and stands by itself, its policy significance is best appreciated if viewed within the context of how domestic and international science policies have been, and often currently are being, formulated and implemented.

As the second decade of the 21st century opens, most societies are facing difficult decisions concerning how to appropriately use, or reject, the dramatic new opportunities offered by modern scientific advances and the technologies that emanate from them. Advanced scientific research programs, as well as commercially viable technologies, are now developed globally. As a consequence, many societal issues related to science and technology (S&T) necessarily involve both domestic and international policy decisions, both in the public and private sectors. The daunting challenges to simultaneously recognize immediate technological opportunities, while identifying those emerging and "at-the-horizon" S&T achievements that foreshadow transformational advantages and risks within specific societies, are now fundamental governmental responsibilities. These responsibilities are especially complex since policy makers must consider the demands of different segments of society, which often have conflicting goals. For example, decisions must balance critical commercial interests that promote economic prosperity with the cultural sensitivities that often determine if, and how, S&T can be successfully integrated into any society.

Many of our most significant geopolitical policy and security issues are directly connected with the remarkably rapid and profound S&T accomplishments of our time. Consequently, it is increasingly important that the S&T and policy communities (public and private) communicate effectively. With a seemingly unlimited number of urgent S&T challenges, both wealthy and less-wealthy societies need their most accomplished members to focus on effective, real-world solutions relevant to their specific circumstances. Some of the most prominent challenges involve (i) infectious diseases and pandemics, (ii) environmentally compatible energy sources, (iii) the consequences of climate change, (iv) food safety, security, and defense (v) the cultural impact of stem cell applications, (vi) nanotechnology and human health, (vii) cyber security for advanced telecommunication, (viii) the security implications of quantum computing, and (ix) the cultural radicalization of societies.

Recent history suggests that most societies would benefit from improving the effectiveness of how scientifically credible information is used to formulate and implement governmental policies, both domestic and international. Specifically, there is a critical need to have the relevant S&T information concisely presented to policy communities in an environment that promotes candid questions and debates led by those nonexperts directly engaged in decisions. Such discussions, sequestered away from publicity, can help to clarify the advantages and potential risks of realistic S&T options directly relevant to the challenges being faced. Eventually, this same degree of understanding, confidence, and acknowledgment of risk must be communicated to the public to obtain the broad societal support needed to effectively implement any decision.

The ISGP mission

The ISGP has pioneered the development of a new type of international forum based on a series of invitation-only conferences. These ISGP conferences are designed to provide articulate, distinguished scientists and technologists opportunities to concisely present their views of the credible S&T options available for addressing major geopolitical and security issues. Over a two-year-plus period, these ISGP conferences are convened on different aspects (e.g., synthetic biology) of a broad, overarching topic (e.g., 21st Century Borders). Among the most challenging S&T advances transcending many types of borders (e.g., geographical. cultural, ethical, and political) are the diverse forms of the genomic revolution, including those aspects related to the creation of living material via SB.

ISGP programs rely on the validity of two overarching principles:

1. Scientifically credible understanding must be closely linked to the realistic policy decisions made by governmental and societal leaders in addressing both the urgent and long-term challenges facing 21st century societies. Effective decisions rely on strong domestic and global public endorsements that motivate active support throughout societies.
2. Communication among scientific and policy communities requires significant improvement, especially concerning decisions on whether to use or reject the often transformational S&T opportunities continually emerging from the global research communities. Effective decisions are facilitated in venues where the advantages and risks of credible S&T options are candidly presented and critically debated among internationally distinguished subject-matter experts, policy makers, and private sector and community stakeholders.

Historical perspective

The dramatic and rapid expansion of academic and private sector scientific research transformed many societies of the 20th century and is a major factor in the emergence of the more affluent countries that currently dominate the global economic and security landscape. The positive influence of these S&T achievements has been extremely impressive and in many ways the hallmark of the 20th century. However, there have also been numerous negative consequences, some immediately apparent and others appearing only recently. From both perspectives, it would be difficult to argue that S&T has not been the prime factor defining the societies we know today. Indeed, the 20th century can be viewed through the prism of how societies decided to use the available scientific understanding and technological expertise to structure themselves. Such decisions helped shape the respective economic models, cultural priorities, and security commitments in these societies.

It remains to be seen how the prosperity and security of 21st century societies will be shaped by the decisions made by our current leaders, especially with respect to how these decisions reflect sound S&T understanding.

Given the critical importance of properly incorporating scientifically credible information into major societal decisions, it is surprising that the process by which this is achieved by the public and its political leadership has been uneven and, occasionally, haphazard. In the worst cases, decisions have been based on unrecognized misunderstanding, overhyped optimism, and/or limited respect for potentially negative consequences. Retrospectively, while some of these outcomes may be attributed to politically motivated priorities, the inability of S&T experts to accurately communicate the advantages and potential risks of a given option must also be acknowledged as equally important.

The new format pioneered by the ISGP in its programs seeks to facilitate candid communication between scientific and policy communities in ways that complement and support the efforts of others.

It is important to recognize that policy makers routinely seek a degree of certainty in evaluating S&T-based options that is inconsistent with reality, while S&T experts often overvalue the potentially positive aspects of their proposals. Finite uncertainty is always part of advanced scientific thinking and all possible positive outcomes in S&T proposals are rarely realized. Both points need to be reflected in policy decisions. Eventually, the public needs to be given a frank, accurate assessment of the potential advantages and foreseeable disadvantages associated with these decisions. Such disclosures are essential to obtain the broad public support required to effectively implement any major decision.

ISGP conference structure

At each ISGP conference, eight internationally recognized, subject-matter experts are invited to prepare concise (three pages) policy position papers. For the December 4–7, 2012, ISGP conference in Tucson, Arizona, these papers described the authors' views on current realities, scientifically credible opportunities and associated risks, and policy issues concerning SB. These eight authors were chosen to represent a broad cross section of viewpoints and international perspectives. Several weeks before the conference convened, these policy position papers were distributed to representatives from governments, societal organizations, and international organizations engaged with the ISGP (the United States, Austria, Italy, the United Kingdom, Australia, Canada, Honduras, the Republic of Korea, and Germany). Individuals from several private sector and philanthropic organizations also were invited to participate and, therefore, received the papers. All participants had responsibilities and/or made major contributions to the formulation and implementation of domestic and international policies related to SB.

The conference agenda was comprised of eight 90-minute sessions, each of which was devoted to a debate of a given policy position paper. To encourage frank discussions and critical debates, all ISGP conferences are conducted under the Chatham House Rule (i.e., all the information can be used freely, but there can be no attribution of any remark to any participant). In each session, the author was given 5 minutes to summarize his or her views while the remaining 85 minutes were opened to all participants, including other authors, for questions, comments, and debate. The focus was on obtaining clarity of understanding among the nonspecialists and identifying areas of consensus and actionable policy decisions supported by scientifically credible information. With active participation from North America, Australia, Europe, and Asia, these candid debates are designed to reflect international perspectives on real-world problems.

The ISGP staff attended the debates of all eight policy position papers. The not-for-attribution summaries of each debate, prepared from their collective notes, are presented here immediately following each policy position paper. These summaries represent the ISGP's best effort to accurately capture the comments and questions made by the participants, including the other authors, as well as those responses made by the author of the paper. The views expressed in these summaries do not necessarily represent the views of a specific author, as evidenced by his or her respective policy position paper. Rather, the summaries are, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the debates.

Following the eight debates, caucuses were held by small groups each representing a cross section of the participants. A separate caucus for the scientific presenters also was held. These caucuses focused on identifying areas of consensus and actionable next steps for consideration within governments and civil societies in general. Subsequently, a plenary caucus was convened for all participants. While the debates focused on specific issues and recommendations raised in each policy position paper, the caucuses focused on overarching views and conclusions that could have policy relevance both domestically and internationally.

A summary of the overall areas of consensus and actionable next steps emerging from these caucuses is presented here immediately following this introduction under the title of **Conference conclusions.**

Concluding remarks

ISGP conferences are designed to provide new and unusual (perhaps unique) environments that facilitate and encourage candid debate of the credible S&T options vital to successfully address many of the most significant challenges facing 21st century societies. ISGP debates test the views of subject-matter experts through critical questions and comments from an international group of decision makers committed to finding effective, real-world solutions. Obviously, ISGP conferences build on the authoritative reports and expertise expressed by many domestic and international organizations already actively devoted to this task. As a not-for-profit organization, the ISGP has no opinions nor does it lobby for any issue except rational thinking. Members of the ISGP staff do not express any independent views on these topics. Rather, ISGP programs focus on fostering environments that can significantly improve the communication of ideas and recommendations, many of which are in reports developed by other organizations and institutes, to the policy communities responsible for serving their constituents.

ISGP conferences begin with concise descriptions of scientifically credible options provided by those experienced in the S&T subject, but rely heavily on the willingness of nonspecialists in government, academe, foundations, and the private sector to critically debate these S&T concepts and proposals. Overall, ISGP conferences seek to provide a new type of venue in which S&T expertise not only informs the nonspecialists, but also in which the debates and caucuses identify realistic policy options for serious consideration by governments and societal leaders. ISGP programs are designed to help ensure that S&T understanding is integrated into those real-world policy decisions needed to foster safer and more prosperous 21st century societies.

Conference conclusions

Area of Consensus 1:

As a continuum of remarkable advances in biotechnology appearing in recent decades, there are immediate and long-term positive and negative impacts of synthetic biology having implications well beyond the life sciences. Given the potential for misuse of such a dual-use technology, academic and private-sector practitioners of synthetic biology, as well as those involved in providing oversight, have the responsibility to minimize security risks, while ensuring that potential benefits are realized.

Actionable Next Steps

- Foster a culture of responsibility in which all practitioners, public, academic, and private, are appropriately trained in biosafety best practices and that their expertise is widely shared (e.g., recommendations and nonproliferation mechanisms from the National Science Advisory Board for Biosecurity [NSABB]).
- Continue to strengthen the engagement between law enforcement and synthetic biology communities to promote awareness of dual use, security, and safety issues.
- Utilize approaches such as modeling, gaming, and information sharing to identify possible positive and negative impacts of synthetic biology, as well as gaps in current safety and security mechanisms.
- Promote the adoption of lifecycle management practices for biotechnology facilities to safeguard against the misuse of retired equipment.

Area of Consensus 2:

Synthetic biology has the potential to substantially impact food and agriculture practices locally, regionally, and globally. Contributions to agricultural biotechnology are currently limited to a small number of large private sector companies because of the cost of regulatory approval. As a result, the current focus has been on areas of commercial benefit, such as insect and herbicide

resistance. Synthetic biology enables scientists to focus on other important societal goals, such as broader environmental tolerance of crops (e.g., drought tolerance and marginal water availability), lower input costs (e.g., increasing efficiency of nitrogen use), and increased nutritional quality (e.g., better amino acid balance, and micronutrients).

Actionable Next Steps

- Streamline the regulatory evaluation processes for agricultural biotechnology products (e.g., introducing a single assessment by a joint, interagency committee in the U.S.).
- Broaden the focus of research and development in agricultural synthetic biology from introducing traits that primarily benefit large private companies (e.g., insect and herbicide resistance) to those that benefit a wider group of producers and consumers (e.g., better environmental tolerance, lower input costs, and increased nutritional quality).
- Build the capacity of less-affluent countries to utilize synthetic biology for the development of products that improve food security and economic advancement in those countries.

Area of Consensus 3:

While the interests, aspirations, and risk/benefit ratios vary by society and are best understood by individuals in a specific population, synthetic biology is a potentially powerful economic driver. Rather than focusing on exporting synthetic biology technologies, more-affluent countries need to focus on capacity building including efforts to promote technologies that offer benefits in less-affluent communities

Actionable Next Steps

- Expand availability of university resources found in more-affluent countries for a variety of programs (e.g., through Massively Open Online Courses, collaborative research and development, building local capacity through access to state-of-the-art synthetic biology techniques, personnel exchange programs, and seed money and mentoring for educational programs such as the iGEM competition).
- Develop more balanced intellectual property systems that protect the rights of technology developers without unduly restricting the accessibility of less-affluent countries to synthetic biology technologies developed elsewhere.

- Establish international forums for articulating the concerns of less-affluent countries concerning policies developed elsewhere.

Area of Consensus 4:

Since governance systems concerning synthetic biology are complex and cover a wide spectrum of societal needs, they require innovative and dynamic approaches, including policies for academic research, product development, environmental release and product deployment, acceptable dual-use characteristics, identification, and resolution of misuse. Such governance policies encompass issues concerning self-governance, best practices, enforcement guidelines, regulations, and legal procedures, which influence transparency, disclosure, and accountability.

Actionable Next Steps

- Assess current best practices worldwide and identify existing gaps prior to the development of new governance frameworks for synthetic biology (e.g., through the appointment of an expert commission using multidisciplinary stakeholders).
- Empower regulatory agencies to review synthetic biology products in a timely manner (e.g., via funding, clear agency responsibilities, and streamlined approval processes).
- Expand access to existing facilities (e.g., community colleges) to serve the interests of the Do-It-Yourself Biology (DIYBIO) community and to improve the oversight and management of DIYBIO activities.

Area of Consensus 5:

The broad acceptance of synthetic biology activities, products, and governance needed to support innovative policies requires extensive public dialogue and understanding of credible information based on an effective communication strategy. Since stakeholders in synthetic biology (e.g., the DIYBIO community, private sector biotechnology companies, and academic researchers) vary greatly in their professional expertise, promoting broad-based support is critical to the implementation of effective public policy.

Actionable Next Steps

- Develop and implement strategies for the public based on the credible understanding that biotechnologies derived from synthetic biological

methods are not inherently more risky than those introduced by conventional methods. The development of such strategies much involve multidisciplinary academic, private sector, and DIY teams.

- Synthetic biology practitioners need concentrated and sustained engagement with legislators and policy makers to discuss and clarify the risks and benefits of synthetic biology for economic prosperity, and protection of human and environmental welfare.
- Harness the educational potential of DIYBIO, performed safely and responsibly, to engage the public, and young people in particular, in promoting the beneficial impact of synthetic biology.

ISGP conference program

Tuesday, December 4

12:00 – 17:00 **Arrival and Registration: Hilton El Conquistador**

16:00 – 17:00 **Conference Meeting: Science presenters**

17:00 – 18:00 **Caucus Meeting: All presenters and participants**

18:00 – 19:00 *Reception*

19:00 – 19:10 ***Welcoming Remarks***
Dr. George Atkinson, Institute on Science for Global Policy (ISGP) Founder and Executive Director

19:00 – 20:30 *Dinner*

Wednesday, December 5

07:00 – 08:45 *Breakfast*

09:00 – 09:10 ***Welcoming Remarks***
Dr. Eugene Sander, 20th President, University of Arizona

Presentations and Debates: Session 1

09:00 – 10:40 **Prof. Paul Freemont, Centre for Synthetic Biology and Innovation, Imperial College London, United Kingdom**
Synthetic Biology – DoWe Need New Regulatory Systems?

10:40 – 11:00 *Break*

11:00 – 12:30 **Dr. Amy Smithson, James Martin Center for Nonproliferation Studies, Monterey Institute of International Studies, United States**
Renovating Governance Strategies for Synthetic Biology and Other "Dual-Use" Technologies

12:30 – 14:30 *Lunch and presentations by University of Arizona scientists*

Presentations and Debates: Session 2

14:30 – 16:00 **Dr. Maria Mercedes Roca, Zamorano University, Honduras**
The Challenges of Deploying Synthetic Biology Technologies in Developing Countries

16:00 – 16:30 *Break*

16:30 – 18:00 **Prof. Eliot Herman, School of Plant Sciences, University of Arizona, United States**
The Challenge To Meet Global Need For Protein Sources For Animal Production

18:30 – 19:30 *Reception*

19:30 – 20:30 *Dinner*

20:30 – 21:00 **Evening Remarks**
Dr. Drew Endy, Assistant Professor of Bioengineering, Stanford University

Thursday, December 6

07:00 – 08:45 *Breakfast*

Presentations and Debates: Session 3

09:00 – 10:30 **Dr. Markus Schmidt, Biofaction KG, Austria**
Safeguarding the Genetic Firewall with Xenobiology

10:30 – 11:00 *Break*

11:00 – 12:30 **Ms. Leili Fatehi, Humphrey School of Public Affairs, University of Minnesota, United States**
Policy Innovation in Synthetic Biology Governance

12:30 – 14:00 *Lunch*

Presentations and Debates: Session 4

14:00 – 15:30 **Dr. Todd Kuiken, Science and Technology Innovation Program, Woodrow Wilson International Center for Scholars, United States**
Do-It-Yourself Biology: Reality and the Path Toward Innovation

15:30 – 16:00 *Break*

16:00 – 17:30 **Dr. Robert Friedman, J. Craig Venter Institute, United States**
Governance of Synthetic Biology

Caucuses

17:30 – 22:00 **Focused group sessions**

Friday, December 7

07:00 – 08:45	*Breakfast*
09:00 – 12:10	**Plenary Caucus Session** Dr. George Atkinson, *moderator*
12:10 – 12:30	**Closing Remarks, discussion of ISGP conferences 2013–2014** Dr. George Atkinson
12:30 – 13:30	*Lunch*
13:30	*Adjournment*

Synthetic Biology – Do We Need New Regulatory Systems?**

Paul Freemont, Ph.D.
Co-director, Centre for Synthetic Biology and Innovation,
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London, United Kingdom

Summary

Synthetic biology (SB) is a new interdisciplinary field that aims to establish a systematic framework for the engineering of biological systems and cells to both address fundamental questions and provide new applications. The potential economic promise of SB is such that numerous countries are developing strategies for establishing SB in both academia and industry. Part of these strategies is the early inclusion of social scientists and policy makers, although there remains uncertainty as to how rapidly the field will develop and to what scale. Given that chromosome synthesis and assembly are now technically feasible, are new national and international regulatory and governance structures required? Can current and future SB research be accommodated within existing genetic modification (GM) regulatory systems and is self-regulation a suitable *modus operandi* for SB?

Current realities

Synthetic biology has been rapidly growing as a new research discipline since the early 2000s. However, while it is widely accepted by many researchers, funders, and policy makers that SB as a multidisciplinary approach aims to make the engineering of biological systems easier, there still remains confusion as to why this field has emerged now, despite enabling engineering work that has been ongoing for the past 20 to 30 years. The major drivers for the emergence of SB are the availability of complete genome sequences enabled by low-cost DNA sequencing, advances in bioinformatics, data mining and modeling, and the rapid development of cheap chemical synthesis of DNA. All of these strands now come together, which when combined with the development of an engineering framework, allows researchers to start thinking about designing biological systems and genetic circuits much like an engineer designs new electronic circuit boards. This powerful analogy results in complex biological systems being broken down into an engineering-like

hierarchy of parts, devices, and systems where DNA forms the parts (termed 'bioparts' or 'biobricks') that when combined give rise to biological devices that together form biological systems. Current realities, however, do not allow such smooth transitions between the different hierarchies. For example, designing a biological system at the DNA sequence level does not guarantee that such a constructed system will perform as predicted in a living cell. This remains one of the key challenges of SB, although the rapid development of foundation technologies and frameworks for systematically engineering cells may allow this vision to become a partial reality in the next few years. One notable new project that illustrates this is the international consortium led by Jef Boeke of Johns Hopkins University to build the first synthetic genome for the budding yeast *Saccharomyces cerevisiae.* The project brings together international, public-funded researchers from the United States, China, India, and the United Kingdom, based on open-source and sharing of results, similar to the publicly funded human genome project. The success of the project will not only provide researchers with tools to study yeast biology but also provide a host cell that can be easily engineered using SB approaches for specific applications.

The current environment to achieve such a vision is formed from a number of important strands. First, a developing SB academic community is emerging, driven in part by the continuing success of the International Genetically Engineered Machine (iGEM) undergraduate student competition. Second, government funding agencies around the world are targeting SB research for significant investment with the increasing realization that, as an application-driven field, there may be significant economic benefits to be realized. Third, higher education institutes have responded to the new field by creating interdisciplinary teaching and research programs in SB. Finally, biotechnology, energy, and pharmaceutical industries are exploring how SB could accelerate their existing product pipelines as well as research and development. There is also an expanding and energized "start-up" culture in SB driven in part by iGEM and the youthful nature of the field. In summary, the current reality is that we are at the early stage of an exciting and developing interdisciplinary application-driven field that aims to establish a legitimate engineering framework for biological engineering based in part on an open-source philosophy and the energy of youthfulness and optimism.

Scientific opportunities and challenges

Opportunities: The application areas that have been linked to potential SB solutions include energy and fuels, greener production of commodity chemicals, biomaterials (e.g., spider silk or bacterial cellulose), specialty chemicals and pharmaceuticals,

protein-based bioproducts (e.g., enzymes), medical applications (e.g., biosensors, smart therapeutics, and tissue engineering), bioremediation solutions for pollution, biomining to increase yields from mineral ores using biological organisms, and engineering crops and soil organisms to increase global food yields. Although many of these opportunities have not yet been realized, by applying a systematic engineering approach to biological design, a series of platform technologies is emerging that will enable many different applications in the short and long term. Examples include new, efficient methods for rapid combinatorial DNA assembly; the rapid characterization of biological parts libraries and specific host cells (chassis) for SB; and the integration of modeling and computer-aided design (bioCAD) to aid biological design *in silico*. These platform technologies will inevitably lead to standardization as part of the field of SB that will accelerate the uptake of the technology both in academia and industry.

Technical challenges: As stated above, SB aims to apply engineering principles to biological systems but there are significant technical challenges to achieving this. For synthetic biologists, it is important to realize that although living cells are not electronic circuit boards, they do utilize many regulatory elements in their decision-making processes which mimic the behavior of human-defined electronic components (e.g., genetic switches that act as logic-like inverters), but at a biological time scale of seconds to minutes. Cells can also use sensors (e.g., small molecule inducers) to activate transcription of specific genes or environmental sensors (e.g., light) that activate specific gene networks or cell-cell communications systems that signal between cells. Cells are thus exquisitely evolved to sense and adapt to their living environments and have genetic circuits that encode these functions. It is these circuits that synthetic biologists are now adapting for different applications As we begin to fully understand the function of single cells at a systems level though experimental and mathematical modeling (which is the aim of systems biology), our ability to predictably intervene in such systems will be significantly increased. It is important to note that similar situations exist in other fields of engineering, such as with semiconductors (e.g., transistors), where physicists and engineers have worked for many years to obtain optimal performance. It is also interesting to consider naturally occurring DNA-encoded functional modules like bacterial operons, where biological context and complexity have been already encoded within the DNA sequence through evolution. The challenge here is to correctly interface such modules, which again requires a systematic approach.

Societal challenges: One interesting aspect about the developing field of SB has been the early engagement and exchange among social scientists, scientists, and

engineers. The cynical view is that synthetic biologists are trying to prevent an unfavorable public reaction to their work and thus by engaging with social scientists, they can somehow achieve a level of acceptability through professional scrutiny. This is a very simplistic and incorrect view and a more realistic assessment is that SB is a research field that requires and encompasses the interdisciplinary work of social scientists. It is perhaps obvious that to create a vision of engineering biology based on SB, the final outcomes will rightly be open to public questioning.

