PROACTIVE AND ADAPTIVE GOVERNANCE OF EMERGING RISKS
THE CASE OF DNA SYNTHESIS AND SYNTHETIC BIOLOGY

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Contents

INTRODUCTION

Like conventional biological engineering, synthetic biology rests on revolutionary advances in DNA sequencing and synthesis technologies. Unlike most recombinant DNA work, synthetic biology seeks to do biological engineering with standardized biological parts, modularized design, and routinized methods of assembly. By emphasizing standardization and modularity, synthetic biologists seek to cut costs by permitting outsourcing, to reduce barriers to entry in advanced biological engineering by reducing requisite skill levels, and to extend the range of useful applications of biological engineering.

Risk governance of this emerging technology is complicated by the existence of complex and shifting tradeoffs between benefits and risks, whose terms can only be imperfectly understood in advance of development and diffusion of the technology. On the one hand, synthetic biology has designed organisms to synthesize drugs and fuels, to detect and break down toxics, and to fix carbon for sequestration. On the other hand, these applications pose environmental risks associated with release of synthetic organisms. The standardization and modularization that are distinguishing features of synthetic biology also have dual implications. By lowering costs and skill levels required to practice biological engineering, synthetic biology may allow developing countries and small firms to derive greater benefit from synthetic biology than is typical for advanced emerging technologies. However, by lowering costs, reducing barriers to entry, and encouraging mass use, modularization and standardization may amplify any negative environmental and security externalities associated with this technology. Benefits and risks attributed to synthetic biology are typically two faces of the same coin.

This paper describes the emergence of security risks associated with DNA synthesis and synthetic biology and evaluates the international conventions, national guidelines, transnational protocols and voluntary actions that have evolved to govern those risks. It then extracts some more general lessons for governance of emerging risks from experience to date in this domain.

Part I. Sequencing, Synthesis and Synthetic Biology: This section provides a primer for non-biologists on the foundational technologies that have enabled the development of synthetic biology and on features of synthetic biology that differentiate it from conventional genetic engineering. It is drawn from Mukunda, Oye, Mohr 2009.

Part II. Security Risks: This section reviews stimuli that have prompted attention to emerging security risks, include the 2000 Australian mouse pox experiment, the 2002 post 9-11 anthrax attacks, the 2004 reconstruction of the 1918 Spanish influenza virus, the 2005 Guardian mail-order smallpox DNA, and 2012 H5N1 experiments. It then turns to three sets of responses to these prompts, the first on risks associated with the synthesis and distribution of potentially pathogenic DNA sequences, the second on risks associated with the diffusion of skills required to practice biological engineering, and the third on risks associated with synthetic biology research and publication.

Part III On Implications for Risk Governance: This section draws lessons for more effective governance of emerging risks from these cases. Relative to other emerging technologies at comparable stages of maturity, potential risks associated with synthetic biology have been the object of more early stage data risk assessment, more public and private sector collaboration in formulating risk governance strategies, more systematic efforts at risk communication, and greater acceptance of accountability. However, best practices from synthetic biology may not transfer easily to other domains. Absent the stimuli that prompted engagement in synthesis and synthetic biology, neither regulators nor technologists would likely have developed and refined the risk governance practices that have worked reasonably well in addressing security, safety and environmental risks of synthetic biology.

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PART I. A PRIMER ON SEQUENCING, SYNTHESIS AND SYNTHETIC BIOLOGY[i]

Synthetic biology is based on the transformation of biology brought about by the ability to determine the complete sequences of the DNA molecules that constitute an organism's genome and on a parallel revolution in ability to synthesize sequences of DNA. DNA encodes genetic information in a linear string of molecular groups called "bases" symbolized by the initials of their chemical names A, C, G and T. To be sure, epigenetic factors, interaction effects and path dependencies not captured by DNA sequences complicate the practice of biological engineering. Nonetheless, sequenced genomes of existing species represent a treasure trove of biological functions that have evolved during the 4 billion years since life on Earth began.

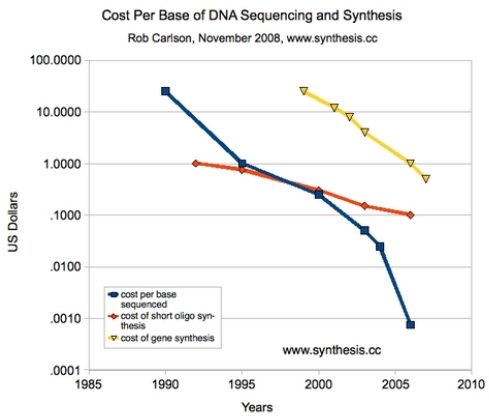

Figure 1: Cost of DNA Sequencing and Synthesis

DNA sequencing and synthesis technologies are in the midst of more-than-exponential change. "Carlson's Curves" presented as Figure 1 plot the cost of sequencing and synthesis per base pair over the years 1985 to 2009. Note that the vertical axis is a log scale with each tick representing an order of magnitude of change in cost. The pace of advance depicted by Carlson's Curves exceeds that of Moore's Law on the density of semiconductors on microchips and speed of information processing. Advances in information technology, scale effects as the volume of sequencing and synthesis orders have risen, and the application of industrial process management methods to what the arcane activities of academic laboratories are among the factors that have produced these remarkable changes in productivity in the foundational technologies of biological engineering.

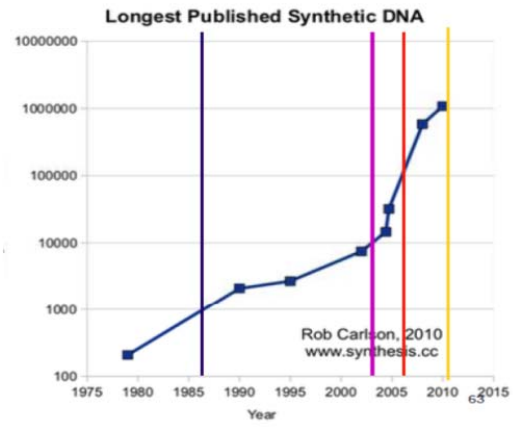

Figure 2A: Longest Synthesized DNA

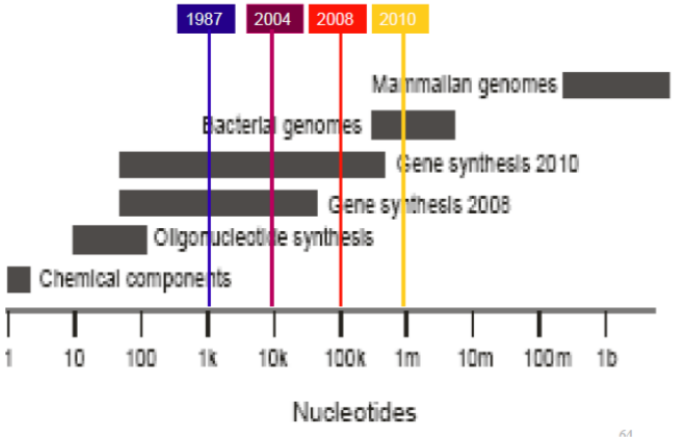

Figure 2B: Natural Nucleic Acids with Overlay of Synthesized DNA

Figure 2A presents the length of the longest published synthesized DNA over the years 1980 to 2009. The vertical axis here is also a log scale, with the length of synthetic sequences changing at a faster-than-exponential rate since 2005. To place these changes in context, Figure 2B overlays longest synthesized DNA sequences over the length of naturally occurring nucleic acids.

These changes in technology and the knowledge that they have produced have enabled the development of synthetic biology. Figure 3 below shows the dramatic growth of public genome databases, particularly since 2008. Sequenced genomes are available in the public domain on the internet through GenBank (USA), EMBL (Britain), and DDBJ (Japan), which share and exchange sequence information on a daily basis. Nucleotides submitted to the classical version of GenBank are shown as diamonds and nucleotides submitted to the Sequence Read Archive (SRA) are shown as circles. Second generation sequencing technologies and single-molecule sequencing are reflected in the table. SRA surpassed classical GenBank in less than a year and now accounts for over 95% of sequence deposits.

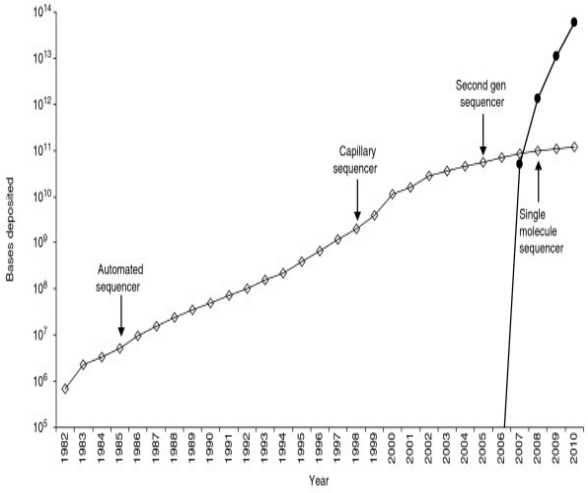

Figure 3: Sequence database submissions from 1982 to 2010**.** Thompson and Milos *Genome Biology* 2011 **12**:217.

In this context, the motivating goals of synthetic biologists are twofold: to confirm our understanding of how genes function by putting them to use in designed systems (many of which mimic the components of natural cells); and to use sets of genes to create novel engineered organisms with useful functions. Synthetic biology thus straddles the divide between basic science and engineering with emphasis on the latter. [ii] It differs from conventional recombinant DNA research in several key respects.

First, synthetic biology is built around the concept of assembling useful modularized devices from standardized components. Thomas Knight, Drew Endy, Jay Keasling and colleagues advance the principle of assembling useful complex devices from simple standardized genetic components as the core principle of the field. Knight defined this idea in general form: "The key notion in the design of our strategy is that the transformations performed on component parts during the assembly reactions are idempotent in a structural sense. That is, each reaction leaves the key structural elements of the component the same. The output of any such transformation, therefore, is a component which can be used as the input to any subsequent manipulation."[iii] This means that properly designed synthetic biology devices will minimize interaction problems that bedevil conventional genetic engineering efforts.