Policy issues

- Although humans have been carrying out genetic manipulations for centuries through selective breeding, and more recently through modern molecular biology techniques, it is clear that the scale and vision of SB require a reassessment of the public value. Much progress has been made in public dialogues around SB primarily in the U.S. and U.K., and these activities need to continue, perhaps with even greater vigor and responsiveness. It is important to note that at least in the U.K., all publicly funded researchers in SB must have social scientists as collaborators and co-investigators on any SB project. The overall aim is to integrate social scientists and scientists/engineers at the early stage of project development and the term "responsible research innovation" used to describe this is being discussed widely. If society in general does not see any real and/or tangible benefit to the adoption of SB technologies, then the field will be in real danger of fizzling out before it has started.
- SB poses a number of key policy issues around regulation and governance, in particular whether existing international regulations are sufficient to govern this emerging field or whether new policies and/or structures are needed. This is a difficult question, as any newly emerging technology with transformative potential has by inference some unknown outcomes. The main issue is whether national and international regulatory structures currently in place are sufficient to govern access to DNA synthesis capabilities, encompass large-scale genome engineering, monitor the environmental release of synthetically engineered organisms, and oversee the synthesis and potential design of human chromosomes.
- In relation to the U.K., there are already significant GM regulations in place that cover most of the current SB research within contained laboratory facilities. The regulations are implemented locally as part of a government licensing system, with every GM and/or experiment using

biological material formally registered (locally) and approved before commencement. The formal registration form covers areas such as Risks and Control Measures, Personal Protective Equipment and Hygiene, Waste, Maintenance, Training, Emergency Procedures, Access, Occupational Health, Containment Level, and GM class. In terms of GM release, another rigorous set of regulations is already in place, with each project requiring, in effect, government approval.

- Whilst I feel that the U.K. system has the right balance of regulation (although under continual review), I am concerned that the scale, scope, and potential of SB internationally leads to the need for global forums, agreements, and perhaps even governance standards for SB. This should not only include government-funded research and companies (often global), but also public activities like do-it-yourself biology and service provider companies (e.g., DNA synthesis). Such forums should also include all stakeholders and be transparent at all levels. I would argue that because SB is at an early stage of development but rapidly growing and evolving, there is an urgent need to develop international forums, which can also evolve and change as the field develops.

*** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) Dec. 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona*

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Prof. Paul Freemont (see above). Prof. Freemont initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Prof. Freemont. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Prof. Freemont, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Because the definition of synthetic biology is contested, ranging from it being a new emerging engineering discipline to a continuation of biotechnology, it is not clear whether synthetic biology can be covered by existing regulation and oversight mechanisms, or requires new measures. However, any new measures must remain adaptable to the many changes anticipated as the technology advances.
- Although the inclusion of social scientists in synthetic biology research is widely supported, the question remains as to how much such collaboration should influence the field. In general, younger generations of synthetic biology researchers view collaboration with other disciplines as the norm.
- While educational curricula in synthetic biology education in some countries include social sciences, their inclusion require consideration of differing cultures its impact on establishing a single set of educational requirements. Diversity of values in varying populations must also be considered in regard to setting up an infrastructure conducive to two-way dialogue.
- To avoid adverse public responses to synthetic biology, there is a need to "democratize" the science through greater public engagement in governance based on communicating credible scientific understanding.

Current realities

Debates regarding the classification of synthetic biology largely centered on whether synthetic biology should be defined as a new engineering field, as opposed to simply an advance in the existing field of biotechnology. Those who consider synthetic biology a new engineering field argued that synthetic biology brings concepts and designs at molecular and cellular levels that have not previously existed in biotechnology, and which are distinctly different from biotechnology products derived from metabolic engineering. Within the engineering paradigm, synthetic biology is a new and emerging field and there is still much to learn from engineering design processes and engineering production in regard to quality management and safety. As the field develops, questions of standardization (e.g., what is a standard and what are its limitations?) are emerging as increasingly important issues.

Because advances in engineering generally have benefited from the involvement of social scientists and since synthetic biology (e.g., the building of genomes) is viewed as an advance in engineering, similar involvement of social

scientists could be equally as beneficial. This was exemplified by the yeast synthetic genome project, which aims to produce the first synthetic eukaryotic cell in approximately 2017. The issues that are anticipated to arise from the yeast synthetic genome project were asserted to require interactions with social scientists. This was believed to be particularly relevant in the U.K., where involving social scientists in advancing the field of synthetic biology has proven necessary given historical anti-gene modification sentiment. However, it was cautioned that mandating involvement of social scientists, or dictating the type of involvement, could be counterproductive with regard to public opinion.

Alternatively, the argument was made that synthetic biology is a new science, at a very early stage of development, akin to the field of electronics in the 1940s. Like nuclear fission before it, synthetic biology has "dual-use" properties that need to be considered. The technology was described as having the potential to accelerate quickly, through improvements in DNA sequencing and synthesis, which also made the case for bringing an engineering framework into biology.

Efforts have been made to embed the importance of interdisciplinary research in younger generations as an important part of synthetic biology research design. At some institutions in the U.K., social science lectures are included in the undergraduate course curriculum for synthetic biology studies, though it was noted that this has not been an easy undertaking.

The role of the media in relation to public education was acknowledged. In the U.K., although the media is unregulated and makes an important contribution to democracy, it was often viewed as engaging in sensationalist reporting. More scientifically accurate reporting in the U.K. is improving through initiatives such as the Science Media Center, which aims to counterbalance sensationalism by giving journalists access to scientifically credible sources of information.

Public engagement and transparency were also discussed via the example of the public perception of salmon in Panama that has been genetically modified to grow twice as fast as ordinary farmed salmon. While statutory constraints exist on how much regulators may interact with the public, the importance of transparency was emphasized. The U.S. Food and Drug Administration (FDA), which is committed to be as transparent as possible, released a draft environmental assessment on genetically modified salmon, including data on biological and physical containment, for public comment before any formal approval was made.

In the U.K., funding agencies were viewed as being serious about public engagement, with publicly funded researchers in the U.K. expected to be able to discuss their work openly with the public. While scientists as communicators can

be both good and bad, publicly funded scientists have extra pressure to communicate well.

Calls for the "democratization" of science stem from failures in communication following crises such as the introduction of genetically modified organisms (GMOs) and the response to bovine spongiform encephalopathy (BSE). These communication failures were not attributed to a lack of information being provided to the public, but rather to lack of effort in understanding the implications of regulatory and/or institutional distrust among the public. In addition, an experiment conducted in the U.K. in which randomly selected community members were included as part of scientific funding panels, found their judgments correlated to self-interest, which was seen as evidence of the limitations of including the public in decision-making about scientific applications.

Invoking the "precautionary principle" by different countries in the European Union was generally agreed to inhibit GM technology. In addition to the U.K., the E.U. was seen as quick to overregulate, as evidenced by its response to genetically engineered crops. In the U.S., regulators reviewed the risks and allowed gradual deployment of GM crops, but because of the precautionary principle utilized in Europe, those same products are only now being approved. The U.S. risk assessment process, described as adequate and rigorous, was not applied in Europe and therefore, resulted in delaying consumer choices and to some resulted in economic harm. This was illustrated by the fact that the current bulk of synthetic biology work is happening in countries where the precautionary principle is not invoked.

Scientific opportunities and challenges

Rather than determining regulatory frameworks far in advance of the technologies themselves, the challenge is to consider how to build a robust structure of regulations that can evolve in a way that is simultaneously democratically accountable and scientifically productive. While it was suggested that a dynamic style of innovative regulation by government for be promoted, there was disagreement as to whether traditional molecular biology and synthetic biology can be treated in the same way.

From the perspective that synthetic biology is a new engineering field, it was argued that synthetic biology provides a new framework to allow genetic engineering to be done systematically and through protocols that can be shared. This framework allows an open, noncompetitive, and innovative atmosphere for companies to potentially find economically productive opportunities.

While it was generally agreed that opportunities for social scientists to be more involved in synthetic biology projects need to be fostered, there was dissent

concerning how to extend such involvement to a societal, legal, or ethical issues that "tax" government-funded programs. To prevent the requirement of public impact studies from hampering advances in synthetic biology, the two activities could be funded separately. However, it was contended that including social scientists would help the field of synthetic biology progress. In many settings, the collaboration between social scientists and lab scientists has proven useful, and younger generations of synthetic biologists view the interaction as a natural part of the development of the field.

Alternatively, social scientists could be engaged as appropriate, rather than in a prescribed way. For example, if basic science was being conducted with the understanding that it would be applied to making a food source, then relevant food safety experts, economists, and social scientists should be consulted at the start of the project to understand issues related to eventual acceptance of such food products. However, if basic science was being conducted for the purpose of answering a fundamental physiological question, then it would perhaps not be necessary to involve social scientists at all. Those who advocated early collaborations with social scientists in the research lifecycle described the need to understand the impact on society from an early stage in the research. The purpose is to have those doing the research engaged in social issues as part of the research process and as part of the wider discipline. The success of this type of collaboration remains uncertain. No firm conclusions were reached regarding the extent, and at what stage of research, social scientists should be involved in the field of synthetic biology.

The public has increasingly become aware of failures in traditionally trusted institutions in the wake of previous crises having negative outcomes. A current challenge being faced is how to communicate with the public in the wake of previous crises. Different democratic institutions have an opportunity to prevent similar communication failures through an emphasis on two-way dialogue. Such an opportunity exists primarily for the FDA, given its role as the most recognized regulatory authority by the public in the U.S. It was generally agreed that the FDA has done a masterful job over the last century of navigating the often-conflicting expectations of industrial stakeholders and the expectations of the public. This has allowed the FDA to effectively maintain a reputation that the public trusts, and thereby it has been delegated authority by the public. Consequently, the FDA is well positioned to consider emerging risks, yet still encouraging environments for innovation.

Policy issues

Governance over the lifecycle of a technology may be better referred to as oversight rather than regulation. Regulation implies a statutory responsibility and authority that can both be expansive and restrictive to innovation. Therefore, considering the range of bodies able to conduct oversight (i.e., international, federal, local, and professional organizations, and their overlapping responsibilities), more effective approaches to minimize regulation and focus on oversight activities of the daily development of the technology. The aim of such oversight would be to implement the delicate balance between encouraging new technologies and protecting the public interests.

The point was made that the distinction between regulation and oversight needs to be nuanced and could be denoted as "adaptive management" or "anticipatory governance" (i.e., having the ability to adapt and change as necessary). Research from Columbia University has investigated this idea of experimentation in governance, using a variety of mechanisms. Regulation alone was thought to be unable to keep pace with advances in modern technology. Traditional government mandates, such as regulation, are one part of a complex regulatory strategy that involves other forms of governance (e.g., codes of conduct and supply chain management issues). Involving all relevant stakeholders to consider the variety of governance tools and approaches within the context of a specific social culture was generally agreed to be an appropriate way to implement effective risk management.

Regulation of synthetic biology was described as the ability for scientists to actively engage in research within a harmonized framework. Because individuals or organizations conducting unregulated genetic modification experiments (e.g., do-it-yourself biology) operate beyond the required regulations, it was argued that risk assessments needed to be performed by focusing on identifying proper regulatory frameworks that protect, but do not inhibit productive innovation.

The framework for regulating environmental release of modified microbes, bacteria, or viruses requires special attention. There was a strong advocacy in the U.K., due to an environmental lobby that continuously challenges the development of genetically modified technologies, for balanced regulation. Such broach public attention requires policies that promote research and innovation while anticipating future technological developments.

A strong case was also made for ensuring that social scientists (e.g., behavioral scientists, ethicists) are involved in the earliest stages of synthetic biology projects, including the preparation of grant proposals. Their inclusion would bring a different perspective that could provoke, critique, and negate ideas in constructive ways. Identifying social scientists with the correct expertise as part of a bottom-up process was recommended. Embedding social scientists in synthetic biology

programs, and proactively teaching the next generation of scientists the importance of this inclusion, needs to be promoted as best practices in synthetic biology centers around the world. Additionally, once social scientists are embedded within synthetic biology research groups, they can be utilized to help address public concerns through improved communication. Journalism students could also be invited to participate in designing communication strategies that will avoid public misunderstandings and potential mistrust of the science.

In addition to existing international forums, a new type of international forum was proposed, which would bring together researchers and policy makers from around the world to address different cultural views on synthetic biology. This would be a valuable venue to share differing international views and build on best practices. Whether such forums could be incorporated into existing international organizations or would require a new organizational structure altogether remains to be clarified.

It was argued that a wide range of stakeholders must be engaged in policy-making processes to ensure that a broader community of thought is considered before products enter the market. A continual review process is necessary because of the uncertainty associated with the development of the field and the types of products produced. Two-way dialogue requires ensuring that the correct infrastructure is in place for effective cross-communication. Cultural considerations will prove crucial in developing the appropriate forums for this type of interaction.

Synthetic biology was considered a part of the continuum of biomedical life sciences and a large amount of work needs to be directed toward public education, concerning an understanding of the basic science and an appreciation of both the potential benefits and risks. However, the point was made that cultural and societal differences play a part in the acceptance of various sciences (e.g., genetic modification viewed as a more important issue in the U.K. than in the U.S.) and the diversity of values in varying populations must be considered before any policies are implemented across a culturally diverse region.

Renovating Governance Strategies for Synthetic Biology and Other "Dual-Use" Technologies**

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Summary

The life sciences offer tremendous societal benefits and are diffusing worldwide, but this scientific revolution carries potentially devastating risks. Synthetic biology has opened the door to *de novo* assembly of appalling contemporary pathogens and those responsible for eradicated diseases, such as smallpox, while other vanguard life sciences technologies could be hijacked to manipulate the human immune, nervous, and endocrine systems. Some gene synthesis companies have voluntarily taken steps to prevent the rogue assembly of dangerous pathogens by screening customers and orders for genes. Similarly, after the September 11, 2001, attacks, the Federal Bureau of Investigation (FBI) forged a public-private screening partnership with manufacturers of various "dual-use" goods and services that could be diverted from legitimate purposes to cause harm, a quietly effective tool in efforts to disrupt and prosecute terrorist and criminal activities. Government and academia, respectively the traditional guarantors of national security and fountains of innovation, will be hard-pressed to keep pace with the life sciences revolution and fashion new governance approaches. If industry more fully enters the nonproliferation fray, society will have better leverage to keep one step ahead of the bad guys.

Current realities

Assuring the security of a state is traditionally a government responsibility, one that justifies armed forces, the cultivation of trading partners, military alliances, intelligence, diplomacy, and the negotiation of treaties to draw behavioral boundaries and cement common interests. Industry's customary role vis-à-vis security is to supply material to a state's armed services or to comply with regulations on the manufacture and sale of product(s), including the declaration of activities deemed pertinent to treaty-controlled weapons systems, such as the production of chemicals that are precursors to warfare agents, and the acceptance of inspections

to ascertain treaty compliance. Individual governments can also stipulate the review and licensing of weapons-critical products before sales to countries of proliferation concern. In addition, major supplier nations have harmonized export controls on numerous items via the Australia Group, the Nuclear Suppliers Group, and the Missile Technology Control Regime. Thus, for the most part, industry is reactive when it comes to nonproliferation.

Decades ago, the pace of discovery in the life sciences began ramping up with the emergence of molecular biology, cell biology, and genomics. The discovery rate turned revolutionary with the convergence of life sciences, engineering, the physical sciences, and information technology, giving rise to entirely new disciplines, including synthetic biology. With promising new applications in health, energy, agriculture, and the environment that will elevate the quality of life and drive economies, the life sciences are diffusing worldwide. Nations with flourishing biotechnology industries or that are laying the foundation to become biological powerhouses include Brazil, China, Cuba, Egypt, India, Mexico, Russia, Singapore, South Korea, and Taiwan. Furthermore, automated equipment that "de-skills" previously labor-intensive techniques and processes is enabling those with rudimentary science know-how to perform advanced life sciences work. These circumstances expose serious vulnerabilities in traditional government-designed nonproliferation tools.

Following in the footsteps of the military, which of necessity became a path-breaker in technology and societal change, large companies have also taken on unanticipated roles as they expanded operations across multiple borders. Accordingly, in 2010, the International Standardization Organization issued ISO standard 26000, which lists six pillars of corporate responsibility: consumer issues, fair operating practices, the environment, labor practices, human rights, and community involvement and development.

Scientific opportunities and challenges

The benefits of the life sciences aside, panels of distinguished scientists have recognized the challenge of preventing the abuse of vanguard life sciences technologies, such as RNA interference and nanobiotechnology. To illustrate, malicious actors could combine sophisticated targeted-delivery technologies with bioregulators to manipulate the human immune, nervous, and endocrine systems. Synthetic biologists have artificially created the polio and 1918 influenza viruses, which crippled and killed tens of millions in the 20th Century, and recovered Marburg, a hemorrhagic fever virus, from a full-length cDNA clone. In 2010, scientists required 1,080,000 base pairs, which cost a few dollars apiece, to generate

the Mycomplasma genome *de novo*. Variola major, the virus that causes smallpox, has a comparatively modest number (186,102) of base pairs, which can be purchased for a few dollars apiece. Synthetic biology has opened the door to the assembly from scratch of appalling contemporary pathogens as well as those responsible for eradicated diseases. Such factors prompted geneticist and molecular biologist Matthew Meselson to warn in 2000 that, in the hands of those with malevolent intent, new life sciences knowledge and technologies present "unprecedented opportunities for violence, coercion, repression, or subjugation."

Responding to the potential misuse of synthetic biology, the companies of the International Association of Synthetic Biology and the International Gene Synthesis Consortium have voluntarily fashioned safeguards to prevent the rogue assembly of dangerous pathogens. They are screening orders for genes to ensure they will not add up to something dangerous like anthrax, and they are screening customers to check that they are affiliated with legitimate scientific enterprises and have no criminal histories or terrorist associations. To screen customers, gene synthesis companies are accessing various government-compiled "bad guy" lists, such as the United States' Specially Designated Nationals, Denied Persons, and Statutorily Debarred Parties lists and Germany's Handbook of Export Controls list.

This screening activity mirrors a public-private partnership initiated after the September 11, 2001, attacks, when the FBI reached out to manufacturers of "dual-use" goods and services that could be diverted from legitimate purposes to harm U.S. citizens and property. Neither the FBI nor the companies want to see such products hijacked for terrorist or criminal purposes. Moreover, each partner has something the other wants. Governments want to halt proliferation, and the companies, which may be contacted by aspiring proliferators, have information useful in that quest. Governments, which devote staggering resources to identify terrorists, front companies, black marketeers, and organized criminals, among other unscrupulous types, have databases that can help companies avert ill-advised sales. Thus, mutual interests and needs forged common-sense partnerships wherein corporations notify the FBI of suspicious sales requests so that questionable customers could be screened against its databases. This quiet practice currently involves hundreds of businesses, including chemical and Internet companies, resellers of dual-use equipment, and agricultural goods and services firms. Annually, the FBI receives thousands of notifications of suspicious activity that enable law enforcement authorities to disrupt and prosecute terrorist and criminal activities. This experience proves that voluntary data sharing can help thwart the acquisition of dual-use goods for malicious purposes.

Policy issues

The main international barrier to the spread of germ weapons is the Biological and Toxin Weapons Convention, which lacks verification measures to unmask state-level bioweapons programs. Impediments to the misuse of synthetic biology by nonstate actors are similarly wanting. The sentinels on alert for angry spouses, disgruntled employees, and terrorists with biological mayhem in mind, namely, local law enforcement officers, have no training to recognize the Nipah virus, for example, much less to be able to spot someone trying to synthesize this killer. Thinking about how to govern the life sciences and other fast-moving areas of technology needs to be jump-started:

- Governance is lagging behind the life sciences revolution, in part because policy makers, challenged to follow technical developments in this arena, are not well-suited to devise governance approaches. These circumstances do not presage government as the incubator of new, effective life science governance measures, nor are there favorable odds that the international community can agree on control measures, which would be less effective unless universally applied. Moreover, another traditional wellspring of invention, the academic community, is unlikely to widely support new life sciences controls, which are seen as conflicting with academic freedoms.
- Whether the perpetrator is a state, group, or lone-wolf actor, today's advanced technologies could facilitate acts that cause horrific death tolls and massive economic and societal disruptions. A seventh pillar of corporate responsibility is needed: industry best practices to prevent the diversion of products for malevolent purposes.
- In the end, industry may be the best engine for fresh, effective self-regulation and, when needed, carefully balanced regulation in the life sciences. Private sector scientists, savvy in both the technological developments and business trends, are well positioned to identify choke points, tactics, and avenues to prevent misuse of the life sciences. Governments should incentivize life sciences companies to participate in the governance discussion.
- Only the exigent circumstances of September 11, 2001, gave rise to the voluntary data sharing program, which the FBI has not exported. This type of public-private nonproliferation partnership is more broadly

applicable to other sensitive technologies, equipment, and materials. For starters, the U.S. government should lobby nations that are major suppliers of advanced technologies to adopt this model.

***** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) December 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.***

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Amy Smithson (see above). Dr. Smithson initiated the debate with a 5-minute statement of her views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Smithson. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Smithson, as evidenced by her policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

As a potential dual-use technology, governmental, private sector, and public attention increasingly focuses on synthetic biology as a field requiring significant oversight and/or regulation designed to prevent nefarious use and to monitor do-it-yourself practitioners.

- Public-private partnerships involving governmental entities and industry stakeholders need to focus on voluntary self-regulation (e.g., screening orders and customers) to mitigate concerns over the dual-use potential of the rapidly evolving activities associated with synthetic biology.
- Alternative approaches using regulation to block nefarious applications and/or unwanted public uses must also be considered even though they can be cumbersome and time consuming to implement and potentially have significant negative consequences on financial investments and innovation.

- Ongoing discussions concerning oversight and regulations of specific aspects of the synthetic biology industry are limited by the dearth of experts with the specialized knowledge and the networks of worldwide connections required to make effective decisions that do not impede innovation.

Current realities

Although some legally binding regulations exist, synthetic biology is still an emerging element of the life sciences, and largely unregulated. In this environment, more flexible best practices and standards could be implemented on a voluntary basis for self-regulation. The debate centered on the merits of a public-private partnership in which industry stakeholders cooperate with international governmental organizations to screen customers and their orders to prevent the malicious use of synthetic biology.

There was consensus that imagination and flexibility are required to identify the right questions concerning what can be realistically expected for the proper and nefarious uses of synthetic biology. The September 11, 2001, attacks on the United States were used several times as an example to illustrate the failure of imagination on the part of policy makers regarding the potentially dangerous uses of technology. The same mistakes need to be avoided when evaluating the benefits and risks associated with synthetic biology. The conclusions concerning how to balance productive innovation with potential dangers need to come from discussions involving the private sector, government, and the public.

Concerns about synthetic biology were considered to be analogous to those expressed about nuclear, chemical, and biological warfare that led to the establishment of two public-private partnerships: the Financial Action Task Force and the United Nations Security Council Resolution 1540 Committee. Similar to these cases, it was suggested that global databases on synthetic biology already established through the Federal Bureau of Investigation's (FBI) voluntary data sharing program, the International Association for Synthetic Biology, and the International Gene Synthesis Consortium be expanded.

Private sector stakeholders are actively employing voluntary self-regulation. Since many of their products are susceptible to being hijacked for malicious purposes, these companies are subject to significant economic losses either directly or through injury to their public images. Business-related concerns extend to products made using synthetic biology that once released to the public, either accidentally or purposefully, become part of the environment. In many cases, the

private sector considers self-imposed regulation (e.g., screening customers and orders) to be preferable to new governmental regulations.

Some governments (e.g., the United States and Australia) were seen as establishing sound oversight policies (e.g., certification processes, compiling quality databases, and establishing liability protections both for businesses and consumers). Questions were raised about how to properly monitor smaller, DIY-type practitioners involved in synthetic biology. While no generally agreeable solutions were proposed, it was emphasized that communication between the private sector and governments concerning how to share screening databases designed to comprehensively identify nefarious users was essential.

Another major concern was the availability of technology used by the DIY community and those working in "garage" establishments that might be used in an unsafe manner or for nefarious purposes. Questions were also posed concerning the availability of new, cutting-edge equipment (e.g., desktop machines that allow users to "print" DNA) as well as older unused and surplus machines that the private sector and/or universities might sell at relatively affordable prices. There was debate about how to ensure that the historical use of such equipment be organized to avoid inappropriate uses (e.g., "matchmaking" old equipment for proper use in less-wealthy countries). The U.N. Resolution1540 Committee has an element of such matchmaking in its charter, but it could be expanded or offered through another organization.