To encourage work on production of standardized biological parts with standardized means of assembly, synthetic biologists have spearheaded construction of what they call "BioBricks," functional pieces of DNA designed to be easily assembled and to interact predictably when made part of a larger structure. BioBricks are registered within a publicly-accessible database called "The Registry of Standard Biological Parts" (http://www.partsregistry.org). Analogous to the interchangeable parts that were a cornerstone of the Industrial Revolution, BioBricks are meant to make the *de novo* construction of novel biological systems considerably easier, decreasing the time, expense, and skill level necessary to develop biological systems that can perform tasks as varied as producing artemisinin, converting cellulose to fuels, or increasing the drought resistance of plants. In theory, modularized biological engineering could transform significant sections of the world economy, create biological weapons and improve defense capabilities against natural and artificial biological threats.[iv,v]

Second, synthetic biology seeks to replace *ad hoc* experimental design and tacit knowledge with a set of standard and reliable engineering procedures to remove much of the tedium and uncertainty during assembly of genetic components into larger systems. Altering living systems using conventional recombinant DNA techniques

currently requires significant degrees of tacit knowledge. Tacit knowledge is knowledge primarily gained from experience instead of formal education. Tacit knowledge in biology is usually acquired through prolonged apprenticeships with senior scientists. This is essentially a cottage industry within academic and commercial biotechnology. Such tacit knowledge is currently among the most significant barriers to bioweapons proliferation. Even the creation of a synthetic poliovirus from commercially available DNA required significant tacit knowledge.[vi,vii]

Synthetic biology is unique in the extent to which it is *explicitly devoted* to the minimization of the importance of tacit knowledge. For example, the NSF Synthetic Biology Engineering Research Center (SynBERC) has focused upon the elimination of tacit knowledge from the manipulation of living systems. SynBERC Director Jay Keasling described the high demands for tacit knowledge that currently hinder even the most skilled bioengineers, then observed that SynBERC's vision "is to make biology easier to engineer."[viii] The emphasis here is crucial. SynBERC certainly seeks to produce specific application but that is not its primary goal. Instead it seeks to eliminate barriers that make it more difficult for *everyone* to engage in advanced bioengineering. For example, SynBERC researchers are working on automated cloning, on automated assembly of DNA segments, and on software for the computer-aided design of living systems.[ix] These efforts mark a fundamental divide between synthetic biology and traditional bioengineering.

De-skilling and modularity are likely to have several effects. With sufficient resources, skilled genetic engineers using conventional techniques could already make significant contributions to an offensive bioweapons program. De-skilling and modularity have the potential to both rapidly increase the diffusion of skills and decrease the skill gradient separating elite practitioners from ordinary ones. Similarly, the high degree of tacit knowledge involved in traditional genetic engineering means that today less-skilled practitioners can have significant difficulty replicating the achievements of elite ones, even if all the necessary data has been published. These same two traits of synthetic biology are, however, likely to make replication of these achievements easier, substantially leveling the gradient between elite and peripheral practitioners.

Standardization of parts, modularization of designs and reductions in the levels of skills required to do advanced biological engineering are both the basis of the economic appeal of synthetic biology and the foundation of potential security and environmental risks. As a consequence, the design of risk governance regimes for synthetic biology that do not vitiate potential scientific and developmental benefits is challenging.

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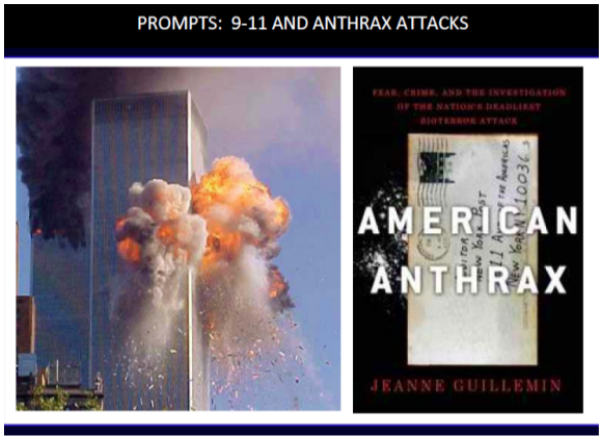
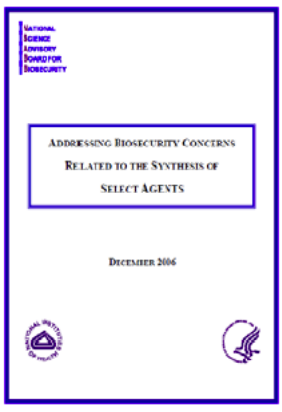
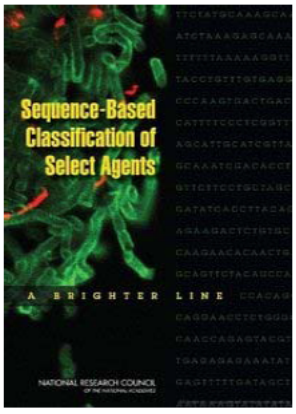
PART II. ON THE EMERGENCE AND GOVERNANCE OF BIOSECURITY RISKS

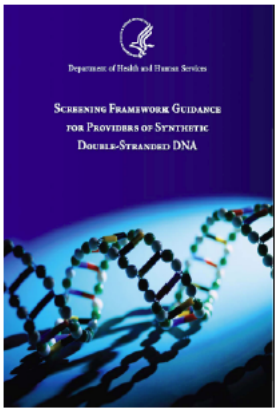
Soon after the September 11 attacks, a series of anthrax attacks by a rogue scientist from a U.S. weapons laboratory resulted in 5 fatalities and 17 infections, the paralysis of the US postal system, and massive panic.[x] The anthrax strains used in the attack, the methods of weaponization of the anthrax and the modes of delivery did not use advanced biological engineering methods. However, this incident, combined with continuing advances in the ability to manipulate living systems, motivated official and unofficial reassessments of the threat from biological weapons, particularly in the hands of non-state actors. The combination of 9-11 as a vivid demonstration of dangers from terrorism and the anthrax attacks as a concrete illustration of the effects of even a small scale biosecurity attack had the effect of magnifying the significance of the specific prompts on risks described below.