Synthetic biology has the potential to improve human access to the most fundamentally important elements of life such as clean air, food, and water. It was acknowledged that less-wealthy countries have a vested interest in pursuing synthetic biology to develop everything from hardier crops to immunization for their citizens. Through such applications, synthetic biology could help less-wealthy countries transition from poverty to wealth. While a reasonable argument can be made for countries such as Iran and Iraq to own dual-use technologies for peaceful purposes (e.g., modifying foods or vaccine production), as a dual-use technology synthetic biology poses a potential threat to regional and global peace via its potential use to develop chemical and/or biological weapons. Voluntary data sharing programs, governmental and private sector oversight of products and users, and registration of dual-use equipment are all essential components of a comprehensive system designed to ensure the peaceful use of synthetic biology.

Discussions about a self-regulation system for synthetic biology have already begun with several private sector leaders worldwide. While private sector leaders have been receptive to the idea of self-regulation, there are currently few regulatory experts working in this area. Discussions among private sector stakeholders, public

interest watchdog organizations, and governmental policy makers are also under way on a small scale, but it was deemed important to bring such discussions to a higher, more inclusive global level.

Scientific opportunities and challenges

The applications of synthetic biology span genetically modified organisms used in foods to chemicals used for medicine to products of potential use in warfare. This broad spectrum of applications means that synthetic biology and its methodologies will be used in ways that are difficult to anticipate. These differences may materialize as more- and less-affluent countries determine how synthetic biology may best benefit their respective societies. Based on these potentially different approaches (e.g., higher crop production and improving public health beyond the poverty level versus enhancing corporate profits by reducing costs or developing more efficient energy sources), extensive discussions centered on ensuring that synthetic biology methodologies were made available to both more- and less-affluent countries while maintaining effective systems for public safety.

There was general agreement that while anything from gasoline to bricks could be used for good or bad, there exists a point where the potential for the malicious uses of a technology requires governmental intervention, including regulations designed to limit its use. It was agreed that many aspects of synthetic biology rise to this level. It was noted that while there are such protocols already available (e.g., the Australia Group list for controlling exports of potential chemical and biological weapons material), prioritized guidelines are needed that consider materials associated with synthetic biology that have the potential to be proliferated quickly and affect large populations.

It was suggested that it would be useful to utilize gaming methods focused on gathering groups of experts and policy makers to brainstorm unintended consequences of synthetic biology or how they would try to circumvent existing laws and regulations. This type of brainstorming is important because if an organism produced by synthetic biology is released into the environment, either unintentionally or with malfeasance, that organism may not be able to be recovered or eradicated and may become a permanent part of the ecosystem.

Much of the debate centered on the hypothesis that a large opportunity for public-private partnerships exists in which governments share a database of bad actors with the private sector, which uses the information for voluntary self-regulation. Described as "win-win," such programs are already in practice with some companies, and it was considered more expedient and effective than spending years debating policies and legislation. Governments such as the United States

already have detailed databases of potentially unsafe practitioners. These databases could be improved and aspects shared with the private sector by combining or integrating information produced by individual agencies (e.g., FBI, Central Intelligence Agency, and Drug Enforcement Administration). In addition, these agencies have computerized systems using triggers/thresholds to identify a potential buyer who needs to be scrutinized (e.g., purchasing too many ingredients or technologies that, when combined, might result in illegal substances). Such surveillance can prevent sales to potentially dangerous individuals or groups. It was also suggested more funding must be made available to individuals who have credentials and good connections in the private sector to allow them to seek out voluntary partnerships for self-regulation and to identify more stakeholders in the synthetic biology arena.

While it was suggested that synthetic biology practitioners be screened and undergo background checks using current models for nuclear experts and workers, dissenters argued that regulations in academia are already restrictive and that adding such hurdles could reduce innovation. There was no consensus regarding imposing these types of screenings for researchers in the private sector and academia, but it was generally agreed that there must be some level of self-regulation. There is incentive to self-regulate because of potential negative outcomes for companies and institutions, such as bad publicity and financial liability resulting from misuse of their products or research.

Bringing the public and nonexpert policy makers into the discussion is an important part of the process, but it was acknowledged that both groups are often not well informed about the current status of the science and technology. It was suggested that to better educate the public and policy makers, media boot camps and science media centers could be established to allow journalists to report more easily and accurately on science stories.

Policy Issues

Governments are already aware that the life sciences, including synthetic biology, must be monitored for dual-use concerns. In addition to the private sector's preference for avoiding new regulations, it was also widely agreed that government processes are extremely slow, and entangled in complex bureaucracy. Knowing that new government regulations are under development, the private sector will often wait until the last possible minute to comply. Voluntary agreements can be put into place much more expediently than regulations, (e.g., it took 24 years for the Chemical Weapons Convention to be ratified).

While government and academia may not be well positioned to innovate governance strategies for the life sciences, including synthetic biology, the major focus of the debate centered on the reality of high-level, global, voluntary self-regulation on the part of private sector stakeholders. Talks with members of private sector have already begun at an unofficial level, and they have been receptive to this model. By compiling and sharing comprehensive databases of buyers and orders, some of which already exist with separate government agencies, self-regulation could be an effective component of synthetic biology governance. However, more individuals with credible connections, knowledge, and funding are needed to promote the idea of voluntary data sharing and self-regulation.

It was suggested that academia assume more responsibility in defining the appropriate level of governance for synthetic biology. Unlike the nuclear arena where researchers are expected to participate, be held professionally and criminally accountable for their actions, and interact with and educate the public, life scientists have been uninvolved with many aspects of regulation.

For many in the public, synthetic biology remains a mystery. Participating in helping to educate the public needs to be mandatory for practitioners to encourage the use of best practices, and to improve the acceptance of synthetic biology in both the general public and among influential policy makers.

Regarding DIY practitioners in synthetic biology, it was noted that both cutting-edge technologies such as "desktop" DNA printers and older, unused machinery are becoming available on the open market. Industry must have an incentive (i.e., minimizing financial liability) to restrict the sale of cutting-edge technologies to unknown entities. Perhaps a matchmaking organization could provide a way for older machines and instruments to be used safely. There also needs to be an incentive for recycling or destroying those machines and instruments that have the potential for nefarious uses of synthetic biology.

Realistically it is impossible to have all synthetic biology practitioners voluntarily use best practices, but it is equally unrealistic to effectively police the field through government regulation alone. Voluntary self-regulation using government databases could be an effective compromise because of the speed of implementation, incentive for private industry to participate, and the ability to continually update databases for future use.

The Challenges of Deploying Synthetic Biology Technologies in Developing Countries**

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Summary

The planet faces a "perfect storm," caused in large part by a growing population and environmental degradation. This will require producing more biomass for food, feed, bioenergy, fabric, and materials with less land, water, and oil, and in the face of climate change and rapid loss of biodiversity. Maintaining the status quo, especially in developing countries, is *not an option;* we must act now. These formidable challenges are also incredible opportunities for change. Humanity is embarking on a new powerful genomic revolution, coupled with the digital and nanotechnology revolutions. The field of synthetic biology (SB) offers the promise of revolutionary new products to enhance health and create wealth. Like biotechnology, SB will likely be regulated under the guidelines of the Cartagena Protocol on Biosafety to the Convention of Biological Diversity (CP) for signatory countries.

Policy makers must acknowledge both the potential of SB and the public's deep mistrust of new, untested technologies they feel are outside their control. The future success of SB depends to a large extent on whether public policy is well-crafted. To build public confidence in the governance of SB, transparency, together with adherence to high safety and environmental standards and ethical principles, is essential. However, the all-important safety aspects of policy must be guided by scientifically defensible, risk-based approaches rather than public opinion, especially when the latter is driven by activist groups and political agendas. To promote sustainable development and global harmony, industrialized countries also have a moral imperative not to influence policies that limit development of other less advanced countries and to learn from the missteps of regulating genetic engineering that illustrate that choosing a flawed paradigm has critical implications for a technology.

Current realities

In 2009, Sir John Beddington, United Kingdom Chief Scientific Adviser, warned that the world of the 21st century faces a "perfect storm" of problems that include food shortages, scarce water, environmental degradation, and insufficient energy resources. These challenges threaten to unleash public unrest, cross-border conflicts, and mass migration as people flee from the worst-affected regions. Rising standards of living in developing countries will trigger a surge in demand for food, water, and energy over the next two decades, at a time when governments must also make major progress in combating climate change. These formidable problems are all intimately connected. In the same way countries and regions are interconnected, the actions, decisions, and policies applied in one region can have profound social, economic, and environmental impacts in other regions. An example of this is the excessive oversight of agricultural biotechnology, especially in the European Union. This oversight has deeply influenced and could be potentially devastating to agricultural development and food production in the poorest nations of the world.

The formidable challenges need to be addressed with approaches that include adhering to ethical behavior and deploying new technologies. The field of SB offers the promise of revolutionary new products that could greatly benefit society, both in industrialized and developing countries, by enhancing health, contributing to care for the environment, and creating wealth. Building public confidence in the governance of SB by following ethical principles and high standards of safety for human health and the environment is critical. A key ethical principle is the sharing of benefits from those technologies beyond the industrialized nations that are pioneering the technology.

Many argue that care is needed to involve the public in discussions and decisions relating to the development and use of new technologies (Sunstein, 2002) — especially those who invoke a strong version of the precautionary principle in regulating new technologies like biotechnology, nanotechnology, and SB. Building confidence in the governance of SB is necessary in assuring the acceptability of the products of SB, along with ensuring that SB products meet the necessary safety requirements and environmental standards. However, policy makers should also learn from the example of genetic engineering, which illustrates that choosing a flawed paradigm and "democratic decision-making" that involves many segments of civil society who may not fully understand the complexities of the technology can also have critical implications for successfully deploying that technology. Sometimes, especially in developing countries, the general public, with a low level of education, may not fully appreciate the technical complexities related to the

oversight of new technologies and the complex dimensions of risk science that must form the basis of decision-making.

Scientific opportunities and challenges

Great challenges offer great opportunities for change. Technologies as powerful as those offered by nanotechnology, the digital revolution, and the genomics revolution can significantly contribute to solving global problems. The risks posed by these technologies must be carefully weighed against the benefits and the risk of inaction and maintaining the *status quo.* This especially applies to developing countries with the greatest increases in population, which arguably have the greatest challenges. It may least apply to industrialized regions where population is shrinking, food is plentiful, and health care and sanitation are adequate. There, the main concern is not poverty, but continued economic growth and environmental conservation. Environmental activist groups and self-styled "intellectual elites" who purport to represent the public interest have negatively influenced the adoption of agricultural biotechnology and demonized genetically modified organisms (e.g., pest-resistant crops or sterile mosquito vectors to manage diseases in developing countries). Many of these groups originate in regions, such as the E.U., with challenges other than food security and widespread tropical diseases (e.g., dengue).

SB is a logical extension of genetic engineering and will probably be regulated, for signatory countries, under the auspices of the CP. Countries that have signed and ratified the CP include the E.U. and most developing countries in the world, although not the United States. The debate around the oversight of SB has been initiated by NGOs active in the CP debate. These NGOs have asked the member countries to adopt a *de facto* moratorium on synthetic biology, and to apply the precautionary approach to field releases of synthetic life into the environment, acknowledging states parties' rights to suspend such releases.

Policy issues

Given the global challenges that need to be urgently addressed, regulation and oversight should avoid unjustifiably inhibiting innovation, stigmatizing new technologies, or creating trade barriers. As with the oversight of modern biotechnology/genetic engineering, a case-by-case approach is necessary for SB. We must not assume that all products or organisms derived from SB will be safe or that all will be dangerous, and the U.S. approach of *regulating the product and not the process* seems sensible. An identification of key "categories of risk" that includes

intellectual property (IP), biosecurity, biosafety, and ethics, and a categorization of SB products and applications as proposed by Kuzma & Tanji (2010) offers an obvious first step to develop appropriate international regulation. Further recommendations include:

- To adhere to ethical principles of benefit sharing and to contribute to solving global problems under the principle of "shared but differentiated responsibilities" (Rio +20), and to develop guidance frameworks that take into account global interests, not only domestic.
- What is an acceptable risk in a developing country will be different in a developed country, particularly given the scale of the challenges faced in the former. As such, the risk of testing new, unproven technologies versus the risk of maintaining the status quo must be considered.
- Take into account lessons learned from the oversight of other technologies, such as agricultural biotechnology, and use informed risk assessment for decision-making and not solely public opinion and political agendas.
- Most of the training for the regulation of agricultural biotechnology has been undertaken by UN agencies and NGOs involved in environmental, and not agricultural, activities, which has distorted and slowed the rate of adoption of this technology. National governments and the scientific community, especially those in developing countries, should pay close attention to capacity-building in risk science and biosafety regulation by experts in relevant areas.
- Carefully consider the balance of "democratizing" decision-making by involving the public in an effort to build confidence in the governance of SB and assuring acceptability of products versus adding great complexity and different agendas to the decision-making process that could result in inaction. Different regions have different agendas for public involvement (e.g., environmental conservation in Europe and California versus access to clean water in Central America). Discussions of certain issues should involve wider society, but in developing countries, highly technical issues, such as the regulation of genetically modified or SB products, are beyond the general understanding of the public, who will not see past the demonizing publicity of activist groups. Unfortunately, regulators in developing countries will carefully watch what regulators in more-advanced countries decide, especially when they don't understand a technology, such as genetic modification.

- Expand the capacity for the global scientific community to solve global problems by having open access to information, without excessive restrictions from intellectual property issues or excessive and costly regulation.
- Heavily regulating a technology to limit bioterrorism also limits its potential to contribute to solutions. The excessive regulation and thus high cost of agricultural biotechnology has resulted in the almost exclusive dominance of this technology by big industry and the exclusion of public-sector institutions (universities) and small companies. This fact should outweigh the threat of bioterrorism and should influence the regulation of SB.
- Allow the initial technical or biosafety problems from the first-generation products of SB to be solved by approaches developed in second-generation products, without unjustifiably inhibiting innovation by excessive oversight.

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***** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) Dec. 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.***

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Maria Mercedes Roca (see above). Dr. Roca initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those

responses made by Dr. Roca. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Roca, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- While regulation may be necessary to control synthetic biology and other emerging technologies, it can stifle innovation to the detriment of society, particularly in less-affluent countries.
- Given that risk-benefit framework is useful when evaluating a new technology and may also be applied to regulation as well, the risk-benefit equation will vary widely as it is applied to various countries and cultures. Consequently, there can never be a "one-size-fits-all" solution to regulation.
- Synthetic biology has engendered widespread support and excitement, especially among young scientists, and is advancing at a faster rate than is generally seen with emerging technologies.
- The democratization of decision-making is a necessary tool for engaging all stakeholders, in the effort to build a consensus around effective policy decisions and educating the public to ensure broad-based support.

Current realities

Although synthetic biology is generally thought of as a transformative technology, both exciting and frightening in its potential, there is also an aspect of routine or "ordinariness" in the application of synthetic biology. It was noted that one of the initial manifestations of synthetic biology will likely be in the area of vaccine production. While synthetic biology will be used to create a synthetic virus, that can be grown on a production scale, it will then need to be killed to be used to produce a vaccine. There was general agreement that the regulatory process to approve the distribution of that vaccine would largely be unchanged from that used currently. There will be only a few modifications to the approval procedure since the end product vaccine will be similar, if not identical, to vaccine products manufactured by traditional means. From the point of view of the consumer, the vaccine is essentially the same as prior versions, having just been produced more efficiently. Consumers' negative views concerning new technologies that are used to produce vaccines (e.g., synthetic biology), may result in their reticence to use, or even outright reject, such products.

The promise and excitement of synthetic biology as a new technology, driven by young people who have formed their own communities, was highlighted as one of the most important aspects of this emerging field. It was proposed that this aspect of the technology will be a primary driver in its adoption and dissemination and that the excitement factor should be used when discussing synthetic biology with policy makers and the general public. It was suggested that synthetic biology almost has "a life of its own," and that over-regulation could stifle progress in the advancement of the technology.

Although the concept of a risk-benefit evaluation for a new technology (or technology product) is well-understood, there was general agreement that the application of such an evaluation process will result in a different conclusion for a less-affluent country than for a more-affluent country. As an example, the benefits from genetically modified mosquitoes were recognized as a potentially life-saving advancement in several less-affluent countries, but regulators in more-affluent countries may have difficulty understanding the importance of such a mosquito. Safety standards were considered an important part of the risk-benefit equation, and must not be relaxed. Rather, pragmatism and economic reality may result in different applications of safety standards, especially in less-affluent countries. The example cited was the development of a genetically modified banana, resistant to black sigatoka disease, which was halted due to anticipation of rejection by European markets/regulators.

There is a historical context of public and scientific reactions to various technologies. In the late 1980s, with agricultural research funded by the international community, food distribution was the major concern in certain low-income countries. However, in the early 1990s, there was a shift in international development and research from agricultural issues to issues surrounding the environment, particularly in regards to climate change. The decline in agricultural funding was quite pronounced, shrinking by 67% over two decades, resulting in the elimination of basic agricultural services (e.g., extension services) in some less-affluent countries. In the last five years, these conditions have resulted in higher food prices and supply shortages, and agricultural issues are now beginning to once again gain the attention of the international development community.

Major policy issues tend to have long lives, but the public perception surrounding these issues tends to vary over time, swinging like a pendulum. The analogy of women's rights was presented, comparing a previous generation that fought for women's rights in the face of a very traditionalist environment with the next generation, in which the pendulum swung back. Presently, this issue is near equilibrium, with a healthy mix of personal and professional lives and priorities.

This analogy was then compared to environmental activism, which was also once quite strident, but may be approaching a balance between environmental protection and scientific progress.

Scientific opportunities and challenges

The notion of synthetic biology being isolated and identified as an autonomous and unique element of biotechnology and biology was debated. Treating synthetic biology as a separate and distinct technology, as opposed to "just another advance" in biotechnology, may result in heightened scrutiny by regulators and by activists who generally oppose emerging technologies.

Involvement of a variety of stakeholders in discussions and decisions around synthetic biology and also in scientifically complex issues was considered important. This "democratization" of decision-making is a consequence of the instantaneous and pervasive dissemination of information, primarily through the Internet. However, it was also argued that involvement of nonscientific and, in some cases, community stakeholders with lower levels of education, actually resulted in such stakeholders deferring to experts, or expressing opinions without a complete understanding of the issues at hand. Democratization of decision-making was recognized as a benefit and a necessity, but it was also described as a double-edged sword that increased the complexity of decision-making.

Limiting development of synthetic biology and other such emerging technologies in high-income countries may lead to unintended consequences. The first of these may be that the lack of advancement of such technologies in more-affluent countries may prevent countries with fewer resources from being able to advance and utilize these new technologies on their own. A second unintended consequence is the possibility that multinational organizations/corporations may seek out countries with less robust regulatory environments in which to conduct research into these new technologies. Another related aspect of regulation of new technologies is the extent to which a body of regulation may act as a barrier to entry or advancement of said technology by certain stakeholders. This "mountain of regulation" may prevent university researchers from pursuing synthetic biology and other advances, as it is too expensive for them to even consider. Small start-up companies were also noted as potential casualties of what may be perceived as excessive regulation.

Animal cloning was discussed as an example of a technology with differing regulatory and risk assessment stances in various countries. Several years ago, a cloning risk assessment group was convened in the United States to consider the safety of consumption of food from cloned animals, and concluded that such food

was safe to eat because it was produced through traditional sexual reproduction. However, when a similar group of scientists was convened and came to a similar conclusion in Europe, the risk assessment was sent back by the European Commission five times for re-evaluation, and still has not been resolved in Europe.

The need to educate on a variety of levels was debated. A science curriculum for children and a program focused on biotechnology for secondary education were noted as essential, as well as the need to educate and provide resources for science teachers. Several countries, such as Cuba, Venezuela, Brazil, Argentina, and Colombia, were noted to have significant programs to engage young people in science. The education and engagement of policy makers in scientifically complex issues was also introduced. While scientists may not always be the most effective communicators to the lay public, it was proposed that scientists continue to develop and utilize communication and advocacy skills.

While reducing the degree of regulation may raise concerns about exploitation of the public, if scientists were prohibited from pursuing certain areas of research in their home country, they may attempt to move to regions that are welcoming to outside scientists. In this scenario, it is possible that, even with good intentions, scientists may implement protocols that are perceived as exploitative of their research subjects and/or the community in which they are working. The possibility of this happening is particularly strong when scientists are working outside of their own cultural framework.

Policy issues

Aspects of global harmonization of regulations and policies relating to biologics and emerging technologies were discussed. While it was agreed that general multinational guidance in these areas provided a useful framework, it was important to allow and encourage specific policies and regulation at the country level, to allow and encourage autonomy, as well as interweaving demographic, cultural, socioeconomic, and political beliefs into the regulatory fabric.

The need to get political leaders to understand the risks involved in these technologies as well as the costs of inaction was raised in the context of the ease with which special interest groups can exploit such an issue. This political reality was considered a significant and pervasive problem. While not directly addressing this problem, it was suggested that more-affluent countries could focus on demonstration projects in less-affluent countries as a way to show progress and to gain comfort with new technologies.

While there was consideration of a *de facto* moratorium of synthetic biology, the precautionary principle leads logically to a research agenda that could serve

the public interest and is not driven by individual organizations. Alternative approaches to synthetic biology applications have been considered. As an example, a genetically modified mosquito is being researched to alleviate or eradicate Dengue Fever, and a vaccine for Dengue Fever also is being developed. It was proposed that one way of evaluating these alternative approaches would be to compare both by conducting full and inclusive assessments of the implications of this technology, including a comprehensive means of assessing human health effects, environmental and sociological impacts of synthetic biology, and preventing negative outcomes.

The possibility that regulations applied by a high-income country have actually hindered research in a low-income country was raised. For example, a collaboration between U.S. and Honduran laboratories for a genetically modified tomato had allowed the laboratory research work to be easily transported and translated between countries. But the cost for the Hondurans to effectively address and adhere to the regulatory framework was prohibitive. Certain countries (e.g., Brazil) with less onerous regulatory environments exist that are large enough to fund and advance research on their own.

The Convention on Biological Diversity (CBD) was characterized by some as simply an effort by the less-affluent world to level the playing field. Others argued that CBD was primarily a vehicle to protect biological diversity in less-affluent countries and to be able to derive the benefits that emerge from biological diversity. However, due to three other unanticipated and uncontrollable realities, the CBD may have less leverage and relevance than originally hoped. The first reality noted was the strength and reach of multinational corporations. Second, genetic engineering is even more robust than it was when CBD was first enacted. Third, agricultural, food, and energy issues and problems are now impacting forefront policy decisions. While this analysis was not disputed, it was argued that it is difficult for any large multinational treaty to appropriately address the needs of a diverse group of individual countries.

While research to develop a recombinant banana resistant to black sigatoka was not pursued because this genetically modified fruit would not sell in Europe, it was suggested that given the declining population in Europe, serious consideration needs to be given to moving marketing focus away from Europe toward rapid-growth countries that are more supportive of the benefits of emerging technologies. It was further argued that people who are facing famine and food security issues in less-affluent countries may soon apply direct political pressure on their leaders to adopt synthetic biology and other emerging technologies that ameliorate these challenges.