In effect, 9-11 and the anthrax attacks raised biological security risks above the threshold of public recognition and political salience. The combined effect was to stoke demand for the assessment of risks and for controls on information, materials and technologies. The Central Intelligence Agency (CIA) Office of Transnational Issues (2003), the National Research Council (2004) and the National Science Advisory Board Recombinant DNA Advisory Committee (NSABB/RAC) (2007) are among many organizations directing attention to the assessment security and safety threats. Nongovernmental organizations, science reporters, and science fiction writers have echoed these official concerns.[xi,xii,xiii] In 2008, the U.S. Commission on Prevention of WMD Proliferation and Terrorism – usually called the Graham-Talent Commission after its Chair and Vice-Chair - issued a report titled "World at Risk" (2008). The Commission concluded that it is more likely than not that a terrorist attack using a weapon of mass destruction will occur somewhere in the world by the end of 2013, and concluded that "terrorists are more likely to be able to obtain and use a biological weapon than a nuclear weapon." There thus exists a broad consensus that progress in biotechnology is likely to increase biosecurity risks, even as there is heated debate on the current level of threats presented.







The devil is in the biosecurity details rather than in broadly defined and ambiguous trends. The balance of this case treats three specific sets of biosecurity risks, each with its own distinctive prompts and responses.

Case 1: Risks Associated with De-materialization: Biosecurity regimes have been premised on the assumption that physical controls over access to pathogenic organisms would limit security risks. DNA synthesis and assembly have created pathways that can circumvent materials controls. This case discusses how perceptions of risks in this domain have emerged and how risks are now being governed by a mixture of public policies and private consortia.

Case 2: Risks Associated with Skills Diffusion: As the "primer" on synthetic biology above suggests, tacit knowledge represents a significant barrier to activities that may pose security risks. Synthetic biology educational activities such as iGEM have been remarkably effective in promoting the diffusion of skills and in reducing the importance of tacit knowledge. This case discusses how risks that may emerge from educational activities are now being addressed through private voluntary action in cooperation with international and domestic authorities.

Case 3: Risks Associated with Information Creation and Distribution: The most delicate area of security risk governance associated with synthetic biology cuts to the core of the scientific enterprise. Is there research that should not be conducted? Are there results that should not be published? Attention to these issues has been prompted by the Australian Mousepox project and University of Wisconsin and Erasmus Institute projects that modified H5N1 to facilitate mammal to mammal transmission. This case discusses briefly the status of the ongoing debate over risk governance through controls on research and publication.

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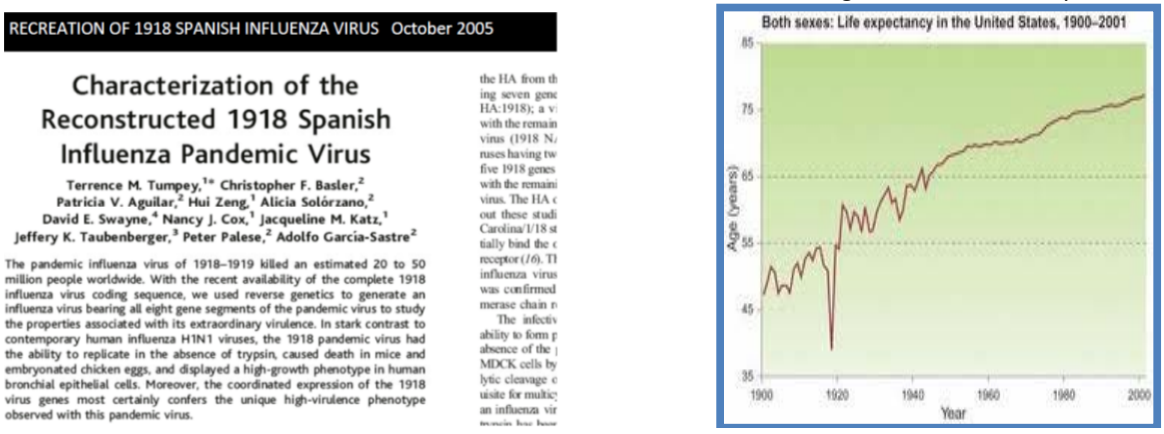
CASE 1: RISKS ASSOCIATED WITH DNA SYNTHESIS AND MATERIALS CONTROLS

Security risks associated with DNA synthesis are addressed by a hybrid regime that combines international agreements including the UN Bioweapons Convention and Australia Group; national advisory and regulatory bodies including the NSABB/RAC and Health and Human Services; and self governance by transnational consortia of firms that produce synthetic DNA. This paper suggests that control measures that have been effective in addressing current security concerns may also accelerate diffusion of technologies and ultimately undercut measures to manage security risks.