The Challenge to Meet Global Need for Protein Sources for Animal Production**

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Summary

Increasing prosperity in populous countries has accelerated animal production at a much higher rate than the growth in human population. The current annual global feed need is 1 billion tons and there is an emerging crisis for increases in high-quality protein feed sources to support animal production. Today, animal production is reliant on soybeans, which form the bulk of world commerce of feed protein. Current trends and needs show that soybean and alternative protein crops will be needed to keep pace with demands for global livestock feed. Biotechnology using new synthetic biology methods can provide the means to enhance soybean production and develop new feed sources by reconfiguring other crops as protein production platforms comparable to soybeans.

Current realities

Efficient animal production requires feed with high protein content. While maize (875 million tons produced in 2011) provides much of the carbohydrate source enabling animal production, other crops provide much of the protein. Current global feed protein supplies are dominated by soybeans, canola meal, animal by-products, fishmeal, as well as many other less abundant and regional sources. Only soybeans, canola, and fishmeal are truly products of global commerce, where the feed protein sources from one part of the globe are used to support animal production in other parts of the world, and often with delivery of the animal products to yet another part of the globe. As more populous nations become prosperous, there is and will be greater pressure to increase animal production. The impact this will have on land and water resources, competition between food, feed, and fuel, and the need to escalate feed and animal production is a global concern. Global animal production is growing much faster than the rate of human population growth.

For the foreseeable future, soybeans will remain the single greatest protein source to support animal production. The meal from 85% of the 251 million tons of soybeans produced globally (2011) is used to produce animal feed. Soybeans produced in the Americas are a global commerce product and form the basis for expanding livestock production in Asia, a region where growth in animal production has been most rapid. Canola meal, a byproduct of seed oil production, is another major source of vegetable protein, although it constitutes only a fraction of the soybean commerce. Although only 2%–3% percent of global protein commerce, fishmeal remains an important contributor to protein sources for animal production. In fact, 25% of all fish caught are processed to make fishmeal. The use of fishmeal leads to human health issues by concentrating mercury and PCB pollutants that has attracted the attention of government regulators, who have issued warnings against consumption of fishmeal-fed aquaculture products. The use of fishmeal also has a negative impact on the marine environment by removing the forage fish base of the food chain. Terrestrial animal byproducts remain a significant reprocessing source of feed protein (4%–6%), although in the aftermath of the Mad Cow episode in Europe their use has been greatly diminished by regulation and by consumer choice.

There has been limited use of synthetic or transgenic biology to improve the content and quality of plant protein products used for animal feed; more effort has been directed at improving the protein quality for crops directly consumed by humans. However, the development of these products has been stymied by anti-GMO politics. The Gates Foundation has funded biotechnology projects directed at improving protein content and quality in staple crops, especially in Africa. Other international programs have used conventional breeding to create rice and maize with enhanced essential amino acid balance, and there have been similar breeding efforts to enhance the major feed protein crops (soybeans and canola), with limited impact.

Scientific opportunities and challenges

The improvement of current feed crops through biotechnology is critically needed to enhance their production and quality. As the major global supply of feed protein, the soybean's critical role in the feed industry has made its long-term enhancement a strategic objective. However, because soybeans only grow productively in certain regions of the world, additional sources of plant protein are needed, especially if the crops can be grown productively and economically in global regions where soybeans are not produced. Such crops might be targeted for the cooler northern

regions currently dominated by cereal production and/or be able to tolerate the arid and more saline regions of the globe.

The use of synthetic biology to enhance crops is still in its infancy. Almost all of the current transgenic crops exhibit traits designed to limit the impact of insects, viruses, or competitive weeds, which primarily benefit producers. Only recently have consumer-valued traits begun to emerge, such as low *trans*-fat soybean oil conferring a health benefit as a source of fry oil. Engineering a plant's protein quality and quantity to date has largely been in the context of attempting to improve protein content and quality in the starchy staple crops used as human food in less-developed nations. Biotechnology may be able to create a new "soybean" from other crops. By using genomics as the basis to alter the genetic program of other crops, it is feasible to use synthetic biology to engineer other crops to possess protein qualities similar to soybeans. One example is our project at the University of Arizona where we have altered *Camelina*, an oil seed crop related to canola, to have output traits very similar to soybean plants. This plant grows in northern climates, tolerates arid and marginal conditions, and can be grown as a winter crop between soybean crops, enhancing the productivity of existing farmland. We are developing this as a potential feed source engineered by synthetic biology because, from an agronomic perspective, it can be grown in competition with maize and soybeans, including on marginal land. *Camelina*'s other favorable characteristics are that it is not used as human food, thereby avoiding issues of transgenics in food, and being European in origin, there are no native plants capable of genetic out-crossing with *Camelina*. Current *Camelina* production is directed at biofuels with a meal side-product, a situation we envision to reverse, with the meal being the primary product for feed and the oil as a byproduct.

Policy issues

- **International centers for feed research and development.** The increasing need for protein sources for livestock feed is a global concern and should be supported through education and research investments by transnational projects. There are ample opportunities for NGOs as well as governments to use livestock feed for bilateral and multinational projects. There are many international organizations involved in crop improvement, but none of them are specifically directed at animal feed. The Food and Agriculture Organization (FAO), the Pew Trusts, and other organizations have published white papers on the needs and the looming crisis in animal production, but these have not specifically called for

establishing one or more international centers encompassing terrestrial and aquatic animal species. Such centers would, of necessity, need to bridge crop improvement and animal health and production. Animal feed research centers will need funding streams that require government, industry, and foundation support.

- **Enhance the productivity and composition of current feed crops.** For example, as a global commodity, fractional increases in soybean production could have immense impact. Because soybean trait enhancements will likely be transgenic through synthetic biology, there are persistent regulatory impediments.
- **Develop new feed crops.** There are many potential plants that could be developed into enhanced feed using synthetic biology. The *Camelina* research under way at the University of Arizona is but one possible example. The U.S. Department of Agriculture currently funds development of new crops with intramural and extramural programs primarily aimed at human food and biofuels. This program could be expanded to include animal feed crops and serve as an example for the funding agencies in other nations.
- **Address the competition between biofuels and feed.** The use of food crops for fuel is increasingly controversial, exchanging global food supplies for fuel predominantly for industrialized nations. There is a growing world opinion that using food as fuel increases food costs and decreases supply. Moving to next-generation biofuels or nonbiological alternatives will increase global food supply. Transgenic synthetic biology will enable the development of fuel crops or algae to be superior sources of fuel, releasing the crops currently converted to ethanol and biodiesel oil. Current global funding for next-generation biofuels should evolve quickly to support the goal of transferring food/feed crops to their traditional use.
- **Increasing regional production of alternative vegetable feed.** With soybeans and maize as the current primary global feed sources, the center of their production in the Americas is far distant to the growing sites of animal production in Asia. Alternative feed sources from other continents will improve sustainability and economic viability. Alternative feed development should be a priority for international research centers funded by government and/or NGO sources, needing only a small fraction of the funding now expended on research on important human food crops.

- **Abolish the use of fishmeal for animal feed and replace it with sustainable vegetable protein.** Fishmeal provides only a small fraction of global protein for animal production, but its use has a major impact on world fisheries and ocean productivity. By using transgenic synthetic biology approaches, it should be feasible to engineer sustainable vegetable protein substitutes for the small fraction of global feed protein currently supplied by fishmeal.

*** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) Dec. 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.*

Debate Summary

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Debate conclusions

- The potential of synthetic biology to create vegetable-based protein crops with less water and fewer resources may significantly expand the food and feed production in precisely those geographic regions where more food and/or feed is needed.
- The expensive and time-consuming regulatory and approval processes now in place for genetically engineered plants must be streamlined if the looming food and feed challenges are to be met.

- The preliminary indications that plants engineered via synthetic biology could be substituted for fishmeal (an animal feed known to negatively impact ocean sustainability) strongly suggest that such research be significantly expanded.
- Although biotechnology may have the ability to address many parts of the food crisis, sociopolitical factors, as well as geographical disparities in the production and distribution of food among more- and less-affluent countries, need to be considered in formulating and implementing effective policies regulating biotechnology.

Current realities

The impending rapid rise in the human population will require increased animal and animal feed production. While soybean crops are the main animal feed protein source, current production does not constitute enough protein capacity to supply future needs. Although soybeans are largely produced in the Americas, they are exported to areas where the demand for food is surging (i.e., Asia). Finding alternative plant protein sources, grown locally to reduce transportation expenses, was viewed as a priority. Designs based on synthetic biology of new crops arising from genetic modification of currently cultivated plants, or from other plants not currently used in agriculture, was viewed as a potential solution to the impending shortfall in the amount of crops available for animal feed.

Concern was expressed about the time constraints for gaining regulatory approval for crops derived from biotechnology. While the time to develop a new crop averages about 10 years, regulatory approval for a new crop averages about 13 years and costs nearly $135 million in the United States (compared with $10 million in Brazil). Such constraints were seen as a dramatic limitation to the development of new crops because it is unlikely that a company could afford such expenses unless the predicted revenues exceede $1 billion. Given that the shortfall in animal feed is rapidly increasing, regulatory approval was generally seen as a hindrance to development of new crops needed to meet anticipated demands for food.

Scientific opportunities and challenges

Potential solutions for how to achieve the required animal feed production increase were discussed. The near-term shortage of protein-rich feed emerged as the most urgent issue and synthetic modification of crops to achieve enhanced protein content was considered a viable and economically sustainable solution. For example, Camelina has been engineered from being oil-dominant to protein-dominant and

could be used as a soybean proxy in providing protein-rich animal feed. Camelina has been further modified to grow during the winter season, thereby maximizing land use during a previously dormant season. In contrast, other technologies such as tissue culture-based meat (i.e., animal muscle tissue grown *in vitro*), although valuable, were seen as still enormously expensive and not yet possible on a large scale.

While it was argued that animal feed (e.g., soybean and maize) should be produced in the regions of surging demand (i.e., Asia), it was also pointed out that the harvest of these crops is restricted to the temperate regions of the planet and limited to certain periods of the year. Although the U.S. has a huge amount of land available, much of this is not being utilized during winter. In this respect, engineered cold-tolerant Camelina was discussed as a specific genetic change that could be utilized in other plants to help increase animal feed production in countries with increasing demand for animal feed. It was also highlighted that the populations of more-affluent countries are increasingly becoming obese, while those in less-affluent countries are affected by malnutrition and hunger, raising the question of whether the main issue is one of distribution. The debate was dominated by contrasting positions, with some advocating the need for better allotment of resources and others suggesting that enabling less-wealthy countries to use the technology would allow them to ameliorate their own food shortages.

It was debated whether the solution to future food shortages should be technical or sociopolitical. Given that technology innovations influence societal interests and needs, it was argued that a distinction between technical and societal problems should be avoided. In this respect, since some technological changes could be seen as challenging certain social or cultural aspects of some societies, identifying the problems that require technological solutions is a major political challenge. The "white missionaries" approach, seen as the tendency of more-affluent countries to dictate to less-affluent countries regarding how they should solve their problems, was considered a deleterious approach. Therefore, the importance of having both synthetic biologists and social scientists collaborating emerged as crucial, with some countries making this a requirement for grant submissions.

Sociopolitical approaches to countering the animal feed shortfall, such as community education toward a healthier diet (i.e., a lower calorie intake) in commodities-rich areas, setting of export limits, and imposition of new taxes or food rationing, are potential solutions for more equal distribution of resources. In this respect, attention was called to the necessity of reaching a global agreement to ensure that the remaining resources would be equally distributed worldwide. Fostering international accords will be valuable, but this goal will be extremely

difficult to achieve because of the dominance of consumerism and overabundance of food in the more-wealthy countries. For instance, it was seen as unlikely that the U.S. or European countries would drastically reduce meat consumption to achieve equal distribution around the planet.

In Asia, desire for a wider variety of food (quality) is rapidly growing versus a fundamental need for basic food (quantity) in Africa. It was noted that feed resources in Asia would need to be deployed for growing different animals, thus ensuring the availability of different meats, while in the African focus needs to be concentrated on providing enough food to people in the first place. The debate largely centered on the importance of guaranteeing a balanced diet for everyone (e.g., by encouraging the growth of protein-rich grains in Africa to supplement the existing and predominant starchy staple crops).

Particularly debated was the topic of fishmeal as a protein source in animal feed, in relation to its sustainability and possible alternatives. At present, the amount of wild fish caught to feed farmed fish is between 20% and 40% of the total biomass of fish in the ocean. Because of a rise in protein demand, the amount of fishmeal required is projected to increase. While the presence of omega fatty acids makes carnivorous fish a healthier food source, the use of fishmeal is environmentally harmful because of the reduction of ocean biodiversity. Creating a plant that contains the appropriate protein and fatty acid content was suggested as a potential solution to overfishing. However, though modern technology may be capable of engineering new plants as an alternative to fishmeal, no government has made this a funding priority. Moreover, since the digestive tract of carnivorous fish is unable to digest plants, it would be necessary to further genetically modify a plant fed to such fish to make it more digestible.

The ecological sustainability of protein-enriched plants was strongly questioned regarding the potential increase in soil depletion and unintended gene flow. It was countered that the impact of nutrient-enriched plants on the land is not different from that of conventional crops. The lesson learned from genetically modified soybeans was that not only were the water consumption and soil depletion the same as for the wild plant, but that there was no evidence of gene flow. However, it was agreed that the impact of new genetically modified plants needs to be assessed on a specific case basis and potential undesired gene flow (e.g., herbicide resistance in Johnson grass) must be avoided.

Public research and academic institutes, as opposed to private research and development departments, have encountered difficulties in the development of new crops, due in part to unrealistic expectations from funding agencies when compared with the relatively small amounts of grant money they provide. Given

the high costs worldwide of regulatory processes, there was general consensus that public research laboratories with relatively low operating budgets would be unable to advance their research to a market level. A solution to both speed and cost issues was identified with the necessity of quickly moving beyond the existing rules and concentrating on the nonregulated aspects of the proposed new product.

Policy issues

To ameliorate the upcoming shortfall in food supply, crop production, and food distribution, it was suggested that governments should fund and encourage the use of synthetic biology to engineer new plants with optimized nutrient ratios and/or physiologies.

To address issues of unequal distribution and access to food resources, policies need to be created to reduce food waste and educate people from more-affluent countries to eat a healthier diet (including ingesting fewer calories). In addition, it was proposed that technological knowledge should be spread more freely to less-affluent countries so that they can produce the crops they need.

To preserve the environmental sustainability of the oceans, there was general agreement that the use of fishmeal for animal feed needs to be abandoned and substituted with a vegetable source of feed. Most of the agricultural industry has already expressed willingness to limit the use of fishmeal, primarily because of problems such as the concentration of PCBs and mercury in fish that have raised safety concerns. While creating new institutions or international regimens for the creation of bioengineered crops was proposed, it was argued that most of the existing regulatory framework is already focused on these topics. For instance, the U.S. Department of Agriculture (USDA) is already monitoring open field use of genetically modified plants, while the Food and Drug Administration (FDA) reviews the nutritional components of engineered crops.

Since nitrogen and phosphorus are the most important elements for growing any type of plant, export of crops could be considered as the export of nitrogen and phosphorus themselves. This view raised the issue of importing the same nutrients back to nourish the land. The economics of crop export and nutrient import must be carefully managed and the soil depletion rate closely watched.

While there are many examples of new scientific discoveries for which an application has not yet been found, there are numerous needs for which basic science is not investigating. In this context, there was disagreement regarding whether the scientific advancements should develop after the policies have been created, or if regulations should be imposed after the potential of a new technology has been evaluated. It was proposed that regulations and policies be formulated

after problems with the technology have been raised and solutions developed, although there was not consensus on this point.

An ongoing competition exists between biofuel feedstocks and food crops for both land and plant uses. Biofuels are currently produced from food crops (e.g., corn) despite the fact that 854 million people are undernourished and the demand for food and animal feed supplies is projected to rapidly increase in the next 40 years. Although new approaches may be contested by the agricultural, environmental, and energy stakeholders, it was proposed that biofuels of the future not be produced from food crops but rather alternative biofuel crops (e.g., switchgrass or algae) be created through bioengineering.

The lack of food supply in less-affluent countries was attributed to distribution issues caused by more-affluent countries (e.g., unequal partitioning of supplies and a failure to act responsibly to cut food waste). However, others rejected an equal food distribution policy, suggesting less-affluent countries could solve their problems within their own borders. That the U.S. Agency for International Development (USAID) spends 85% of its budget with U.S. corporations while only 15% is actually assigned to aiding less-affluent countries raised a discussion on the need to re-think USAID spending. For instance, by shifting the USAID budget toward more substantial grants, research groups from less-affluent countries would have more resources to develop new crops. At the same time, by allocating more funding to the development of less-affluent countries, capacity could be built to engage foreign research institutions, educate local people, and utilize local knowledge to develop new crops derived from plants that more-affluent countries may not have considered.

There was agreement that it is critical to streamline and accelerate the regulatory process. In particular, it was suggested that rather than constantly re-evaluating aspects of biotechnology that have been examined in the past, regulatory agencies focus only on new or novel components. Accelerating the approval process was seen as crucial for engineering new plant types to address key societal challenges, especially in lower-income countries.

Safeguarding the Genetic Firewall with Xenobiology**

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Summary

While progress is being made in synthetic biology to make biology easier to engineer, the safety regulations and risk assessment practices will soon be rendered outdated and inadequate to handle upcoming developments of synthetic biology functions, organisms, and products. Xenobiology, the science of biological systems made out of alternative biochemical structures, may provide a new set of tools to establish an innovative solution, a genetic firewall, to future biosafety challenges. This genetic firewall will provide a stronger safety framework than would a series of small ad hoc fixes to a set of regulations designed for genetic engineering. Decisive and collaborative action by scientists, policy makers, and other stakeholders is needed to face the medium- to long-term biosafety risks of synthetic biology.

Current realities

The potential future release of deeply engineered or novel synthetic microorganisms raises the issue of their intentional or accidental interaction with the environment. Containment systems, risk assessment, and safety regulations designed for genetic engineering in the 1980s and '90s, for the purpose of limiting the spread of genetically engineered organisms and their recombinant traits, are still largely viewed by regulators and scientists as sufficient for contemporary synthetic biology products.

Progress in synthetic biology is expected to yield a staggering growth in the number of new biological functions and modified organisms with useful purposes. These developments will sooner or later pose a significant problem for established biosafety and risk assessment practices. A technological development that is outpacing its safety regulation is going to end up in (i) a series of unintended consequences and unforeseen accidents, (ii) a legal bottleneck for further product development because of a lack of a clear legal and regulatory framework, and/or (iii) increasing, and well justified, public resistance toward synthetic organisms if they are not considered to be "safe enough." So far, no safety mechanism is available to provide a sustainable solution to this dilemma. Past suggestions such as so-

called "suicide circuits" (that would kill the cell once it escapes into the environment) have failed to provide a sufficient degree of safety for industrial, medical, or environmental use. No strategy beyond the decades-old approach to biological containment is currently envisaged, despite significant investments and first successes in synthetic biology that have made biology easier to engineer.

Scientific opportunities and challenges

Most synthetic biologists try to convert biology into an engineering discipline by redesigning *existing*, natural biological systems for useful purposes. This means that synthetic biologists are using genes found in nature or designing new ones that closely resemble natural genes. Some bioengineers, however, are not satisfied with the biochemical substrates found in nature and try to construct new forms of life, called xenobiology, that have no counterpart in the extant world.

The synthesis of alternative biological structures focuses mostly on the three universal molecules: DNA, RNA and proteins. Recent research shows, for example, that all subunits of the DNA (base, deoxyribose, and phosphate group) can be replaced by alternative chemical structures. A DNA with three instead of only two base pairs has been made, and other carbon ring structures such as hexose or cyclohexenyl were incorporated to give rise to HNA and CeNA respectively (for all non-DNA, non-RNA molecules the term XNA is used, which stands for xeno nucleic acids). It was even possible to incorporate non-natural amino acids into proteins, so they are made up of 21 or 22 instead of 20 amino acid building blocks. First attempts have been made to come up with a biochemistry that has the opposite chirality of natural building blocks. So, instead of using left-handed proteins, future "mirror life forms" might use right-handed proteins. These experiments have mainly been carried out *in vitro* and very few if any (depending on the definition) living organisms exist with an altered biochemistry. However, sooner or later we will see the construction of new-to-nature or xenobiological systems that are increasingly farther away from their natural counterparts.

Xenobiology provides three main opportunities

1. Better understanding of the origin of life. Looking at all the possible alternatives to "life as we know it," the different variants of XNA, the hundreds of amino acids not used in proteins, the universal genetic code, or the selection of one type of chirality, the questions are: Why was this basic chemical make-up evolutionarily successful while others were not? Were these chemistries more robust, more likely to emerge under the

conditions of early Earth or was it by chance? And, is there room for an artificial biodiversity?

2. More efficient industrial biotechnology production systems. Although Earth has experienced billions of years of evolutionary trial and error, nature has (by far) not "tested" all possible biological systems. This means that it is likely possible to find new and more efficient biological functions than those provided by nature. This approach constitutes a promising way to design a new class of chemically diversified biocatalysts for industrial, medical, and environmental biotechnology. Industrial strains with a fundamentally different genetic code would suddenly be immune to natural phages or viruses.
3. A solution to the upcoming biosafety challenges. Xenobiological systems could be used as a fundamentally new biosafety system. Since they are not capable of horizontal gene transfer between the natural and new-to-nature organisms, the separation from the extant biology acts like a "genetic firewall" (see Figure 1).

While the first point addresses deep philosophical questions, the last two points deal with real-world implications for society, economy, industry, policy, and the environment. The use of xenobiology in industry, however, will primarily depend on whether it will be safe to use. Therefore, it ultimately comes down to xenobiology as a way to provide a genetic firewall to improve biosafety.

Constructing a xenobiological organism and a genetic firewall is a very difficult task, and beyond the current capabilities of science and engineering. Not only is it difficult, it might provide hardly any return of investment over the short-term future, since the establishment of a xenobiological toolkit and expertise will take some time before reaching a level that is remotely comparable to bioengineering with traditional biochemistries. But over the mid- and long-term the investment will pay off, both in terms of increased efficiency of biotechnological processes and in terms of providing a safe and reliable mechanism that avoids unintended consequences, accidents, and legal uncertainties.

Policy issues

Synthetic biology, extrapolated into the near future, will result in a radical increase in the number of synthetic biological functions, organisms, and products. Policy makers need to realize that these developments will render the current regulatory safety framework (designed for genetic engineering) outdated in a not-so-distant future.

- The response to this development may either be (i) inert, ad hoc, tactical adaptations of obsolete safety regulations and risk assessment without a clear strategy, or (hopefully) (ii) a collaborative approach that leads to a strategic vision of how to deal with upcoming safety challenges of synthetic biology, to avoid biological accidents, legal uncertainties, and safety-based public resistance. Adaptations may still be needed, but this time they would be based on a solid framework.
- The genetic firewall could at the same time improve industrial processes and establish safer biosystems, but only if a collaborative action among international scientists, policy makers, and other stakeholders can be established.
- Instead of resuscitating the limited concept of genetic suicide circuits, scientists, safety experts, and policy makers may discuss radical innovations as a strategic answer to upcoming biosafety challenges. The pros and cons of xenobiology and the support and deployment of the genetic firewall need to be discussed among international stakeholders.
- Decisive action to radically improve future biosafety issues is required from policy makers, concerned with the governance of biotechnology in Europe and the United States, in the form of (i) support to the technical development of a genetic firewall, and (ii) preparation of a regulatory framework that details in which circumstances the genetic firewall has to be deployed.

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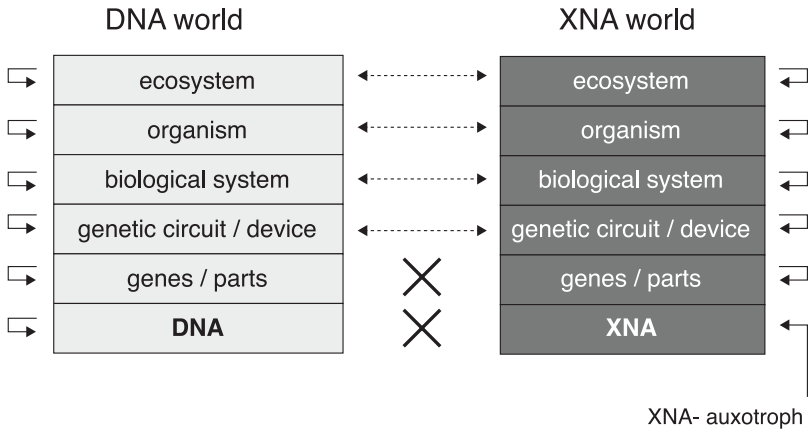
*** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) December 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona***

Figure 1: **DNA and XNA organisms would be able to interact on the level of whole organisms but would not exchange genetic material through horizontal gene transfer or via sexual reproduction (genetic firewall). Also, the XNA world needs to be completely dependent on external supply of essential chemicals that it cannot synthesize itself (XNA-auxotrophy).**



Debate summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Markus Schmidt (see above). Dr. Schmidt initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Schmidt. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Schmidt, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Xenobiology, with its potential to reveal fundamental information about biology and the origin of life and even life on other planets, is a potentially transformative technology.

- The regulation of xenobiology, especially with respect to the safety of its procedures, its impact on human and environmental health and public safety, and its toxicity, presents significant challenges. Although much can be learned from the regulation of other biotechnologies, xenobiology will likely have unique aspects concerning the creation of a foolproof genetic firewall and the appropriate levels of physical and biological containment.
- Given the public concern over recent advances in genetic engineering, including the public, policy makers, and legislators in discussions characterizing the benefits and risks of xenobiology is critical to shaping effective policy.
- Concerns about public safety and security requires a level of governmental control of xenobiology that may not be welcome by those who wish to have open access to the technology and who promote its uninhibited, rapid innovation.

Current realities

Xenobiology was generally acknowledged as an early-stage scientific field, which is rapidly evolving. Although the assertion was made that xenobiology could create a "genetic firewall" that would protect the natural environment from synthetic organisms, this was strongly disputed. Given the extremely early stage of its development, there are numerous unknown aspects of xenobiology related to its safety, toxicity, and environmental interactions that were seen as potentially dangerous. Although XNA may not be able to interact genetically with natural DNA, XNA, or non-natural amino acids, may have a toxic effect on natural organisms by interacting with the DNA replication machinery, or through immune system effects. This would require additional layers of containment for any xenobiology experiments or production. Xenobiology was not regarded as a perfect firewall, and it was suggested that presenting it as such was an overstatement with potentially harmful consequences.

The premise behind xenobiology was also questioned: Given that organisms created via synthetic biology are already fragile, was there a need for xenobiology? If xenobiology could be shown to be safe and commercially viable, it could be a transformational technology.

Much of the debate centered on the appropriate way to regulate a new technology such as xenobiology under current regulatory frameworks. Historical parallels were drawn to the introduction of other major technologies, such as the

automobile or the airplane, where safety guidelines took some time to catch up with the demonstrated capabilities of the technology. To avoid similar lags in ensuring safety, it was proposed that regulations for xenobiology be implemented in advance. The key component in providing effective regulation is assessing risk, and while it is difficult to foresee all risks associated with such a new technology, several proposals were made (e.g., gaming, modeling exercises, risk registers) for methods to examine potential outcomes. Asking the right questions, and continuing to ask questions as the technology progresses, were seen as critical to accurately assessing risk. Carefully constructing a robust risk assessment framework was considered to be a more effective approach than regulation through legislation or government regulation alone. However, it was acknowledged that the complexity of xenobiological systems would make assessing their potential impact challenging, and require extensive testing and re-evaluation.

The public security questions involve determining who can be trusted to work on or have access to information about organisms derived from xenobiology, particularly if the fears about toxicity or autoimmune responses were realized. The potential validity of these concerns were acknowledged, but not seen as especially different from challenges being faced by the synthetic biology community, or for any other new, potential dual-use technology.

There was disagreement over whether conducting research into xenobiology would divert attention or resources away from research into proven, well-known natural DNA, RNA, or protein systems. Many technical issues remain to be resolved in these areas, including through synthetic biology, and proposing a shift toward xenobiology may distract from these efforts. However, industry is already doing xenobiology and will continue to do so. A particularly attractive aspect of xenobiology for industry would be the ability to "switch off" an engineered organism as a way to protect intellectual property (IP).

Scientific opportunities and challenges

Many of the challenges posed for xenobiology are the same as those being faced by synthetic biology. There was concern that the discussion was being framed as the two technologies in opposition to each other, whereas given the similarities between them, coordination would be more productive perspective. Creating division between the two may provide an opportunity for opponents of biotechnology to "divide and conquer" and limit progress in both fields.

A significant opportunity from xenobiology is the potential to provide information about fundamental questions of biology. If xenobiology shows that living organisms can be built with material other than the naturally occurring four

bases of DNA, the three base codon, or the naturally occurring 20 amino acids, the basic concepts of the origins of life would be challenged. Additionally, information gleaned from xenobiology research could provide details about how life evolved on Earth. Space agencies in the U.S. and Europe have taken a particular interest in xenobiology because of the potential to inform the search for life on other planets (exobiology). In the anticipation that life may one day be found elsewhere in the solar system (or universe), agencies such as the National Aeronautics and Space Administration (NASA) are using xenobiology as a model to determine how any extraterrestrial life should be handled (i.e., containment, worker protections, safety protocols) if it can be returned to Earth. There are also resultant issues about how to communicate with the public about any changes to our fundamental understanding of life, either as a result of xenobiology or exobiology.

Safety concerns around xenobiology were viewed as a significant challenge. Questions were raised concerning how organisms created via xenobiology would interact with other natural organisms in the environment, what effect (if any) these organisms would have on humans, whether these organisms or their products would bioaccumulate in the environment or be degraded, and how readily would they spread? Answers to these questions would be critical to making accurate risk assessments, but it will be challenging to test each parameter safely. Particular examples included the difficulty of assessing effects on humans with existing rodent models, and the published autoimmune reaction to some types of xenobiology products. Assessing these risks in theory or *in silico* is unlikely to be adequate.

The implication that xenobiology could provide a foolproof safety system for synthetic biology was also seen as problematic. It was stated repeatedly that nothing should be regarded as foolproof. Because it would be unwise to rely solely on xenobiology to "contain" a synthetic biological organism (i.e., prevent it from interacting with the environment), other physical containment systems would be required. In this respect, xenobiology likely would not alleviate many of the concerns around synthetic biology escaping from the laboratory or fermenter to interact with the environment, as it would be difficult to definitively test such interactions in advance of an escape. As a first step, preparing a detailed plan for evaluating and testing each aspect of the release (intentional or accidental) of a xenobiological organism would be important to provide some comfort to those worried about potential adverse effects on the environment or human health.

There were concerns expressed about the potential for industry to monopolize this technology as a way to simply protect its intellectual property. The example of terminator technology, or genetic use restriction technology (GURT), was raised. This technology would prevent farmers from using second-generation seeds from

genetically engineered plants, hence protecting the IP of the company that created the plant. A similar situation could occur with xenobiology, with the public and citizen scientists denied access to the technology should it be developed by big industry. This would raise a number of political, social, and ethical issues, and potentially lead to a backlash against xenobiology, similar to what occurred with agricultural biotechnology, especially in Europe.

A significant challenge in advancing xenobiology is the extent to which the public should be included in discussions about costs and benefits. The question remains as to how much effort should be devoted to acquainting the public with the terminology, potential, and pitfalls of the technology. The role of mass media (e.g., movies and documentaries) was raised as an illustration of how xenobiology could be presented to the public, either in a positive or negative light. The ability to use these media to either enhance public understanding and support, or seed fear in the public and lead to calls for limits or moratoria on research, were considered. It was felt that the public should be included in the discussion about xenobiology from the outset. Although there was the potential for creating a backlash, trying to exclude the public from the discussion would likely be more detrimental in the longer term. Achieving a positive outcome (i.e., having the public assess the technology in a rational way), would depend on the types of outreach and inclusion employed. It was generally acknowledged that public discourse about this subject would be difficult.

Policy issues

Preparing governance structures for xenobiology was presented as a challenging task, given the early-stage of the technology's development. It was acknowledged that excitement alone is not enough to warrant significant investment in the field. The field of xenobiology would need to mature before concrete progress could be made on regulatory systems. However, it was noted that xenobiology is already starting to show promise from a research perspective (e.g., using organisms to crack hydrocarbons, building enzymes from nonnatural amino acids, constructing a six base pair DNA to aid in HIV diagnosis). Some of these applications, although still at the demonstration stage, are particularly exciting because the reactions they catalyze cannot be performed in natural biological systems. Projects such as the European Union's Metacode program are already investing in such applications.

A substantial portion of the discussion involved the nuances of regulatory policy and how to apply different approaches to xenobiology. The regulatory guidance for synthetic biology as it stands in the U.S. is relatively unclear, and certainly not prescriptive in terms of conducting meaningful risk assessments.

Specifically, the guidance for synthetic biology research has been issued by the Office of Biotechnology Activities (OBA), which suggests that risk from a genetic element should be considered the same as the risk posed by the organism from which it came. This leaves a significant gap, as many synthetic biology genetic elements may be derived from no organism at all. Thus how can risk be meaningfully assessed?

This problem would likely be even more relevant in xenobiology, where the very components of such an element are completely new. There were some suggestions that approaches and analyses could come from the engineering field. While it was emphasized that asking the right questions was important, the issue of how to regulate such an unknown technology was largely left unanswered. Views differed as to whether the approach should be anticipatory (i.e., through regulation enacted in advance) or dynamic (i.e., by continually asking questions to shape the response).

Governance of xenobiology through self-regulation also was suggested. Some felt this term to be problematic, as it might suggest an unwillingness to have oversight from outside the community, so the alternative term "safeguards" was proposed. A project in 2007 examined attitudes of European scientists toward different governance approaches, and self-regulation was not a popular course of action, in contrast to the preference of U.S. scientists. This highlighted the need to provide culturally appropriate governance mechanisms.

Questions were raised as to who should control such genetic firewall technology. Specifically, it was proposed that such a powerful and potentially dangerous technology should remain under government control, although this would raise issues as to who should be given access and under what circumstances, and which governments should have control. Xenobiology, it was countered, needs to be an open source, publicly available resource, as this would allow for the greatest impact as a safeguard against misuse. Control and access are ultimately political issues that will need to be resolved at the political level.

Given the difficulty in communicating xenobiology to the public, there also would be issues concerning how to regulate xenobiology in communications with policy makers. It was cautioned that being seen to be asking for early regulation could result in overly restrictive controls, especially if the distinction was not made effectively among regulation, guidance, and frameworks. It was agreed that communicating this science effectively would be a key policy challenge as the field progresses.

Comments suggested that existing safety regulations were obsolete for dealing with a technology such as xenobiology. Regulatory systems vary widely among

different countries, and some nations, such as the U.S. and Australia, were viewed as having quite robust systems in place. Much could also be learned from the pharmaceutical sector, particularly in the area of self-regulation. Pharmaceutical companies have been dealing with the need to ensure safety for new products for a long time, and there may be lessons that can be extrapolated to xenobiology.

Policy Innovation in Synthetic Biology Governance**

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Summary

Governance for synthetic biology (SB) is a topic of current policy discussions. This paper argues that the framing of the governance debate is overly simplistic in practice and theory, and thus governance is lagging behind technological innovation. It calls for "innovation in governance" to match technological innovation. To do so, three specific approaches are suggested. First, in the practical realm, SB has not been appropriately unpacked for meaningful conversations about governance. Disagreements in governance often arise from different conceptualizations of what SB is. In this article, the development of a typology (aka a classification system) of SB applications is suggested to move governance discussions from the very general to more nuanced, actionable items. Second, in the theoretical realm, framing SB governance as a continuum of approaches, rather than a dichotomy, is recommended to allow for stakeholders to express different values, but transcend the old, contentious, and unproductive debate over precaution versus promotion. Finally, because SB will change and develop rapidly, governance should be dynamic. Decisions about movement along the continuum should allow for more responsive governance and better opportunities for compromise among stakeholders with divergent opinions. However, these discussions should not be left only to those developing or regulating the technology, as they do not hold all the requisite expertise. A more diverse set of stakeholders and citizens with local knowledge and expertise need to be included.

Current realities

SB has made the transition from science fiction to reality. A minimal cell has been produced; undergraduate students use SB to make bacteria do novel things such as smell like bananas or take pictures; people are developing SB in their own homes; and the field is taking off in labs and markets. What remains is a sensible plan for governance. Currently in the United States, agency hands are tied by ambiguity of the SB field, politics, a lack of resources, and the fixation on decision-making based

solely on the natural sciences. In addition, the science is young, especially the risk science needed for input into decisions. Moreover, current laws do not seem to be enough for safety evaluation of new and emerging products of SB, as they are already challenged by genetically engineered (GE) organisms. For example, GE insects pose an interesting case where the Food and Drug Administration (FDA) may regulate them as new animal drugs. Questions arise such as: How can a GE insect be a drug? What expertise does the FDA have in ecology and ecological risk analysis? What goes unchecked with this jurisdictional arrangement? In another example, the Environmental Protection Agency (EPA) is responsible for genetically engineered microbes (GEMs) under the U.S. Coordinated Framework for the Regulation of Biotechnology using its regulations under the Toxic Substances Control Act (TSCA). These regulations, however, do not cover "intrageneric" organisms (i.e. GEMs with engineered genes from the same genus). One could overexpress several bacterial toxins via SB in a GEM without U.S. regulation. This GEM could be deployed in the environment to perhaps remediate pollution in soils without oversight. Confidence in the U.S. regulatory system is affected by such regulatory loopholes.

Scientific opportunities and challenges

The technology has moved rapidly, but governance is lagging, especially for environmental applications like those mentioned above. While policy discussions about SB governance have increased over the past five years, the focus has largely been on biosecurity, publication standards, and DNA synthesis security standards. The publication of the H5N1 research describing how to make a hybrid virus that moves from mammal to mammal received much public attention. Medical applications of SB have received some attention from policy scholars (e.g. bacteria engineered to fight cancer); however, agricultural and environmental applications of SB have received almost none. These applications come with very different portfolios of risk and benefit issues, ethical dilemmas, and socioeconomic impacts. The agglomeration of sectors and issues related to SB stifles progress in SB governance

Another problem stifling progress in the debate on SB governance is the precaution-promotion dichotomy. For example, precautionary thinkers (such as some ecologists, risk scientists, and consumer and environmental groups) and technology promoters (such as some bioscientists and biotechnology companies) have rigorously debated the oversight of GE organisms with little consensus built. The contested climate has sparked lawsuits by consumer organizations against companies or the U.S. Department of Agriculture (USDA) over the adequacy of environmental assessments, affected markets for products, and impacted trade.

Policy issues

- With SB products just beginning to enter markets, now is the time for anticipatory governance exercises that engage stakeholders and the public upstream of SB technological deployment. These exercises should provide a forum for diverse stakeholders to come together on neutral or balanced grounds and provide real opportunities for nuanced discussion and input into decision-making. Stakeholder and public deliberation has been demonstrated in case studies to improve the quality of decisions (NRC 1996). Engagement with real input into decisions, if done well, has been shown to increase legitimacy, bidirectional learning, and mutual respect among stakeholders. Furthermore, it is the right thing to do: in a democracy, people paying for a service have the right to be informed, be heard, and make choices about that service. Indeed, taxpayers fund the majority of SB research in academe and also pay for subsequent discoveries in industries that are based on publicly funded science and, therefore, should have input into SB governance.
- In the past, most discussions about governance of emerging technologies have been largely limited to "the science." However, by necessity, values underlie conversations about governance and it is crucial that governance discussions engage stakeholders on a broader range of ethical and societal issues.
- There is a need to unpack and to develop a typology for diverse SB applications to move governance discussions from the very general to more nuanced, actionable items. Policy debates currently fail to differentiate between specific applications of SB. However, social science research indicates that the public is unlikely to uniformly accept or reject SB and public polling indicates that the public is able to distinguish among SB applications. In our own work with nanotechnology and food applications, we found that participants in public forums care about the purpose of the technological product, the point of deployment, and the risk/benefit distribution. To facilitate meaningful discussion about SB governance options, we need more specificity. We have previously developed a typology for SB products based on sector of application (human medicine, consumer products, energy, food and agriculture, chemical production, or environmental application) and technology type (non-living biological parts, systems of non-living biological parts, highly engineered cells, highly engineered systems of living cells, artificial living

cells, or systems of artificial cells) (Kuzma and Tanji 2010). Here, a third dimension is suggested: technological purpose (improve human health, improve environment, improve economic well-being, improve social well-being, national security, enjoyment/entertainment, education, etc.). The purpose dimension might be broken down differently, dependent on the sector.

- SB governance should be framed as a continuum covering preventive, precautionary, permissive, and promotional approaches. This continuum framing would allow stakeholders to transcend the old, contentious, and unproductive debate over precaution versus promotion. In prior work (Kuzma and Tanji 2010), we identified four governance policy areas (biosafety, biosecurity, ethics, and intellectual property) in which this continuum operates, with further differentiation based on the sector and type of SB technology. For example, for artificial systems of living cells released into the environment for food and agricultural applications, a preventive approach may be the first choice for biosafety reasons; whereas, for non-living biological parts used for biofuel production in the lab, a highly promotional approach may be the first choice given fewer concerns about biosafety. It is suggested here that even more nuance be added to this framework as particular SB applications are considered.
- Currently, oversight systems are almost static and, in the absence of crisis, it takes years or decades for statute or regulation development. SB requires the development of a new governance system that is dynamic and able to consider and adapt to significant new data and information as they emerge (i.e., advances in technology, biosafety, biosecurity, socioeconomic impacts, law, or ethics). While garnering the political will for such a system may take years, it will save us time and resources and promote better decisions in the long run. We suggested a similar dynamic system in the context of nanobiotechnology with principles of responsiveness, inclusion, and anticipation in previous work (Ramachandran et al. 2011). For products yet to hit the market, initial approaches to governance would be considered according to the typology and continuum analysis described above. As new information arises, a regulatory advisory group of stakeholders would convene to consider changes in governance from more to less preventive, or from mandatory to voluntary programs, or vice versa.

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***** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) Dec. 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.***

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Debate conclusions

- A more dynamic model applicable not only to synthetic biology, but also to other scientific and technological advances with inherently high levels of uncertainty concerning potential benefits and risk is needed. An advisory body responsible for evaluating regulatory policies with respect to transparency, public dialogue, and effective coordination within and across agencies is essential for identifying a broad range of effective governmental options.

- While the feasibility of extrapolating domestic policies to the international stage depends on the specific policy, an effort to apply best practices and lessons learned, as well as to develop appropriately detailed modes, is required to integrate policy decisions into different cultural and social contexts.
- Allocation of resources toward governance innovation, in addition to funding the development of the scientific research, is a necessary short-term spending priority to allow development of a more cost-efficient system long term.

Current realities

Current governance structures allow for predictability, but serious inadequacies have begun to be revealed in terms of their capabilities to cope with advances in science and technology (S&T). Suggestions were made for new approaches to governance and oversight, which were broader than regulations and comprised of a full battery of options (e.g., ranging from soft to hard approaches), and were made available to provide responsible and watchful oversight for a particular area, such as synthetic biology.

There was disagreement as to whether the regulatory processes in place in certain countries such as the U.S. and the United Kingdom were thorough enough. In regard to the U.S., there was considerable disagreement on how strong current governance structures were.

A distinction was made between horizontal and vertical approaches in relation to technology and governance. Horizontal approaches refer to different regulatory regimens, products, and techniques, while vertical approaches refer to predictions for the future of the technology, such as potential changes. It was deemed important to be aware of these dynamic scales in both directions.

The need to discuss regulation beyond the dichotomy of precaution and promotion was raised. The precautionary principle could be considered in a more nuanced, proportionate, and reasonable way, as opposed to simply preventing scientific progress based on the elimination of all risks, and it was agreed that precaution and prevention were not the same principle. These terms are often mistakenly used interchangeably, and therefore inhibit a technology from advancing. It was suggested that precautionary principle could be rehabilitated to describe an approach that allows more time to collect more information rather than to delay scientific progress. This was said to already be the case in existing U.S. regulations, which are quite precautionary in nature, but concurrently there are cases where the risk ratio is relatively higher in allowing applications to proceed.

There was debate over whether to differentiate regulation by product or by process. The *status quo* of regulating by product was largely regarded as more manageable and more likely to prevent unnecessary precaution. Switching to a process-run system of regulation would require a significant overhaul that would be costly, difficult, and time consuming.

Nanotechnology has set the precedent for a more dynamic approach toward governance and for the use of softer methods (i.e., voluntary, guidance approaches) to determine whether harder methods (i.e., legislation, enforcement) must be subsequently implemented. The oversight of synthetic biology is being developed based on the adaptive governance and interactive regulation (e.g., public dialogue) approaches utilized for nanotechnology. The purpose of such approaches is to optimize the outcomes of oversight, based on the absence of sufficient data and scientific certainty.

Carrying out risk evaluations through various tools (e.g., modeling, gaming) was emphasized as necessary prior to any policy development. However, it was posited that decisions could still be made in the face of uncertainty and absence of data, and that a dynamic system of governance could accommodate such cases.

While there may be a lack of coordination within and across different oversight authorities, Canada was used as example of where coordination efforts have brought regulatory bodies together to establish a process for defining regulatory roles for new technologies. In regard to the U.S., the point was raised that perhaps more coordination is happening than is believed (i.e., the relevant EPA, FDA, and USDA officials do communicate with each other about synthetic biology) and particularly concerning biotechnology.

It was emphasized that there exists an urgent need to define a framework that can be invoked if a biosafety problem is reported. Following such a report, there is normally a mandate to regulate unless it is found that all predetermined agreements were correctly followed. Mandated regulations require rapid implementation, particularly in the U.S. and Canada, with the result most likely to be inappropriately heavy regulation.

Scientific opportunities and challenges

There was considerable debate as to whether current regulatory systems were obsolete, and concern was raised that novel systems to evaluate products and processes might pose inherent risks by moving too quickly and making mistakes. It was argued that a new dynamic system would not be applying approaches that had not previously been tested, but rather would allow for a full range of hard and soft governance options (i.e., from codes of conduct to top-down approaches) as

part of the governance structure. This would allow for an approach that can change and adapt over time as new information is introduced.

While a dynamic model of governance may not prove to be very efficient, especially with respect to public involvement, the model could allow for decisions to be made early based on whatever information was available at the time. Soft-approach regulatory decisions are already being made early on by stakeholders and regulators and the concern was raised as to what extent certain bodies inherent to the democratic process (e.g., the U.S. Congress) would potentially be asked to relinquish their final decision-making rights.

The question was posed as to who would be responsible for regulatory decisions made under the proposed new model. Although new (and likely redundant) regulatory entities need not be created, an advisory board-type structure could be charged with making recommendations along the dynamic continuum of soft versus hard approaches to regulation, to be implemented by existing bodies.

The extrapolation to the international context of a framework developed for domestic use could prove difficult. Thus far, the focus has primarily been domestic policy, but the same lessons could translate internationally (e.g., models for decision-making that set priorities and governance steps, such as better public engagement). Therefore, the same lessons may apply despite the specifics of the regulatory structure and whether it is domestic or international.

While international harmonization of product commercialization and its associated processes for risk management may not be feasible because of differing cultural contexts, it was argued that a standard model for deploying substances worldwide can be developed that is fast, implementable, and repeatable. The challenge will be to create a level of detail in the model that is able to accommodate cultural and demographic changes.