1-A. RISK EMERGENCE

Reconstruction of Spanish Influenza: In 2005, the publication of "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus" in *Science* represents both a technical advance and political shock.[xiv] A team of scientists recreated the influenza that had killed millions in 1918, producing the remarkable decline in life expectancy shown in the figure below. No complete sequence of the Spanish influenza virus was known to exist when the team started their work. The scientists reassembled the virus from fragments from a variety of sources.


RECREATION OF 1918 SPANISH INFLUENZA VIRUS October 2005

Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus

Terrence M. Tumpey,[1]* Christopher F. Basler,[2] Patricia V. Aguilar,[2] Hui Zeng,[1] Alicia Solórzano,[2] David E. Swayne,[4] Nancy J. Cox,[1] Jacqueline M. Katz,[1] Jeffery K. Taubenberger,[3] Peter Palese,[2] Adolfo García-Sastre[2]

The pandemic influenza virus of 1918–1919 killed an estimated 20 to 50 million people worldwide. With the recent availability of the complete 1918 influenza virus coding sequence, we used reverse genetics to generate an influenza virus bearing all eight gene segments of the pandemic virus to study the properties associated with its extraordinary virulence. In stark contrast to contemporary human influenza H1N1 viruses, the 1918 pandemic virus had the ability to replicate in the absence of trypsin, caused death in mice and embryonated chicken eggs, and displayed a high-growth phenotype in human bronchial epithelial cells. Moreover, the coordinated expression of the 1918 virus genes most certainly confers the unique high-virulence phenotype observed with this pandemic virus.

Figure 4 Reconstruction of the Spanish Influenza with US Life Expectancy Data

Their recreation of the virus triggered widespread discussion on the benefits and risks of such research, with particular attention to security risks that could follow from the application of such methods to other pathogens. This was a clear demonstration that the synthesis of complex pathogens was technically feasible and that systems

of material controls on virulent biological agents could, at least in theory, be circumvented through DNA synthesis of parts and reassembly into complete organisms.

Mail Order Synthesized Small Pox DNA: In 2006, the Guardian showed that fragments of pathogenic DNA could be ordered from commercial DNA synthesis houses without detection or safeguards. Reporters from the Guardian ordered incomplete DNA fragments that were components of the smallpox sequence. The reporters ordered their parts from different commercial providers of synthesized DNA. None of the houses flagged the orders as suspicious. In June 2006 the Guardian published the results of their investigation in an article entitled "Revealed: the lax laws that could allow assembly of deadly virus DNA." Smallpox has been eradicated in nature and exists only in guarded installations. The Guardian team showed that systems of physical materials control could potentially be circumvented by the combination of information on a pathogenic sequence and the use of synthesis methods to produce incomplete sequences of DNA. The earlier Spanish influenza recreation had showed that the assembly of incomplete sequences of a pathogen into a functioning whole organism was possible.


theguardian

Revealed: the lax laws that could allow assembly of deadly virus DNA

Urgent calls for regulation after Guardian buys part of smallpox genome through mail order

James Randerson, science correspondent
The Guardian, Tuesday 13 June 2006

A plaid containing an incomplete sequence of smallpox DNA, obtained by the Guardian over the internet. Photo: Martin Argles

Before turning to measures that now limit security risks associated with DNA synthesis, consider a counterfactual. The Guardian reporters also sought to order parts extracted from smallpox from iGEM President Randy Rettberg, parts that iGEM did not and does not have in the Registry of Standardized Biological Parts. Rettberg was suspicious of their motives at the time. With benefit of hindsight and improved knowledge of law enforcement procedures, Rettberg states that he would have reported the reporters seeking to order smallpox elements to the FBI had he known then what he knows now as a result of FBI outreach activities. Had he done so, the Guardian story would have lost its punchline, the DNA synthesis industry would have lost its motive for proactive risk governance, and the measures below would probably not have been taken. Ironically, if Randy Rettberg had acted on his suspicions, then the world would be less safe.

1-B. RISK ASSESSMENT AND GOVERNANCE

How are risks now being addressed by public and private sectors? The new field of synthetic biology is governed by a mixture of legacy regimes, national framework guidance, and transnational consortia. The legacy regime has two primary elements – the UN Biological Weapons Convention and the Australia Group. These arrangements were formed to address problems quite different from those raised by synthetic biology, but have been adapted to address security and safety implications of this emerging field. The national, transnational and small scale local measures include the HHS Screening Guidance and transnational voluntary screening consortia.

The UN Biological Weapons Convention: The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and Their Destruction was opened for signature on April 10 1972 and entered into force on 26 March 1975. As of June 2005, 171 states had signed the convention, of which 16 still needed to ratify it, while 23 states had not signed (The Biological and Toxin Weapons Convention Webpage 2005). It supplements the Geneva Protocol of 1925, which prohibits the use of chemical and biological weapons during warfare (League of Nations 1925) and is currently signed by 173 states. Article I of The Biological Weapons Convention prohibits signatory states from developing, producing, stockpiling or otherwise acquiring or retaining "Microbial or other biological agents, or toxins whatever the origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes (and) Weapons,

equipment or means of delivery designed to use such agents or toxins for hostile purpose or in armed conflict." Subsequent articles require states to destroy or divert to peaceful purposes already existing biological agents and toxins, not to transfer or assist other state or non-state actors to manufacture or acquire biological agents and toxins, to take necessary measures to prevent development, production, stockpiling, acquisition or retention of agents within their own territory and to file complaints if it finds that another state violates the convention.