There was disagreement regarding the communication among the scientific community, third parties (e.g., NGOs), and the public. While such discussions were not routinely occurring among groups who have a precautionary or preventative approach toward governance (e.g., the ETC Group), a dynamic continuum of governance could provide a way to have rational public discussions.

One challenge identified was prioritizing governmental spending on innovation in a climate of limited resources. While it was argued that such spending can be viewed as a luxury it was also recognized there are repercussions (e.g. responding to crises) that are attributable to the absence of preventive measures.

In addition to institutionally derived constraints, the issue of cultural constraints on policies is an additional challenge facing efforts to establish dynamic governance. An example of a cultural constraint is the decision of the U.S.

Presidential Bioethics Commission to give practicing synthetic biologists the responsibility for identifying potential societal risks. This decision delegated to the scientific community was given the sole responsibility for characterizing the societal risks associated with synthetic biology.

Synthetic biology has been described as not having been sufficiently "unpacked" (i.e., defined), which was viewed as a point of frustration for both the scientific and policy communities. Scientists have the technical expertise to help policy makers understand the differences in risk parameters and draw appropriate boundaries for acceptable levels of risk. The current concern is that regulations will be drawn up arbitrarily without the evidence-based decision needed for appropriate regulation. Therefore, there appears to be an incentive for scientists to collaborate with policy makers in making decisions about technological applications that raise novel risks, which require some sort of exceptional oversight as compared with applications in which existing systems may suffice.

Policy issues

It was advocated that agencies must be proactive in evaluating the effectiveness of existing regulatory structures and addressing more adaptive procedures for governance where needed. Historical analyses have been carried out in certain areas (e.g., medical devices, drugs, chemicals) in terms of comparing various regulatory parameters (e.g., level of public input, and regulatory outcomes) to an understanding of regulation development. This information was described as highly valuable to agencies as it is used to make decisions for future approaches.

Having a system in place that allows changes in governance approaches as more data emerges and uncertainty levels change was advocated as especially useful for synthetic biology. This call for a paradigm shift in the governance of uncertainty was echoed throughout the debate.

While it was agreed that some sort of coordination mechanism was needed within and across regulatory agencies, regardless of the governance approach, the structure for a coordinating entity remains to be determined. A formal body representing different expertise across the relevant disciplines could be established, including private sector stakeholders and the public. This type of forum has been developed for nanotechnology, which was considered by some as analogous to synthetic biology in that it also required a change in regulatory oversight. More specifically, the National Nanotechnology Initiative (NNI) helped set priorities and encourage communication across agencies, although it was not seen as comprehensive example of what needs to be developed for synthetic biology.

Efforts at coordination could work within existing government frameworks. For example, there exists a Memorandum of Understanding among agencies within the U.S. Government (i.e. FDA, USDA, EPA), which funnels activities to the appropriate body. It was suggested that there could be more deliberation and interagency interaction. The framework is in place, but it is not effective with emerging technologies such as synthetic biology. Improving the existing framework could also address the issue of budgetary constraints in specific agencies. Addressing interagency coordination through the Office and Management and Budget (OMB) could result in improved efficiency and further policy within individual budgetary constraints.

A minority point was made that the ability to develop synthetic biology products for commercialization requires a set of manufacturing protocols for new products that are likely to have little modification from existing, clearly defined, and quality controlled manufacturing processes currently implemented for existing products. This was described as being positive because synthetic biology should not be viewed as an overhaul in current processes, but rather the effort should be to ensure that the processes are fully vetted, transparent, and allow the technology to be made available for real and beneficial applications globally.

Concern was raised as to how adaptive governance could incorporate public engagement and deliberation in a representative democracy. Two alternative routes, formal and informal, were proposed. First, develop a formal protocol for an intra-agency committee representing affected stakeholder groups and the lay population that is charged with making decisions about priorities. Second, implement various public dialogues, based on existing models in Europe, the U.K. and elsewhere, that involve citizen juries and public forums and facilitate dialogue between scientific policy-making and the public.

Do-It-Yourself Biology: Reality and the Path Toward Innovation**

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Summary

The United States has always been associated with innovation, particularly individuals or groups of individuals designing and developing new ideas in their garages and basements. As the Do-It-Yourself Biology (DIYBIO) community has grown, so too has the concern surrounding individuals and groups tinkering with biology. While much of this concern is overblown, the DIYBIO community is better positioned than any other organization to develop a positive culture around citizen science and to set the pattern for best practices worldwide by establishing a code of ethics, developing norms for safety, and creating shared resources for amateur biologists. U.S. policy should enable such exploration and innovation to occur by eliminating barriers to government research funding, harnessing the power of crowdsourcing, encouraging educational opportunities through community laboratories and re-evaluating the current patent/intellectual property (IP) structure for biotechnology and medicine. The question remains whether the U.S. will enable and lead such exploration and innovation or restrict it.

Current realities

Today, thousands of people around the world belong to the DIYBIO community, working on everything from microbial fuel cells, low-cost lab equipment, and environmental surveillance, to personal biomonitoring and new treatments for diseases. A more accurate term may be Do-It-With-Others Biology, as members of this community engage among each other via a global list serve where they exchange ideas, share experimental data, and discuss broader issues affecting the community. While individuals and groups have long been tinkering with biology outside traditional settings, DIYbio.org was officially created at a meet-up in Boston, Mass., on May 1, 2008. DIYbio.org is an organization dedicated to making biology an accessible pursuit for citizen scientists, amateur biologists, and DIY biological

engineers who value openness and safety. Since 2008, the global community has expanded rapidly and now includes community laboratories, which may be the future of DIY science expanding well beyond just biology.

Scientific opportunities and challenges

Education. One of the major opportunities and current focuses of the DIYBIO community is education. The U.S. has fallen way behind in terms of math and science education. Primary school education curriculums in the U.S. contain little to no biotechnology. Community laboratories are beginning to fill that void by providing courses and hands-on experience in the fields of biotechnology and synthetic biology. More importantly, they are providing the impetus and spark to get the next generation of scientists, engineers, and innovators excited about science. They also can provide opportunities for universities and community colleges that may not have labs equipped for synthetic biology and other biotechnology experiments. In 2011, Genspace, the first community laboratory to open in the U.S., provided the lab space, equipment, and advisory role for an iGEM team consisting of students from Cooper Union and Columbia University. In addition, Genspace serves as a node for the Urban Barcoding Project to provide extramural learning opportunities for New York City school children at the kindergarten through 12th grade levels.

Personalized medicine. One of the first major stories about the DIYBIO movement was when Kai Aull, a DIYBIO enthusiast, developed a genetic test for the hereditary disorder hemochromatosis in her apartment in Boston. While commercial DNA tests for hemochromatosis have long been available, she demonstrated that a genetic diagnostic test could be developed in a makeshift lab, arguably for a much lower cost than the commercial version. With the advent of new technologies that enable diagnostics, monitoring, and drug delivery to move from a centralized (e.g., doctor's office, hospital etc.) to a decentralized paradigm, the ability of individuals to take control of their health care with or without a doctor becomes more a reality. Synthetic biology and DIYBIO techniques can potentially enable individuals to design their own diagnostics and treatments (Munro, 2012).

Crowdsourcing. The heightened concern over bioterrorism, increased outbreaks of diseases (e.g., SARS, avian influenza, West Nile virus), and food poisoning raises the question of how best to monitor, track, and defend against such events. One method may be to take advantage of the rapidly decreasing costs of sequencing and the ever-increasing members of the DIYBIO and other amateur communities. One such effort is the BioWeatherMap initiative: a global, grassroots, distributed

environmental sensing effort aimed at answering some basic questions about the geographic and temporal distribution patterns of microbial life. The challenge with crowdsourcing, particularly when dealing with biological and microbial samples, is the verification and accuracy of such information. One could imagine a person or node monitoring for a bacterium such as *Bacillus anthracis* and finding a "hit," which if not verified or put into the proper context, could cause a public panic. However, the distributive potential of monitoring for biological threats is enormous.

Spurring innovation. The DIYBIO movement has already created companies producing low-cost equipment for individuals and community labs (Biba, 2012). While no one can say for certain whether the DIYBIO movement will spur the next game-changing technological breakthrough, the potential is there. However, this will require mechanisms for amateurs to increase their knowledge and skills, obtain access to a community of experts, develop a code of ethics, establish responsible oversight, and assume leadership on issues that are unique to doing biology outside of traditional professional settings.

Access. One of the major challenges the DIYBIO community faces is access to DNA sequences and parts, or biobricks. While the U.S. Department of Health and Human Services (HHS) guidelines for DNA synthesis specifically state that gene sequencing companies should not deny an order based on whether a person is affiliated with a university-type laboratory, gene sequencing companies have shown reluctance to fill orders coming from the amateur community. This reluctance is understandable given the lack of understanding of the DIYBIO community and the liability that a company may be under should something go wrong. However, the HHS guidelines are just that, guidelines, and there is no U.S. law or regulation that mandates to whom a company can or cannot sell. While certain sequences are restricted based on the select agent list, there is still an open question as to whether parts of those sequences would fall under the same rules.

Funding. One of the major challenges for the DIYBIO movement, and community laboratories in particular, is acquiring the resources needed to establish and maintain a working biotechnology laboratory. Even though the cost of sequencing technologies is rapidly dropping, maintaining a working laboratory requires a constant source of financing. While innovative methods and non-traditional fund-raising such as Kickstarter have enabled the DIYBIO community to raise funds to purchase or build their own equipment thus far, some federal agencies such as the Defense Threat Reduction Agency have already begun to explore avenues to utilize and fund the DIYBIO movement.

Intellectual property. Another major challenge for the DIYBIO community and the larger synthetic biology community are issues surrounding IP rights and how DNA sequences, biobricks, and genetic tests are patented. The recent Myriad Genetics case seems to suggest that a person's DNA or specific component of that DNA and the tests to analyze that DNA can be patented. What is more disturbing for the DIYBIO community in particular is that it appears that one cannot design a different testing method to analyze a particular gene or sequence. What Kai Aull did in her apartment in Boston may have violated certain patents on the hemochromatosis test.

Press. The misrepresentation and complete lack of understanding of the DIYBIO community enables those with alternate agendas to use the community as a scapegoat. While there are biosecurity and biosafety concerns associated with the DIYBIO community, the press has by and large overblown those concerns. This can create a false narrative for the general public on the true capacities and motivations behind the DIYBIO movement.

Policy issues

- Federal funding agencies should develop metrics and procedures to allow actors outside the traditional academic or business communities to apply for and receive federal grants. If we want to harness the intellectual power of this movement, federal funding agencies should rethink their mechanisms for awarding grants. There is no reason why a community laboratory or an individual should not be able to apply for and be awarded federal research grants.
- Biosecurity and biosafety surrounding the DIYBIO community should continue to be evaluated. Building upon the Federal Bureau of Investigation's (FBI) outreach program, other federal agencies, along with local law enforcement, should be better trained and engaged with the DIYBIO community to understand and utilize the community for biosecurity monitoring. One method may be to take advantage of the rapidly decreasing costs of sequencing, use of mobile technologies, and the ever-increasing number of members of amateur science communities. The distributive potential of monitoring for biological threats is enormous.
- Access to DNA sequences should not be limited to actors from traditional academic and industrial laboratories. However, screening guidelines should be strengthened and shipping and export control laws updated to

incorporate pieces and components of DNA. This incorporates multiple agencies and an interagency task force should be established with the flexibility to update the guidelines alongside the pace of the technology.

- Patent law regarding DNA sequences and synthetic biology "parts" should be re-evaluated. The advances in synthetic biology and the advent of the DIYBIO movement enable more ubiquitous access to components of DNA. These patent issues will grow more complicated as personalized medicine and the ability of individuals to sequence their own DNA become more readily available. The question becomes whether the IP structure, government regulatory system, and the public will enable it to happen.

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***** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) Dec. 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.***

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Todd Kuiken (see above). Dr. Kuiken initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Kuiken. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Kuiken, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- While DIYBIO has great potential for innovation and education, particularly with regard to fostering curiosity about science in younger generations, the potential for nefarious applications of the technology raise security concerns, especially for the DIYBIO community, which itself might be at risk from those with nefarious intentions. Appropriate mechanisms are being established to facilitate the reporting of suspicious behavior or activity.
- The DIYBIO community has voluntarily made efforts to ensure safe operations by investing in the establishment of DIYBIO community laboratories. While biosafety boards have been established and experts consulted to ensure certain standards of safety, there are no requirements for DIYBIO practitioners to adhere to those rules. There is considerable concern regarding future compliance as the DIYBIO field evolves and practitioners engage in riskier experimentation.
- Because DIYBIO is rapidly progressing and attempts to prevent or delay the movement will likely be circumvented, it is critical that an effective system of oversight be established that encourages the sharing of information and open access to experimental results.
- Community colleges can provide suitable forums for facilitating the oversight of DIYBIO using methods that provide benefits for both the DIYBIO community and society in general. Such an oversight, however, must ensure that diverse types of DIYBIO experimentation, ranging from individual work to participation in community laboratories, remain generally available to qualified practitioners.

Current realities

To address biosecurity concerns, various regional groups from within the DIYBIO community have met to develop codes of conduct and best practices for DIYBIO operations. Creating an open and shared community with mechanisms in place to recognize and report attempts to utilize DIYBIO for nefarious purposes was deemed important to support a productive future for the DIYBIO community. A good working relationship exists between the DIYBIO community in the United States and the FBI, which monitors potentially nefarious and unsafe uses of the science. In addition, many members of the DIYBIO community have cultivated relationships among community, local, and state emergency first responders. Local

authorities have not yet sought to regulate DIYBIO through local ordinances, but efforts to impose such oversight can be anticipated soon.

The FBI also has accepted responsibility for educating community groups on acceptable thresholds of DIYBIO experiments and for what types of materials should be made available to conduct them. The FBI's outreach to the DIYBIO community was described as one aimed at protecting the community from real-world threats (e.g., those with nefarious intentions seeking knowledge or instruction) by promoting cooperation with local law enforcement. Community contacts (e.g., local law enforcement, building inspectors) also have been provided so local information (e.g., required adherence to codes, fire, or safety measures) relevant to proper oversight of safety as community laboratories are developed.

It was noted that the DIYBIO community strives to operate under the safest practices possible and certain groups (e.g., Genspace, Biocurious) have established biosafety advisory boards that must approve projects prior to their commencement. Such approvals often are based on meeting prescribed standards of safety. Because developing a working laboratory that emulates standards of a university laboratory requires large investments of time and money, stakeholders in community laboratories are motivated to promote safety to protect their investments. The DIYBIO community has partnered with the American Biological Safety Association (ABSA) to launch a program that addresses operating safety questions (e.g., how to best dispose of experimental starting materials and products, or how to know whether equipment was decommissioned properly and is safe to use in new experiments). These guidelines are being implemented and could be considered more stringent than regulations in university laboratories.

The DIYBIO community is developing links with biosafety officers to teach best safety practices and foster ongoing dialogues as the technologies develop. However, it was noted that regulations requiring adherence to best-practice or safety recommendations do not generally exist and cases were cited in which advice from biosafety officers was not heeded. While it was argued that improvements have been made in following best-safety practices, it was recognized that there would always be outliers. The ideas that emerged from the two DIYBIO organized congresses (one in Europe and one in the U.S.) were similar with respect to attitudes on open access and safe operating practices, indicating a unity of thought in the global DIYBIO community.

Many DIYBIO community labs have agreed to operate at Biosafety level 1 (BSL-1), but it was predicted there will be efforts to operate at BSL-2, which involves agents of moderate potential hazard to personnel and the environment. Such a change will require addressing additional biosecurity concerns which are not yet

fully understood by the DIYBIO community. While any BSL-2 experimentation with pathogens poses significant safety concerns, it was noted that there is no known work with pathogens being performed in the DIYBIO community.

The technical capabilities of the DIYBIO community are not as advanced as the level implied by some elements of the media (e.g., linking DIYBIO to potential release of engineered H5N1 influenza virus). Even if such technical capabilities existed, any dangerous uses would be considered criminal activity, and any individuals with nefarious intentions would not be included in or supported by the DIY community.

Skepticism was expressed regarding the use of the term "community" to describe those participating in DIYBIO, since many practitioners undertake synthetic biology outside organized groups or laboratories. Federal endorsement for this community (i.e., through grant awards) could have repercussions, including perceived validation of what could be considered a "free-for-all" science.

It was noted that individuals who had been conducting experiments on their own are trending toward more collaborative efforts at community laboratories. This trend was attributed to limitations in working individually or in smaller groups and the perceived advantages of participating in community laboratories (e.g., access, group work, better equipment). While models of operation, codes of conduct, and safety consultation programs have been developed to aid those who are engaging in DIYBIO in community laboratory settings, it was considered important to implement programs for those conducting experiments outside of formalized groups.

Concerns were raised that some level of control and freedom would be lost if community college laboratories were utilized. While there would be positive implications for college recruitment, there would need to be acceptance from the community and controls to assure safety. It was mentioned that different groups within the DIYBIO community could have different levels of willingness to accept federal funding if it altered whether they would still be classified as DIYBIO.

Scientific opportunities and challenges

One perceived benefit of the DIYBIO community was increased public acceptance of advances in science (e.g., GMOs), which would be particularly useful in Europe. Community laboratories provide a niche that allows younger generations to experiment and therefore, serves a critical role in public education that university laboratories likely could not offer. Targeted outreach to a younger demographic group could foster a generation that is more aware of the advances in synthetic

biology and science in general and thus, is more likely to view these advances favorably.

The existence of community laboratories outside the regulatory structure was debated. Since community laboratories in the U.S. and in Europe are partnering with universities to receive permits for genetic experimentation, it was suggested that regulated laboratories could be established for members of the DIYBIO community.

Because regulations can be circumvented as has been seen in other areas (e.g., drug trafficking, pirating), attempts to prevent or delay DIYBIO were described as futile. Restrictions also could result in a technological shift to less-regulated countries (e.g., Brazil, India). A survey of the larger groups regarding their attitudes toward an oversight system would be helpful in understanding what would be required to ensure that experimentation continues to occur openly and is not driven underground. The potential of the DIYBIO community to move to BSL-2 was described to be of serious concern and therefore requires external oversight. While the DIYBIO community laboratories likely will be regulated, it would not be possible to regulate individual experimentation outside of a community laboratory.

The DIYBIO community's endorsement of developing nonstandardized synthetic biology diagnostic testing (e.g., testing for a genetic predisposition) was of concern, given the number of people who have suffered adverse consequences from such amateur efforts (e.g., not seeking treatment for a false negative result). Proponents for the development of DIYBIO diagnostics argued that such activity would not bypass diagnostic systems developed through medical establishments, and such efforts primarily are motivated by personal curiosity about such tests. The real challenge of DIYBIO diagnostic testing is how the medical establishment approaches those who have self-diagnosed. Diagnostic testing was described as a continuum that was moving toward home testing and personalized medicine. However, while formally developed home tests follow standards, DIYBIO diagnostics likely would continue to be developed standards were put in place or not. It was noted that most community laboratories do not allow for diagnostics development, and therefore, a distinction needs to be made between more visible and established community laboratories, and individuals working in private.

Policy issues

It was argued that an oversight system for DIYBIO could be created at the state or local level, but was far more likely to exist at the state level. Basic oversight would include a licensing system that certified some level of competence prior to allowing practice, similar to driving a car.

There was concern that community laboratories are able to perform experiments without the approval process required for other scientific groups. The current regulatory system requires an approval system that is compatible with the realities of experimentation, and places boundaries on what DIYBIO groups are experimentally initiated.

Future liability related to DIYBIO endorsement of certain practices (e.g., developing diagnostics that could present false negatives or false positives) was weighed against the potential educational benefit that DIYBIO could provide. Calls were made for an immediate analysis or review to prevent threats that could create demands from the public to terminate the DIYBIO community and for the development of a framework to deal with any potential threats.

While biosafety advisory boards have been implemented in some DIYBIO settings to ensure safe operations and bolster public confidence, it was agreed that some mechanism or policy must be developed to limit liability in the case of genuine mistakes. In addition, the DIYBIO community should not be held responsible for someone outside the community (but practicing DIYBIO) engaging in criminal activity. Backlash against such an action could lead to excessive regulations to counter the increased perceptions of risk.

The DIYBIO community was characterized as a network of responsible individuals, many of whom come from International Genetically Engineered Machine (iGEM) competition teams. Some of the community consists of amateurs, but the majority are leaders in the field. The future success of the DIYBIO community would require continued mentorship and guidance from these leaders.

A main issue raised was whether governments should fund DIYBIO. Government funding comes with the responsibility that taxpayer money is spent on projects that are consistent with government policies and priorities. Requirements in the form of regulations and qualifications are routinely attached to federal funding to prevent inappropriate spending. Government funding or grants for DIYBIO could be formalized for the purpose of utilizing the educational benefits provided by DIYBIO community (e.g., use of community laboratories as a node to teach more people about biotechnology). Even a small grant (e.g. $5,000) would be useful for many community groups (e.g., Genspace).

It was widely agreed that community colleges were appropriate venues for overseeing and controlling the creation of community DIYBIO laboratories that might qualify for certain types of government funding (e.g., National Science Foundation grants). Such funding might not require the same restrictions that university laboratories have concerning who can participate (i.e., enrolled students only). Community colleges conversely might be interested in partnering with the

DIYBIO community to gain equipment that could improve technician-training courses.

It was agreed that the DIYBIO community should register with a federal department to prevent illegal experimentation (e.g., working with pathogens). Registration could also improve access to types of materials for the DIYBIO community. Mechanisms could be implemented to encourage registration and prevent unregistered experimentation.

It was suggested that a peer-review system is needed to address the quality of results from DIYBIO experimentation. Such peer review would help prevent flawed testing or unsupportable results from being published. While there are mechanisms for testing validity within the DIYBIO community, it was agreed that there is no system in place to verify DIYBIO experiments outside of the community. Controlling potential propagation of noncertified results was deemed important for future consideration.

Governance of Synthetic Biology**

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Summary

Synthetic biology is … biotechnology. From a policy perspective, synthetic biology is a new set of methods for genetic engineering that offers new opportunities, brings several new challenges, and just as important, does little to alter the controversies that have surrounded the use of biotechnology for the last several decades.

I will first review the current governance of synthetic biology and biotechnology to address five key societal concerns: 1. biosecurity, 2. laboratory biosafety, 3. harm to the environment, 4. human health, and 5. ethical issues. I then briefly discuss the potential benefits and risks to society, and finally, present some governance options for policy makers to consider.

Current realities

Over the past eight years, the J. Craig Venter Institute (JCVI), in collaboration with several other institutions, has examined a broad range of societal issues raised by synthetic biology with a view to disentangling the set of concerns that are either **unique to synthetic biology,** or where the use of synthetic biology **significantly adds to societal concerns about the use of biotechnology** in general. Our goal has been to identify governance options that address the new issues raised by, or significantly changed by, this next-generation biotechnology. To provide context, I will first review current governance of synthetic biology in the United States.

Biosecurity was the first societal concern related to synthetic biology to reach the attention of policy makers, beginning with the synthesis in 2002 of an infectious polio virus constructed in the laboratory directly from nucleic acids by Eckard Wimmer and colleagues. The paper demonstrated for the first time in a post-September 11 world the feasibility of synthesizing a complete human pathogen using only published DNA sequence and mail-ordered raw materials.

Over the following decade, two governance activities have been most significant. In 2004, the U.S. National Institutes of Health (NIH) established the National Scientific Advisory Board for Biosecurity (NSABB), a federal advisory

committee chartered to provide advice about "dual-use" biological research (i.e., legitimate research that might also be misused for nefarious intent), including synthetic biology. The NSABB functions at the national level; there are no requirements for individual research institutions to establish mechanisms to review the dual-use implications of the research undertaken by their scientists, though some do. In 2010, the U.S. Department of Health and Human Services (HHS) published the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA,* with the goal "to minimize the risk that unauthorized individuals or individuals with malicious intent will obtain 'toxins and agents of concern' through the use of nucleic acid synthesis technologies." It is now standard practice for suppliers of synthesized DNA to screen orders to see if they contain dangerous "sequences of concern" and to make sure their customers are legitimate research users.

Biosafety concerns related to genetic engineering research have been under the purview of the NIH since 1976, when the agency first issued the *NIH Guidelines for Recombinant DNA Research*. Though the NIH retains some oversight responsibility at the federal level, most is delegated to Institutional Biosafety Committees (IBCs) required at institutions that receive government funding. The *NIH Guidelines* have been revised frequently since that time to stay current with the evolving science. The next revision, which will take effect in March 2013, is the first that will explicitly address synthetic biology research and will be renamed *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. Other than making clear the *NIH Guidelines* apply to research with synthetic biology, as well as recombinant DNA, few substantive changes were made.

Commercial products that might cause harm to the environment or human health are regulated by a long list of federal laws and regulations. The oversight and regulatory framework in the United States for products developed using biotechnology stems from the 1986 *Coordinated Framework for Regulation of Biotechnology*. The *Coordinated Framework* assigned primary responsibility for regulating the products of biotechnology to three agencies: the Food and Drug Administration (FDA), the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA), using an array of laws in place at the time. Figure 1 summarizes the products that are regulated, by which agency, and under what law, as well as the societal risks addressed.

Ethical issues related to synthetic biology were reviewed by the Presidential Commission for the Study of Bioethical Issues. The 2010 study, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, recommended that the government "remain forward-looking about the potential benefits and risks to the public," but did "not recommend that additional agencies or oversight bodies need to be created to oversee synthetic biology."

Opportunities and challenges

Synthetic biology combines methods for the chemical synthesis of DNA with computational techniques for DNA design. These new techniques have the potential to accelerate scientific and technological progress in a variety of areas: from basic research to understand how living cells function, to biofuels to power our cars, and to high-value pharmaceuticals, including vaccines to respond quickly to emerging threats.

However, these advancements present several new challenges. Synthetic biology can be dual-use: in addition to useful advances for society, it provides those with nefarious intent new ways to harm. Improvements in the speed and cost of DNA synthesis are also opening the field to new participants (e.g., engineers and computer scientists). This influx of new practitioners must be trained to work safely in the lab.

The public will likely expect that any living organisms modified by synthetic biology and intended for market will first be reviewed for possible adverse effects to the environment or human health. Though the *Coordinated Framework* for the regulation of products of biotechnology has been in place for more than 25 years, it is still controversial. Known harms to the environment or human health from introduced products have been minimal. However, some view our current system as too lax, others as too burdensome. But two areas appear particularly challenged by the new technology: many plants modified using synthetic biology techniques may no longer be covered by USDA rules, and the increasing number and diversity of microbial products that synthetic biology will enable will likely create a challenge for the EPA.

Policy issues

Biosecurity

- Current HHS Guidance for screening synthetic nucleotides applies to providers of synthetic double-stranded DNA. Similar guidance could be

directed to providers of oligonucleotides (single-stranded nucleotides), from which pathogenic viruses can also be constructed (though with greater difficulty, and with greater technical challenges for affected companies).

- The currently mandated roles and responsibilities of IBCs could be broadened to include review of dual-use research of concern. IBCs would continue to carry out the duties outlined in the *NIH Guidelines* but with review expanded to consider dual-use concerns.

Biosafety

- NIH and the Centers for Disease Control and Prevention (CDC), which currently publish the "gold-standard" lab biosafety manual, could prepare a companion manual for biosafety in synthetic biology laboratories, geared to the background and needs of the new generation of synthetic biologists.

Harm to the Environment

JCVI's ongoing review of the *Coordinated Framework for Regulation of Biotechnology* has identified two key challenges:

- **USDA's current rules will not cover many plants modified using synthetic biology techniques.** Newer plant technologies, including synthetic biology, will be less likely to use plant pests during the transformation process and so largely will not be subject to the assessment process that has been a staple of traditional biotechnology regulation. Options to address this gap include:
  - No action: APHIS maintains a voluntary assessment process for genetically modified plants, but review is required for only those organisms with a potential to be plant pests.
  - APHIS incorporates its noxious weed authorities into biotechnology regulation to add another significant risk to ecosystem health.
- **The increasing number and diversity of microbial products that synthetic biology will enable will likely create a challenge for the EPA.** The Toxic Substances Control Act (TSCA), the primary law governing commercial, genetically engineered microorganisms, was not intended for this purpose and in the view of some, is ill-suited to be the primary regulatory mechanism, particularly as the number of microbes requiring assessment increases. Options to address these challenges include:

- Congress ensures that the EPA is given sufficient resources to adequately undertake the regulatory reviews needed to evaluate the risks posed by commercial microbial products engineered using synthetic biology techniques or, more aggressively, amends the TSCA to strengthen the EPA's ability to regulate such microbes.
- EPA develops a voluntary assessment process for noncommercial microbes, which are currently exempt from regulation.

References

Garfinkel, M.S., Endy, D., Epstein, G.L., & Friedman, R.M. (2008) *Synthetic Genomics: Options for Governance*. Rockville, MD: The J. Craig Venter Institute. Retrieved from http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf

*** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) Dec. 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.***

Figure 1: Biotechnology products are largely regulated based on the following regulatory definitions; synthetic biology products will meet many of these same definitions. Each applicable statute has a main focus; the application of authorities are displayed based on potential risks both within and outisde of that main focus.

Product type	With this characteristic	Meets this definition	Main focus for decision making under applicable statute	Authority to test and assess potential risks (pre-market)	Authority to restrict use or marketing based on potential risk	Authority to address post-market concerns	Authority to test and assess potential risks (pre-market)	Authority to restrict use or marketing based on potential risk	Authority to address post-market concerns
				For impacts within focus			For impacts outside focus		
Any product, including modified plants, animals, and microbes	That will be used as a pesticide or to produce pesticides	Pesticide or Plant-incorporated protectant (EPA/FIFRA)	Human, animal & ecosystem health						
	That will be used as a drug or to produce drugs	Drug or Animal Drug (FDA/FDCA)	Human & animal health				NEPA only		
	That will be used as a food and is not generally recognized as safe	Food additive (FDA/FDCA)	Human & animal health				NEPA only		
	That will be used as or will produce a dietary supplement	Dietary Supplement (FDA/FDCA)	Human & animal health						
	That will be used as or produce a cosmetic	Cosmetic (FDA/FDCA)	Human & animal health						
Any modified organism	That will be used as a food and is generally recognized as safe	"GRAS" and "substantially equivalent" (FDA/FDCA)	Human & animal health	voluntary process					
	That incorporates DNA sequences from a known plant pest	Regulated Article (APHIS/PPA)	Plant health				NEPA only		
Any intergeneric microorganism	That is used for any commercial purpose not listed above	Intergeneric microorganism (EPA/TSCA)	Human, animal & ecosystem health						
Any gene(s) inserted into an animal	That will be used for any purpose	Animal drug (FDA/FDCA)	Human & animal health				NEPA only		

No authority
Limited or uncertain authority
Demonstrated Authority

Acronyms: APHIS (Animal and Plant Health Inspection Service), EPA (Environmental Protection Agency), FDA (Food and Drug Administration), FDCA (Federal Food, Drug, and Cosmetics Act), FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act), GRAS (Generally Recognized as Safe), NEPA (National Environmental Protection Act), TSCA (Toxic Substances Control Act)

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Robert Friedman (see above). Dr. Friedman initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Friedman. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Friedman, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- In general, the current governance framework for synthetic biology is largely appropriate for the technology at this time, because even though the definition of synthetic biology is still debated, the premise that it is part of biotechnology is generally accepted
- While the regulatory burden for the Environmental Protection Agency related to products from synthetic biology is manageable in the near term, it is critical that Congress acts to supplement the resources of the agency or to augment its regulatory authority in the longer term.
- The term "synthetic biology," and specifically the word "synthetic," has a negative perception with nonscientists. While the term seems to be entrenched and unlikely to change, scientists need to be sensitive to this perception.
- Because regulation of synthetic biology and its products necessarily spans a spectrum of governmental agencies, there is a recognized need to create interagency cooperation and communication.

Current realities

Significant discussions centered on the importance of understanding the historical context of regulation of synthetic biology in the United States. Governance of biotechnology dates back to the mid-1970s when the National Institutes of Health

(NIH) first issued the *Guidelines for Recombinant DNA Research*, with a focus on laboratory biosafety and containment. In the 1980s, serious consideration of the governance of the biotechnology products (and not just the process) was undertaken. In 1986, the *Coordinated Framework for Regulation of Biotechnology* was enacted, which assigns primary responsibility for the regulation of biotechnology products to three agencies: the U.S. Food and Drug Administration (FDA), the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) and the U.S. Environmental Protection Agency (EPA). In the 1990s, the Presidential Bioethics Commission was initiated to provide a discussion forum and publication avenue for ethical issues raised by some of the products of biotechnology.

Synthetic biology was recognized as bringing new regulatory and governance challenges as compared with the more traditional recombinant DNA technologies. Specifically in the field of biosecurity, the U.S. government established in 2004 the National Science Advisory Board for Biosecurity (NSABB) to examine dual-use biological research. In 2010, U.S. government guidance was issued to companies that sell synthetic double-stranded DNA. Lastly, a new revision of the NIH Guidelines that applies to both recombinant DNA and to synthetic DNA was anticipated for release in March 2013. While there was consensus that these steps represent significant progress, it was also agreed that there will always be new issues surrounding synthetic biology to consider.

Clarification was requested on the details of the National Environmental Policy Act (NEPA), which was written in the 1970s. It was explained that, although the EPA came into existence at approximately the same time as NEPA, the agency is not governed by the legislation. Thus, the need for EPA approval does not trigger a NEPA analysis. However, undertaking any other major federal agency action (e.g., building a bridge, building a road, or initiating a field trial for genetically engineered mosquitoes) would require an environmental assessment. Within the conditions of use section of the application prepared by the sponsor, the agency evaluates the probability of a significant impact on the human environment in the United States. Upon completion of this assessment, one of two alternatives is generally taken. First, the agency can determine that there are no extraordinary circumstances and grant categorical exclusion. Second, if it is ruled that there are extraordinary circumstances (e.g. first of its kind, or the agency does not have sufficient experience or expertise in the area), then an environmental assessment may be required. At the end of that environmental assessment, a finding is made as to whether there is a significant environmental impact. The agency also has the option to release any environmental assessment as a draft for public comment.

The issue of communication among federal agencies prompted a suggestion that a new agency may be needed for the review and approval of synthetic biology products. A counter-proposal outlined the need to increase synthetic biology skills within the agencies, as well as the need to increase interagency coordination and communication. Genetically engineered salmon was an example of the need for and the ability of agencies, particularly the EPA and the Fish and Wildlife Service, to work together. A brief explanation of the *Coordinated Framework for the Regulation of Biotechnology*, written in 1986, acknowledges that all the agencies should regulate to about the same level of rigor if there is an action involved. Thus, if an agency lacks sufficient expertise from within, it may declare another agency as the lead agency with respect to statutory authority for making a decision. The actual review team may also enlist experts from other agencies, which is what is occurring with the review of genetically engineered mosquitoes.

Perceptions around terminology, specifically the word "synthetic," were acknowledged as being perhaps benign for scientists, yet having negative implications for the general public and policy makers. A question was raised as to whether it was too late to change the term, or "re-brand" the technology. Focus groups have been assembled to gather reactions to the term "synthetic biology" and these exercises were expected to generate reactions about "playing God" and "creating life." However, the focus group participants fixated on the word "synthetic," and linked it to synthetic chemicals, which were perceived as negative and capable of destroying the environment and creating significant pollution.

Scientific opportunities and challenges

Areas of societal concern, specifically human health and ethical issues, were discussed. It was noted that the President's Commission on Bioethics (PCB) has thus far chosen not to make any recommendations in this area. However, the PCB also suggested that the use of novel synthetic organisms and cell therapies of mixed microbial origins may have unanticipated or delayed immunological response issues, as well as the potential for synthetic biology organisms to reproduce or evolve. A new discussion about combining bioethics and engineering ethics, both of which have a significant impact on human health aspects and on new ethical issues, may be useful.

The increasing number and diversity of microbial products that synthetic biology will enable, and the concomitant regulatory challenges that this increase presents for the EPA was discussed. Possible solutions include that Congress ensure that EPA is given additional resources to enable the agency to undertake the regulatory reviews associated with these new microbial products, or that Congress

amend the Toxic Substances Control Act (TSCA) to augment the regulatory authority of the EPA in this arena. However, there was also strong agreement that neither of these solutions was likely to be implemented in the short term. From a synthetic biology product pipeline perspective, the regulatory burden may be manageable for a few years.

New mechanisms for internal controls, codes, and practices may help researchers, both from industry and academia, avoid a catastrophic, "bad news event," or other impediments to the continued development of synthetic biology. This issue is of prime importance in the private sector. Protection of the process of innovation by managing and communicating some of the risks in a proactive way internally and externally to the public may actually avert a major public relations crisis or reduce the need for direct government control. There seemed to be general agreement that this suggestion would be a positive step for industry and academic researchers.

In addition to the regulatory agencies, it was noted that many other agencies that do not have regulatory authority may also play a role in the evaluation and advancement of synthetic biology and related technologies. As to what these agencies should be focusing on, one area readily identified was risk assessment, especially the evaluation of whether the risk is based on scientifically credible information and objective assessment. Another possible focus area was the continued support of the basic scientific research that is ancillary to synthetic biology, but is necessary to be able to bring good products to market. One such area of basic research briefly discussed was the example of microbial ecology.

Performing risk assessments for synthetic organisms raised many issues. Over several decades, studies have included gene transfer in soil samples from an engineered microbe into strains that represent natural microbes, and direct testing of "kill switches" in a variety of biosystems, including sea water and rats. There are precedents for the types of experiments that lead to risk assessment of the biosafety consequences, and there is already limited data that may be useful in assessing risks for living cells. While it was agreed there is a body of literature in this area, and that there is an understanding of some basic principles, there is still much that is unknown, both from a scientific and policy perspective. As an example, it is still unclear exactly what the EPA and the general public may consider adequate from a risk assessment perspective. It was noted that the EPA has limited experience in this type of work (approximately 35 to 40 cases), but that the USDA has considerably more experience and expertise and thus may be a good resource for the EPA.

A question was raised, based on the current policy and governance framework, as to what challenges the U.S. government faces related to synthetic biology

experiments and the ramifications of the technology, especially related to dual-use. The example was of the potential development of a microbe that is accelerated for environmental cleanup of oil spills, but which may also be used to wipe out strategic petroleum deposits. It was acknowledged that, while the NIH and other agency guidelines delineate requirements to consider, only a collaborative review effort among a broad spectrum of scientific experience and thinking will result in an effective evaluation of such experiments.

The ability to perform customer and sequence screening during the routine course of work was acknowledged as a useful and reasonable undertaking. However, this screening has the potential to be a significant bottleneck during a crisis situation, such as an outbreak that occurs on a holiday or over the weekend. While this was recognized as a challenge, advance communication, as well as requests coming from known, legitimate sources, were offered as tools to mitigate this type of situation.

The role of institutes and other stakeholders in bringing about regulatory innovation in governments was discussed. The example of institutes working with the FBI on security issues surrounding synthetic biology was noted as a successful experiment, and the question was raised as to how this success could be replicated. More institutes need to encourage and fund employees who consider the social and political implications of their organization's research, and to work with scientists. This type of engagement could come to be seen part of the responsibilities of individual scientists, universities, industries, and research organizations.

Policy issues

Although synthetic biology is regulated by the same laws, regulations, and other governance mechanisms that currently are applied to other biotechnology efforts, it must be recognized that any emerging technology may pose novel and possibly unique challenges to the existing regulatory framework. Policy makers must appropriately address these challenges to meet five key societal concerns: biosecurity, laboratory safety, harm to the environment, human health, and ethical issues. It is critical that any new or modified regulation undertaken by policy makers also considers the balance of these societal concerns with the potential and actual benefits that may be produced through synthetic biology.

There is currently no jurisdiction over the voluntary assessment for noncommercial microbes and the usefulness of such an assessment was discussed. A key policy question concerns the anticipation of harm, as well as the audience or user of the information that may be gathered. While there was no direct conclusion,

it was recognized that this proposed voluntary assessment was a minor suggestion to fill a perceived gap.

The question remained whether synthetic biology is just biotechnology, or something radically different, as it incorporates new concepts of life and opens new paths of innovation. While the processes and methods are viewed as novel and in some aspects unique, the products of synthetic biology are less novel and can actually be largely identical to products generated by more traditional means. However, plant biotechnology could possibly be entering a new stage in its regulatory oversight, which may be triggered because, for historical reasons, the existing regulations address the process rather than the product. Examples were noted in both the U.S. and Europe of such regulation. It was stated that when regulation focuses on process, a technology change, perhaps unintentionally, requires a regulatory change. An important policy consideration was discussed as to whether, even in the absence of increased risk, such changes in regulation were beneficial, even though they were obviously necessary. It was concluded that consideration of synthetic biology as "just biotechnology" may result in regulatory flexibility with little or no increased risk.

The policy suggestion that the U.S. Department of Health and Human Services (HHS) issue guidance for screening synthetic nucleotides to be directed to providers of oligonucleotides (single-stranded nucleotides, from which pathogenic viruses may be assembled), was debated. Oligonucleotide manufacturers currently operate on such thin profit margins that it may be problematic to require such order screening, which may bolster the argument for outside funding of a screening database. However, even in a highly competitive business environment, there are several regulatory burdens that are absorbed as market conditions, if imposed evenly among all suppliers. It was noted that this level playing field may inadvertently supply foreign oligonucleotide providers with a competitive advantage.

The question was raised whether the FDA can rule on DNA-based or whole-cell based therapeutics. One view was that any therapeutic agent that enters the body, whether it is a whole cell to kill a tumor or DNA inserted into a cell, will be appropriately regulated by the FDA. There was strong concurrence that this view was correct. However, it was undecided whether the agency currently has the appropriate skill sets and experience needed to regulate these products.

The difference between a synthetic biological and a product produced using synthetic biology techniques was discussed. These two products could be regulated, or at least considered, in different ways. The primary distinction noted was that, if

an end product is novel and different, the regulatory and perception hurdles would naturally be higher. However, if a product is the same as an existing product, but was produced in a less expensive or faster way, the current governance framework may be more applicable. The example of generic drugs was offered, noting that if a generic drug is sent to FDA for approval and bioequivalence is shown, it is approved with little or no scrutiny applied to the process through which it was produced.

Acknowledgment

Numerous individuals and organizations have made important contributions to the Institute on Science for Global Policy (ISGP) program on 21st Century Borders (21CB). Some of these contributions directly supported the efforts needed to organize the invitation-only ISGP conference on *21CB/Synthetic Biology (SB): Focus on Responsibility and Governance* convened in cooperation with the University of Arizona at the El Conquistador Hotel and Resort in Tucson, Arizona, December 4–7, 2012. Other contributions aided the ISGP in preparing the material presented in this book, including the eight policy position papers and the summary record, without attribution, of the views presented in the discussions, critical debates, and caucuses that ensued.

We would specifically like to thank our colleagues at the University of Arizona, and especially Dr. Eugene Sander, former President, and Deans Shane Burgess (College of Agriculture) and Joaquin Ruiz (College of Science) for their many, critical contributions toward the success of this conference.

The ISGP greatly appreciates the willingness of those in the scientific and policy communities to be interviewed by the ISGP staff, who organized the content of this ISGP conference. The efforts of the scientific presenters with expertise in SB invited by the ISGP to both prepare the eight policy position papers and engage policy makers in the vigorous debates and caucuses that comprise all ISGP conferences were especially appreciated. The biographies of these authors are provided in this ISGP book

The success of every ISGP program critically depends on the active engagement of all invited participants in the often-intense debates and caucuses. The exchange of strongly held views, innovative proposals, and critiques generated from questions and debates fosters an unusual, even unique, environment focused on clarifying understanding for the nonspecialist by addressing specific questions related to formulating and implementing effective public and private sector policies. The ISGP is greatly indebted to all those who participated in these not-for-attribution debates and caucuses.

The ISGP Board of Directors also deserves recognition for their time and efforts in helping to create a vital and growing not-for-profit organization that has relevance to many of the most important questions of our time. The current

membership of the ISGP Board of Directions and their brief biographical backgrounds are presented at the end of this book.

The energetic, highly professional work of the ISGP staff merits special acknowledgment. Their outstanding interviewing, organizing, and writing skills were essential to not only convening the conference itself, but also to recording the often-diverse views and perspectives expressed in the critical debates, capturing the areas of consensus and actionable next steps from the caucuses, and persevering through the extensive editing process needed to assure the accuracy of the material published here. All of their work is gratefully acknowledged. Their biographies are provided in this book.

ISGP programs are financially supported by government agencies and departments and through gifts from private sector entities and philanthropic individuals. Specifically, the ISGP conference in Tucson, Arizona, received funding from the U.S. Department of Health and Human Services (HHS), the U.S. Department of State (DOS), and the U.S. Department of Homeland Security (DHS) under a 'work for others' arrangement between the HHS and the ISGP. Financial support from the National Intelligence Council (NIC), Federal Bureau of Investigation (FBI), and the Istituto Regionale di Ricerca in Milan, Italy, was also provided to the ISGP. The ISGP also benefited greatly from generous gifts provided by the MARS Corp., Novartis, GlaxoSmithKline, and Mr. and Mrs. Edward Bessey. Finally, the ISGP gratefully acknowledges the ongoing administrative support provided by the Critical Path Institute.

Dr. George H. Atkinson
Founder and Executive Director
Institute on Science for Global Policy
January 29, 2013

ISGP books from previous ISGP conferences listed below are available to the public and can be downloaded from the ISGP Web site: www.scienceforglobalpolicy.org.

ISGP conferences on Emerging and Persistent Infectious Diseases:

- EPID: Global Perspectives, convened Dec. 6–9, 2009 in Tucson, Arizona, U.S.
- EPID: Focus on Surveillance, convened Oct. 17–20, 2010 in Warrenton, Virginia, U.S.

- EPID: Focus on Prevention, convened June 5–8, 2011 in San Diego, California, U.S.
- EPID: Focus on Mitigation, convened Oct. 23–26, 2011 in Edinburgh, Scotland, U.K. at the University of Edinburgh.
- EPID: Focus on Societal and Economic Context. Convened July 8-11, 2012 in Fairfax, Virginia, U.S. at George Mason University

Biographical information of Scientific Presenters

Dr. Drew Endy, Ph.D.

Dr. Drew Endy is an Assistant Professor of Bioengineering at Stanford University. He teaches in the new Bioengineering major at Stanford and previously helped start the Biological Engineering major at MIT. His Stanford research team develops genetically encoded computers and redesigns virus genomes. Dr. Endy co-founded the BioBricks Foundation as a public-benefit charity supporting free-to-use standards and technology that enable the engineering of biology. He co-organized what has become the International Genetically Engineered Machines (iGEM) competition and the BIOFAB: International Open Facility Advancing Biotechnology (BIOFAB). *Esquire* magazine named Dr. Endy one of the 75 most influential people of the 21st century. He serves on the U.S. Committee on Science Technology and Law and is a new member of the National Science Advisory Board for Biosecurity. He chaired the 2003 Synthetic Biology study as a member of the DARPA Information Science and Technology Study Group. He has served as an ad hoc member of the NIH Recombinant DNA Advisory Committee and co-authored the 2007 "Synthetic Genomics: Options for Governance" report with colleagues from the Center for Strategic and International Studies and the J. Craig Venter Institute.