The UNBWC lacks the institutional resources and priority status of the nuclear non proliferation regime, unsurprising since the risks associated with biological security fall more in the realm of future potential than demonstrated present threats of nuclear weapons. The 2012 UNBWC Seventh Review Conference in Geneva did not attract top level participation, unlike ambassadorial representation from the parties, contrasting with the 2012 Nuclear Security Summit in Seoul. UNBWC operational capacity is limited to an Implementation Support Unit, formed in 2007 with a skeleton staff of three professional officers. These material deficits notwithstanding, the UNBWC has one substantial and fundamental advantage relative to the nuclear nonproliferation regime with its world of nuclear weapons have and have not. It begins with equality among the parties, all of whom foreswear development, production, stockpiling, acquisition and retention of agents.

Australia Group Guidelines: The Australia Group formed in 1985 to coordinate national actions to prevent Iraq from acquiring materials for the production of chemical weapons through otherwise legitimate trade. In 2011, the Australia Group included 41 countries, all also members of the UN Biological Weapons Convention. The members include major providers of synthesis services in the advanced industrial world: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, European Union, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Republic of Korea, Latvia, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom, and the United States. The members do not include emerging market players such as China and India. The members have harmonized export controls over materials and technologies likely to contribute to the development of chemical or biological weapons. Biological agents and dual use biological technology were added to the Australia Group guidelines in 1992. An initial control list was published that year, and has expanded since. The group works by consensus, the agreement is non-binding.[xv]

In 2008, the Australia group set up a synthetic biology advisory body to keep up with developments and to suggest responses to innovations. Currently, Australia Group guidelines relating to biological components cover dual-use technology, advanced software not available to an untrained user, and biological components that have pathogenic properties (bacteria, viruses, toxins, etc.). The guidelines also regulate: (1) Genetic elements containing nucleic acid sequences associated with the pathogenicity of any of the microorganisms on the control list. (2) Genetic elements containing nucleic acid sequences coding for any of the toxins in the list, or for their sub-units. (3) Genetically-modified organisms that contain nucleic acid sequences associated with the pathogenicity of any of the microorganisms in the list. (4) Genetically-modified organisms that contain nucleic acid sequences coding for any of the toxins in the list or for their sub-units. The guidelines specify, "Genetically-modified organisms includes organisms in which the genetic material (nucleic acid sequences) has been altered in a way that does not occur naturally by mating and/or natural recombination, and encompasses those produced artificially in whole or in part. Genetic elements include inter alia chromosomes, genomes, plasmids, transposons, and vectors whether genetically modified or unmodified, or chemically synthesized in whole or in part." [xvi]

If the synthesized components do not code for part of a controlled pathogen or toxin, the guidelines do not apply. Also, if the genetic parts do not make up part of a genetic sequence that produces pathogenicity, then the components do not fall under the guidelines of the Australia Group, even if they do come from an organism on the control list. However, as new components are synthesized or isolated, their full functions within the DNA of a controlled pathogen may not be fully understood. This can lead to accidental shipments of components that have possible pathogenic properties.

As synthetic biology advances, more research will be performed on potentially dangerous organisms. Although the Australia Group has set up an advisory board to stay up to date with advances in the field, care must still be taken to ensure that potentially dangerous components are not moved across national boundaries inappropriately. A goal of synthetic biology is to create ways to more easily to modify organisms without advanced skills and equipment. This can allow untrained or even malicious actors to easily create a dangerous organism by assembling parts acquired from many sources. Due to these rapidly developing technologies, the guidelines laid down by the

Australia Group are extremely relevant, and the group's role in the international control of dangerous organisms should not be understated.

US Health and Human Services. In the period 2006 to 2011, HHS conducted a series of assessments and reassessments of synthesis processes and risks associated with creation of synthetic DNA. In 2011, HHS issued the "Screening Framework Guidance for Providers of Synthetic Double Stranded DNA." The HHS Framework Guidance provides voluntary standards, not regulations. HHS defines the key elements as follows: "Briefly, upon receiving an order for synthetic DNA, the U.S. Government recommends that providers perform *customer screening* and *sequence screening*. If either *customer screening* or *sequence screening* raises any concerns, providers should perform *follow-up screening*. If *follow-up screening* does not resolve concerns about the order or there is reason to believe a customer may intentionally or inadvertently violate U.S. laws, providers should contact designated entities within the U.S. Government for further information and assistance. This *Guidance* also provides recommendations regarding proper records retention protocols and screening software."[xvii]

Private Firms and Transnational Screening Consortia: In the aftermath of the Guardian article, leading DNA synthesis companies created consortia to enhance safety and security of DNA synthesis. The International Gene Synthesis Consortium (IGSC), the International Association of Synthetic Biology (IASB) and the International Consortium for Polynucleotide Synthesis (ICPS) provided input into the HHS Framework Guidance and developed protocols for screening customers and sequences consistent with the HHS Guidance. For example, the ICPS suggested the "development and validation of a tiered screening process that clearly identifies the contributions to safety and security due to user responsibilities, corporate practice and corporate technologies." [xviii] This included the requirement that those ordering synthesized DNA must identify themselves and that companies must use approved screening software to ensure compliance with all regulations.[xix] At present, the IGSC and IASB are maintaining software and data bases to check on whether a sequence is part of a pathogen and to verify the legitimacy of customers placing orders. Integrated DNA Technologies (IDT) now serves as the lead company within IGSC while Entelechon now serves as the lead within IASB.