Ms. Leili Fatehi, J.D.

Ms. Leili Fatehi is a Research Fellow in the Science, Technology, and Environmental Policy program area at the Hubert H. Humphrey School of Public Affairs at the University of Minnesota. She is also an Adjunct Associate Professor of Law at the University of Minnesota Law School. Her current research interests include the legal, ethical, and policy dimensions of synthetic biology, genetics, and human enhancement technologies. Ms. Fatehi has participated in several grants related to issues of law and ethics in emerging sciences and technologies, including grants from the National Science Foundation and National Institutes of Health. Prior to joining to the Humphrey School, Ms. Fatehi was Associate Director of Research and Education at the University of Minnesota's Consortium on Law and Values in Health, Environment & the Life Sciences and Joint Degree Program in Law, Health & the Life Sciences. From 2005-2007, Ms. Fatehi was a Research Associate at

Meridian Institute in Washington, D.C., where she researched and published on the implications of nanotechnology for the world's poor.

Prof. Paul Freemont, Ph.D.

Prof. Paul Freemont is cofounder and codirector of the Engineering and Physical Sciences Research Council (ESPRC) Centre for Synthetic Biology and Innovation at Imperial College London. Additionally, he is the Head of the Division of Molecular Biosciences and Chair of Protein Crystallography at the university. He previously was Director of the Centre for Structural Biology, also at Imperial College London. His research on synthetic biology involves developing an engineering framework and new technology platforms to enable synthetic biology research in areas of bioenergy, biosensors, biomaterials, and metabolic engineering. He also maintains an interest in understanding how disease-linked proteins work at the molecular level. Prof. Freemont is a member of the CRUK Biological Sciences funding committee including external five-year reviews, an external review member of several UK Biosciences Departments, and a member of Biotechnology and Biological Sciences Research Council pool of experts. Prof. Freemont has previously been a member of the Wellcome Trust Genes Molecules and Cells panel, a member of the Wellcome Trust fellowships panel, and a member of the Royal Academy of Engineering Synthetic Biology inquiry. Prof. Freemont has published more than 140 peer-reviewed articles and has appeared regularly on radio and television broadcasts on the subject of synthetic biology.

Dr. Robert Friedman, Ph.D.

Dr. Robert Friedman was recently appointed the Chief Operating Officer at the J. Craig Venter Institute. Dr. Friedman also maintains his prior appointment as the Deputy Director for California at the Venter Institute, where he directs the JCVI Policy Center and is also active in several ongoing projects in the Institute's Environmental Genomics Group. Prior to joining the Venter Institute, Dr. Friedman was Vice President for Research at The Heinz Center, a nonprofit policy research organization that brings together collaborators from government, industry, environmental organizations, and academia. Earlier, Dr. Friedman was a Senior Associate at the Office of Technology Assessment, U.S. Congress (OTA). For 16 years, he advised congressional committees on issues involving environmental and natural resources policy. He is a Fellow of the American Association for the Advancement of Science.

Prof. Eliot Herman, Ph.D.

Prof. Eliot Herman is Professor in the School of Plant Sciences at the University of Arizona. Previously, he was Adjunct Professor in the Division of Plant Sciences at

the University of Missouri, a member of the Donald Danforth Plant Science Center, and a Molecular Biologist with the U.S Department of Agriculture/ Agricultural Research Service (USDA/ARS). Prof. Herman's research interests span the disciplines of biochemistry, physiology, cell and developmental biology, genomics, bioinformatics, and systems biology. Prof. Herman is a member of the American Society of Plant Physiologists, the American Society for Biochemistry and Molecular Biology, the Japanese Society of Plant Physiology, Sigma Xi, the American Society for Cell Biology, and the American Society of Oil Chemists. He is on the Editorial Board of PLANTA and, until 2012, was the Associate Editor for the Journal of Experimental Botany. Prof. Herman has held visiting fellowships at the Weizmann Institute in Israel, the Japanese Society for the Promotion of Science, and the U.S. Embassy in Sweden. In 2004 he was awarded the Plow Honor Award by the U.S. Secretary of Agriculture and in 2011 he was elected a Fellow of the American Association for the Advancement of Science.

Dr. Todd Kuiken, Ph.D.

Dr. Todd Kuiken is a Senior Program Associate for the Synthetic Biology Program at the Woodrow Wilson International Center for Scholars. In his current role, he collaborates with DIYbio.org on a project to ensure safety within the rapidly expanding community of amateur biologists and analyzes the potential biosecurity threats associated with such a diffuse community. In addition, he has numerous projects evaluating and designing new research and governance strategies to proactively address the environmental risks associated with synthetic biology. He also works with the Project on Emerging Nanotechnologies at the Woodrow Wilson Center, where he focuses on the environmental health and safety, and public policy aspects of nanotechnology. Dr. Kuiken previously worked at the Oak Ridge National Laboratory, where he studied the biogeochemical cycling of mercury, and for various environmental nonprofits. Dr. Kuiken is a regular speaker on public policy issues related to nanotechnology and synthetic biology and has published a number of articles on nanotechnology, synthetic biology, and mercury cycling.

Dr. Maria Mercedes Roca, Ph.D.

Maria Mercedes Roca is Associate Professor of Biotechnology at Zamorano University, Honduras. Dr. Mercedes Roca joined Zamorano in 1997 as a lecturer in plant pathology, following graduate studies in the United Kingdom. She holds master's and doctoral degrees in plant pathology and virology from the University of London, and a B.S. in microbiology from Kings College, London. Dr. Mercedes Roca has worked as a faculty exchange member at the Norman Borlaug Institute at Texas A&M University, and has organized conferences for the Caribbean Division

of the American Phytopathological Society, and the International Conference on Agriculture and Environment. She is an adviser to the Honduran government on agricultural biotechnology regulation, and was a member of the Honduran delegation to the Rio+20 U.N. Conference on Sustainable Development in 2012.

Dr. Markus Schmidt, Ph.D.

Dr. Markus Schmidt is founder and CEO of Biofaction, a research, technology assessment, and science communication company based in Vienna, Austria. He has an educational background in electronic engineering (B.Sc.), biology (M.Sc.) and environmental risk assessment (Ph.D.). Dr. Schmidt has carried out environmental risk assessment, safety, and public perception studies in a number of science and technology fields. Since 2005, he has pioneered synthetic biology ethical, legal, and social implications (ELSI) research in Europe, being the principal investigator and manager of the European Commission-funded project SYNBIOSAFE, the first in Europe to look into the ethical, safety, security, and governance aspects of synthetic biology. Dr. Schmidt has published extensively on the societal aspects of synthetic biology, and edited and co-wrote two books about the societal consequences of synthetic biology (2009) and its industrial and environmental applications (2012). He served as an adviser to the European Group on Ethics (EGE) of the European Commission and the U.S. Presidential Commission for the Study of Bioethical Issues. In addition to his efforts in technology assessment, he aims to contribute to a better interaction between science and society through public talks, production of scientific documentary films, and the organization of Science Film Festivals (Bio:fiction) and art-science exhibitions (synth-ethic).

Dr. Amy Smithson, Ph.D.

Dr. Amy Smithson is a Senior Fellow at the James Martin Center for Nonproliferation Studies and the co-chair of the Global Agenda Council on Nuclear, Biological, and Chemical Weapons for the World Economic Forum. A specialist in biological and chemical weapons nonproliferation, to reduce threats she often recommends practical steps that blend technical and policy instruments and fashions untraditional issue alliances that cross the private and public sectors and international borders. She holds doctoral, master's, and bachelor's degrees in political science. Before joining CNS, Dr. Smithson worked at the Center for Strategic and International Studies, the Henry L. Stimson Center, and Pacific-Sierra Research Corporation. The author of numerous publications, including *Germ Gambits: The Bioweapons Dilemma, Iraq and Beyond* (Stanford University Press, 2011), she has appeared frequently before Congress and in the electronic and print media.

Biographical Information of ISGP Board of Directors

Dr. George Atkinson, Chairman

Dr. George Atkinson founded the Institute on Science for Global Policy (ISGP) and is an Emeritus Professor of Chemistry, Biochemistry, and Optical Science at the University of Arizona. He is former head of the Department of Chemistry at the University of Arizona and the founder of a laser sensor company (Innovative Lasers Corp.) serving the semiconductor industry. He also served in various capacities in the U.S. federal government as an adviser for the use of science in diplomacy, including as Science and Technology Adviser (STAS) to U.S. Secretaries of State Colin Powell and Condoleezza Rice. He launched the ISGP in 2008 as a new type of international forum in which credible experts provide governmental and societal leaders with the objective understanding of the science and technology that can be reasonably anticipated to help shape the increasingly global societies of the 21st century. Dr. Atkinson has received National Science Foundation and National Institutes of Health graduate fellowships, a National Academy of Sciences Post Doctoral Fellowship, a Senior Fulbright Award, the SERC Award (U.K.), the Senior Alexander von Humboldt Award (Germany), a Lady Davis Professorship (Israel), the first American Institute of Physics' Scientist Diplomat Award, a Titular Directorship of the International Union of Pure and Applied Chemistry, the Distinguished Service Award (Indiana University), an Honorary Doctorate (Eckerd College), the Distinguished Achievement Award (University of California, Irvine), and was selected by students as the Outstanding Teacher at the University of Arizona. In 2013, he became the president-elect of the Sigma Xi Society. He received his B.S. (high honors, Phi Beta Kappa) from Eckerd College and his Ph.D. in physical chemistry from Indiana University.

Loretta Peto, Secretary/Treasurer

Loretta Peto is the founder and Managing Member at Peto & Company CPA's PLLC. She has experience in: consulting on business valuation and litigation, including valuing businesses for buy-sell agreements, estate and gift tax, marital dissolution and employee compensation; consulting with closely held businesses regarding business restructure, cash management, succession planning, performance enhancement and business growth; and managing tax-related projects, including specialty areas in corporate, partnership, estate and gift tax, business reorganizations,

and multistate tax reporting. She is a Certified Public Accountant and accredited in Business Valuations. She is a member of the Finance Committee and Chair of the Audit Committee at Tucson Regional Economic Opportunities. She also is a member of the DM50 and Tucson Pima Arts Council. She received a Master of Accounting - Emphasis in Taxation degree from the University of Arizona in 1984, and was awarded the Outstanding Graduate Student Award.

Dr. Janet Bingham, Member

Dr. Janet Bingham has been President and CEO and a consultant to the Huntsman Cancer Foundation (HCF) since 2006. The foundation is a charitable organization that provides financial support to the Huntsman Cancer Institute, the largest cancer specialty research center and hospital in the Intermountain West. Dr. Bingham also has managed Huntsman Cancer Biotechnology Inc. In addition, she was appointed Executive Vice President and Chief Operating Officer with the Huntsman Foundation in 2008. The Huntsman Foundation is the private charitable foundation established by Jon M. Huntsman Sr. to support education, cancer interests, programs for abused women and children, and programs for the homeless. Before joining the Huntsman philanthropic organizations, Dr. Bingham was the Vice President for External Relations and Advancement at The University of Arizona. Prior to her seven years in that post, she served as Assistant Vice President for Health Sciences at The University of Arizona Health Sciences Center. Dr. Bingham was recognized as one of the Ten Most Powerful Women in Arizona.

Dr. Henry Koffler, Member

Dr. Henry Koffler is President Emeritus of the University of Arizona (UA). He served as President of the UA from 1982-1991. From 1982 he also held professorships in the Departments of Biochemistry, Molecular and Cellular Biology, and Microbiology and Immunology, positions from which he retired in 1997 as Professor Emeritus of Biochemistry. His personal research during these years concentrated on the physiology and molecular biology of microorganisms. He was Vice President for Academic Affairs, University of Minnesota, and Chancellor, University of Massachusetts/Amherst, before coming to the UA. He taught at Purdue University, where he was a Hovde Distinguished Professor, and the School of Medicine at Western Reserve University (now Case Western Reserve University). Dr. Koffler served as a founding governor and founding vice-chairman of the American Academy of Microbiology, and as a member of the governing boards of Fermi National Accelerator Laboratory, the Argonne National Laboratory, and the Superconducting Super Collider Laboratory. He was also a board member of the Association of American Colleges and Universities, a member and chairman of

the Council of Presidents and a member of the executive committee of the National Association of Land Grant Colleges and Universities. He was also Founder, President and board member of The Arizona Senior Academy, the driving force in the development of the Academy Village, an innovative living and learning community. Among the honors that Dr. Koffler has received are a Guggenheim Fellowship and the Eli Lilly Award in Bacteriology and Immunology.

Mr. Jim Kolbe, Member

For 22 years, Mr. Jim Kolbe served in the United States House of Representatives, elected in Arizona for 11 consecutive terms, from 1985 to 2007. Mr. Kolbe is currently serving as a Senior Transatlantic Fellow at the German Marshall Fund of the United States, and as a Senior Adviser to McLarty Associates, a strategic consulting firm. He advises on trade matters as well as issues of effectiveness of U.S. assistance to foreign countries, on U.S.-E.U. relationships, and on migration and its relationship to development. He is also co-chair of the Transatlantic Taskforce on Development with Gunilla Carlsson, the Swedish Minister for International Development Cooperation. He also is an adjunct Professor in the College of Business at the University of Arizona. While in Congress, he served for 20 years on the Appropriations Committee of the House of Representatives, was chairman of the Treasury, Post Office and Related Agencies subcommittee for four years, and for his final six years in Congress, he chaired the Foreign Operations, Export Financing and Related Agencies subcommittee. He graduated from Northwestern University with a B.A. degree in Political Science and then from Stanford University with an M.B.A. and a concentration in economics.

Dr. Charles Parmenter, Member

Dr. Charles Parmenter is a Distinguished Professor Emeritus of Chemistry at Indiana University. He also served as Professor and Assistant and Associate Professor at Indiana University in a career there that spanned nearly half a century (1964-2010). He earned his bachelor's degree from the University of Pennsylvania and served as a Lieutenant in the U.S. Air Force from 1955-57. He worked at DuPont after serving in the military and received his Ph.D. from the University of Rochester and was a Postdoctoral Fellow at Harvard University. He has been elected a Member of the National Academy of Sciences and the American Academy of Arts and Sciences; and a Fellow of the American Physical Society and the American Association for the Advancement of Science. He was a Guggenheim Fellow, a Fulbright Senior Scholar, and received the Senior Alexander von Humboldt Award in 1984. He has received the Earle K Plyler Prize, was a Spiers Medalist and Lecturer at the Faraday Society, and served as Chair of the Division of Physical Chemistry

of the American Chemical Society, Co-Chair of the First Gordon Conference on Molecular Energy Transfer, Co-organizer of the Telluride Workshop on Large Amplitude Motion and Molecular Dynamics, and Councilor of Division of Chemical Physics, American Physical Society.

Dr. Eugene Sander, Member

Dr. Eugene G. Sander served as the 20th president of the University of Arizona (UA), stepping down in 2012. He formerly was vice provost and dean of the university's College of Agriculture and Life Sciences, overseeing 11 academic departments and two schools, with research stations and offices throughout Arizona. He also served as UA executive vice president and provost, vice president for University Outreach and director of the Agricultural Experiment Station and acting director of Cooperative Extension Service. Prior to his move to Arizona, Sander served as the deputy chancellor for biotechnology development, director of the Institute of Biosciences and Technology, and head of the department of biochemistry and biophysics for the Texas A&M University system. He was chairman of the department of biochemistry at West Virginia University Medical Center and associate chairman of the department of biochemistry and molecular biology at the College of Medicine, University of Florida. As an officer in the United States Air Force, he was the assistant chief of the biospecialties section at the Aerospace Medical Research Laboratory. He graduated with a bachelor's degree from the University of Minnesota, received his master's degree and Ph.D. from Cornell University and completed postdoctoral study at Brandeis University. As a biochemist, Sander worked in the field of mechanisms by which enzymes catalyze reactions.

Biographical information of ISGP staff

Dr. George Atkinson, Executive Director

Dr. George Atkinson is the founder and Executive Director of the Institute on Science for Global Policy (ISGP) and is an Emeritus Professor of Chemistry, Biochemistry, and Optical Science at the University of Arizona. His professional career has involved academic teaching, research, and administration, roles as a corporate founder and executive, and public service at the federal level. He is former Head of the Department of Chemistry at the University of Arizona, the founder of a laser sensor company serving the semiconductor industry, and Science and Technology Adviser (STAS) to U.S. Secretaries of State Colin Powell and Condoleezza Rice. In 2013, he became the president-elect of the Sigma Xi Society. Based on principles derived from his personal experiences, he launched the ISGP in 2008 as a new type of international forum in which credible experts provide governmental and societal leaders with the objective understanding of the science and technology that can be reasonably anticipated to help shape the increasingly global societies of the 21st century.

Jennifer Boice, M.B.A.

Jennifer Boice is the Program Coordinator of the ISGP. Ms. Boice worked for 25 years in the newspaper industry, primarily at the Tucson Citizen and briefly at USAToday. She was the Editor of the Tucson Citizen when it was closed in 2009. Additional appointments at the Tucson Citizen included Business News Editor, Editor of the Online Department, and Senior Editor. She also was a business columnist. Ms. Boice received an M.B.A. from the University of Arizona and graduated from Pomona College in California with a degree in economics.

Melanie Brickman Stynes, Ph.D., M.Sc.

Melanie Brickman Stynes is Associate Director with the ISGP. As a researcher focused on the juncture of public health, demography, policy, and geography, she bridges multiple fields in her emerging and persistent infectious diseases research. Her work has paid particular attention to issues surrounding tuberculosis control (historic and contemporary). She is also an Adjunct Professor at Baruch College's School of Public Affairs in New York City. Additionally, Dr. Brickman Stynes spent nearly a decade as a Research Associate for the Center for International Earth Science

Information Network (CIESIN) of Columbia University, where she worked on a range of projects related to health, disease, poverty, urbanization, and population issues. She received her Ph.D. in medical geography from University College London and her M.Sc. in medical demography from the London School of Hygiene and Tropical Medicine.

Sweta Chakraborty, Ph.D.

Sweta Chakraborty is a Senior Fellow with the ISGP. She recently completed post-doctoral research on pharmaceutical regulation and product liability at Oxford University's Centre for Socio-Legal Studies and remains an active member of Wolfson College. Dr. Chakraborty received her doctorate in Risk Management from King's College London and has helped to design and co-teach a summer course in London on Managing Hazards in Europe and the United States with Indiana University's School of Public and Environmental Affairs. Her undergraduate degrees are in Decision Science and International Relations from Carnegie Mellon University.

Anna Isaacs, M.Sc.

Anna Isaacs is a Senior Fellow with the ISGP. She has previously focused on minority health issues and is experienced in field and desk-based qualitative research. She has interned as a researcher at a variety of nonprofit institutions and also at the House of Commons in London. Ms. Isaacs received her M.Sc. with distinction in Medical Anthropology from University College London and a B.Sc. in Political Science from the University of Bristol.

Paul Lewis, J.D.

Paul Lewis is a Fellow with the ISGP. He worked as a Congressional Aide in Washington, D.C., and as a Legal Associate specializing in Federal Immigration Law before working with Google on Maps and Local Search products. Mr. Lewis came to Google through Immersive Media, the company behind Street View camera technology. He was involved in the rollout of Google Street View, and has managed projects involving 360-degree GPS embedded data worldwide. Mr. Lewis earned his Juris Doctor at the University of Arizona and graduated Magna Cum Laude with degrees in Journalism and Political Science from Northern Arizona University.

Harvey Morris, Ph.D.

Harvey Morris is a Fellow with the ISGP. As a Licensed Psychologist he began his work on staff at the New York Health and Hospitals Corporation, and eventually became Director of Clinical Services at a private 100-bed hospital. In the late 1970s he founded and managed a mid-sized specialty consulting firm that assisted major

global corporations and national governmental agencies in accelerating strategy implementation. After retiring, he founded and served as Executive Director of a not-for-profit foundation, and served on an advisory board at the University of Arizona. Dr. Morris received a B.A. in Psychology from the City University of New York, and a Ph.D. in Clinical Psychology from the University of Nebraska.

David Miller, M.B.A.

David Miller is a Scientific/Program Consultant with the ISGP. Previously, he was Director, Medical Advocacy, Policy and Patient Programs at GlaxoSmithKline, where he led the company's U.S. efforts relating to science policy. In this role, he advised senior management on policy issues, and was the primary liaison between the company and the national trade associations, Pharmaceutical Research and Manufacturers of America (PhRMA) and Biotechnology Industry Organization (BIO). He also held management positions in business development and quality assurance operations. Mr. Miller received his B.S. in Chemistry and his M.B.A. from the University of North Carolina at Chapel Hill.

Sara Pistolesi, Ph.D.

Dr. Sara Pistolesi is a Fellow with the ISGP and a postdoctoral research fellow at the National Heart, Lung, and Blood Institute, National Institutes of Health in Bethesda, Maryland. Her research involves investigating the function of several protein complexes involved in key cellular processes using Nuclear Magnetic Resonance. Prior to this, she worked as a postdoctoral researcher at the University of Siena, Italy, where she also earned her Laurea (B.S.+M.S.) in pure Chemistry and her Ph.D. in Chemical Sciences. Dr. Pistolesi is also a freelance editor for Cactus Communications for which she helps non-native English-speaking scientists to publish their work in internationally recognized peer-reviewed journals by revising their manuscripts. Additionally, Dr. Pistolesi served as chemistry judge and special award judge for the Biophysical Society at science fairs at county and government level.

Arthur Rotstein, M.S.J.

Arthur Rotstein is Copy Editor with the ISGP. Prior to joining the ISGP, Mr. Rotstein worked for the Washington D.C. Daily News, held a fellowship at the University of Chicago, and spent more than 35 years working as a journalist with The Associated Press. His writings have covered diverse topics that include politics, immigration, border issues, heart transplant and artificial heart developments, Biosphere 2, college athletics, features, papal visits, and the Mexico City earthquake. Mr. Rotstein holds a M.S.J. from Northwestern University's Medill School of Journalism.

Raymond Schmidt, Ph.D.

Ray Schmidt is a Senior Fellow with the ISGP. In addition, he is a physical chemist/chemical engineer with a strong interest in organizational effectiveness and community health care outcomes. While teaching at the university level, his research focused on using laser light scattering to study liquids, polymer flow, and biological transport phenomena. Upon moving to the upstream petroleum industry, he concentrated on research and development (R&D) and leading multidisciplinary teams from numerous companies to investigate future enhanced oil recovery ideas and to pilot/commercialize innovative recovery methods in domestic and foreign locations. Dr. Schmidt received his Ph.D. in chemistry from Emory University.

Ramiro Soto

Ramiro Soto is a Fellow at the ISGP. He currently is an undergraduate student at the University of Arizona College of Science seeking a Bachelor of Science degree in General Applied Mathematics. Beyond his academic curriculum, Mr. Soto is an active member of the Pride of Arizona marching band since 2010 and recently became a member of the athletic pep band. He completed an internship with the Walt Disney Company Parks and Resorts segment in 2011. After completing his undergraduate education, he plans to apply for a doctoral program furthering his studies in mathematics.

Matt Wenham, D.Phil.

Matt Wenham is Associate Director with the ISGP. He formerly was a postdoctoral research fellow at the National Institutes of Health in Bethesda, Maryland. His research involved studying the interaction of protein toxins produced by pathogenic E. coli strains with human cells. Dr. Wenham received his D. Phil. from the Sir William Dunn School of Pathology, University of Oxford, United Kingdom, where he was a Rhodes Scholar. Prior to this, he worked in research positions at universities in Adelaide and Melbourne, Australia. Dr. Wenham received his bachelor's and honours degrees in biochemistry from the University of Adelaide, South Australia, and holds a Graduate Diploma of Education from Monash University, Victoria.