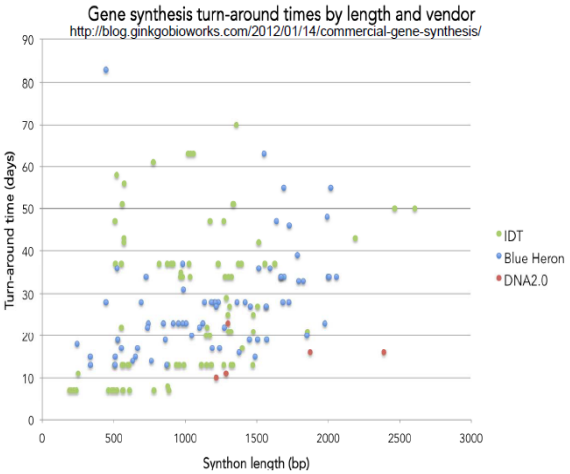
1-C. ASSESSMENT OF ADEQUACY OF RISK GOVERNANCE

Critics of the HHS Guidelines and synthesis screening consortia suggest that voluntary guidelines will prove ineffective. This is wrong, at least at present. In fact, DNA synthesis firms in both IGSC and IASB appear to adhere to the HHS Screening Framework Guidance. This section explains why the system is working well now and discusses how its short term success may erode its viability over the long term.

Why would profit oriented firms comply with a voluntary standard?

First, the synthesis firms found that the direct and indirect costs of screening customers and sequences are not high. The cost of developing data bases of customers and sequences that are known to be parts of pathogens is moderate, and the number of customers whose orders are rejected is low. The synthesis firms have lost customers by automatically rejecting virtually all orders from Iran and Pakistan, by rejecting orders for sequences from customers in other developing countries because of insufficient data, and by rejecting customers in advanced industrial countries without established research records in recognized institutions. Senior managers of three major providers of synthesis services stated to this author that numbers of lost customers were low for now, but would rise as demand for synthesized DNA from developing countries, individuals, and startup firms increased.

Second, synthesis firms report that some customers have complained over delays in filling orders when the firms have sought to establish customer identity or have followed up with customers on the intended uses of sequences. By referencing the HHS Guidelines as requirements in communications with customers, the synthesis firms deflect responsibility for delays and inconvenience from themselves to HHS. In fact, complaints to date over delays caused by screening have been limited. As the figure below suggests, until recently, delays in filling orders were substantial and varied markedly from firm to firm and by length of sequence. Biosecurity related screening delays may have been lost in the noise. However, with recent sharp reductions in the time from placing an order to receipt of synthesized materials, customer pushback on delays caused by screening may be expected to increase.



Third, senior managers of synthesis firms expressed concerns over potential exposure to liability if they were to disregard HHS guidelines and were the source of a DNA sequence that adversely affected humans, livestock, crops or the broader environment. As one manager put it, the interest in screening customers is reinforced by the absence of effective immunity over the malicious use of products that firearms manufacturers enjoy. The manager stated "…..gun companies can argue that guns don't kill people, people kill people. We do not want to be in the position of having to make that argument if something bad happens." While compliance with a guideline or statute typically does not provide a safe harbor, noncompliance with a guideline coupled with an adverse event invites litigation. This incentive for compliance with voluntary guidelines holds more strongly within the US with our tort system than within less litigious societies.

Fourth, leaders of synthesis firms indicated that nonadherence to guidelines would attract adverse publicity and invite command and control regulation, particularly within the European Union. Compliance with voluntary guidelines may obviate the need for regulation. The Guardian subtitled its 2006 piece "Urgent calls for regulation after Guardian buys part of smallpox genome through mail order." The unified voluntary industry response by DNA synthesis firms appears to have had the effect of defusing urgent calls for regulation.

Will the Hybrid Risk Governance System Hold?

The combination of HHS Framework Guidance and IGSC and IASB development of protocols for screening customers and sequences has worked well to date. This public-private partnership has permitted greater flexibility and adaptability with reference to sensing changes in the challenges presented, developing appropriate software tools and data bases, and developing methods of handling customers than more formal international arrangements or national regulations would have permitted. The system is not now broken. But will it hold?

In March 2012, the public and private actors that constitute this hybrid risk governance regime met in Heidelberg Germany to identify emerging problems and to discuss potential responses. Several areas of concern over long term technological changes and economic trends were identified during that meeting.

- First, technological advances may render obsolete the current approach to screening DNA sequences by looking for elements of pathogens listed as Select Agents or in Australia Group Guidelines. In 2010, the National Research Council issued a report on Sequence-Based Classification of Select Agents. The nub of the problem is that DNA sequences that are derived from unlisted organisms or created de novo may pose risks but such sequences would not necessarily be detected as parts of listed organisms.
- Second, technological and economic changes may render the current approach to screening customers obsolete. With the rise of biofabs and intermediaries, the buyers of synthesized DNA will not necessarily be the ultimate users of synthesized DNA. Methods of screening customers will have to take account of these developments by requiring verification and documentation through more complex supply chains.
- Third, economic and political forces are likely to accelerate the international diffusion of synthesis technologies. At the international level, we do know that screening consortia often deny customers in Iran and Pakistan access to synthesized DNA. Iran and Pakistan appear to be constructing synthesis facilities within their borders. At the domestic level, the screening consortia tend to deny DIYB

operators access to synthesized DNA. These potential customers may opt for low end garage or home DNA synthesizers as that technology develops and costs of devices fall.

- Fourth, some high end customers in the US and Europe with established track records, largely in pharmaceuticals, do not outsource for synthesis services. These users value precision, speed, flexibility and quality control, and believe that in house synthesis serves their interests better. Furthermore, users with concerns over information security prefer to synthesize in house instead of relying on assurances of confidentiality by synthesis houses or screening consortia. By creating a market for sophisticated synthesis equipment for in house use, these firms may inadvertently weakening the effectiveness of consortial arrangements that rest on relatively concentrated industrial structure.

The account above is based on the author's participation as an invited expert in the 2012 Heidelberg meeting. Because the meeting was conducted under Chatham House Rules with non-attribution, this case study cannot disclose the names and affiliations of individuals making the points above. However, it is appropriate to take note of the broad based participation of key governmental and private actors in an atmosphere of trust, the spirited and candid nature of discussions, the high level of technical, scientific and security related expertise, and the group's direct engagement with emerging problems. The author walked into the Heidelberg meeting with some skepticism over the current effectiveness and long term viability of voluntary risk governance arrangements. The author returned from the Heidelberg meeting with confidence in the near term viability of the hybrid regime and in the rare coincidence of public and private interests in addressing biosecurity risks, albeit with reservations as noted above over the long term sustainability of this arrangement.

* * * * *

CASE 2: RISKS ASSOCIATED WITH SKILLS DIFFUSION – IGEM

The International Genetically Engineered Machine Competition, known as iGEM, involves high school and undergraduates in synthetic biology projects. Thousands of students have been initiated into the procedures of synthetic biology, developing baseline competence and confidence about their ability to engineer organisms. As the table below suggests, the growth in iGEM global participation and the associated diffusion of biological engineering competencies has been extraordinary.

Year	Teams	Participants
2004	5	70
2005	12	130
2006	32	320
2007	54	540
2008	84	840
2009	112	1120
2010	130	1300
2011	165	1650

iGEM Growth 2004-2012 (Source: R. Rettberg)

iGEM 2005

iGEM 2010

From 2006 to the present, iGEM has required all teams to answer a series of basic questions on safety and security as a condition of participation. A few days before the 2010 competition, iGEM President Randy Rettberg and Board Member Drew Endy asked the author to organize a team to perform a quick review of safety and security aspects of the projects. I formed an iGEM Safety Committee with Piers Millett of the UN Biological Weapons Implementation Support Unit and Todd Kuiken of the Smithsonian Woodrow Wilson Center. The Safety Committee was not satisfied with the quick review of responses to safety questions with on site follow up during the competition, and committed to reforming the review process for the 2011 competition, with more thorough review at a much earlier stage of the iGEM process. This case study describes and evaluates the results of iGEM Safety and Security Screening in 2011.

2-A. SCREENING PROJECTS – RISK EMERGENCE AND GOVERNANCE

During August of 2011, the Safety Committee screened the projects of all iGEM teams, with particular attention to projects using pathogens. All teams are required to provide a project description and to complete a "safety page" by responding to a questionnaire on safety as they began their work. The Safety Committee compared the project descriptions and safety pages of all teams. Almost all iGEM teams were working with BSL1 organisms with adequate safety provisions and under institutional review. Not all safety pages were completed fully, and the Safety Committee asked teams to provide information as required, even where the projects did not appear to present substantive safety issues.

The Safety Committee identified two projects that involved working with genetic elements of a pathogen and that had weak safety declarations, and followed up with inquiries. The Safety Committee was satisfied with the responses of one team and disqualified the other team from competition, with provisions for possible requalification if potential safety problems were rectified. The team subsequently redefined their project as "software only / no wetlab work" and registered the new version of the project with iGEM headquarters. The Safety Committee authorized the team to compete on that basis. To address Safety Committee concerns about team members' safety, Piers Millett of the UNBWC recruited a senior authority on biosafety from the team's home nation to work with the team on its safety practices.

2-B. SCREENING PARTS – RISK EMERGENCE AND GOVERNANCE

The Safety Committee audited past activity by the team and found that it had submitted parts derived from a pathogen to the iGEM Registry of Standard Biological Parts in the previous year. iGEM headquarters determined that none of the parts had been ordered or distributed and placed a freeze on distribution of those parts. One complex risk related policy issue remained.

The Australia Group is an informal forum of 41 countries that seeks to ensure that exports do not contribute to the development of chemical or biological weapons. The Australia Group recommends controls over the export of genetic elements derived from listed pathogens that "contain nucleic acid sequences associated with pathogenicity" as well as those that contain nucleic acids coding for any listed toxin or sub-unit of a listed toxin. The Safety Committee sought advice on the current operational definition of "genetic elements associated with pathogenicity." Todd Kuiken of the Smithsonian Wilson Center sought guidance on the current operational definition of "elements associated with pathogenicity" from many sources and found no clear guidance. The Safety Committee sought other means of determining whether the parts themselves posed a safety issue or legal problem. A search for open lists, software tools and data sets to determine whether parts are associated with pathogenicity was unsuccessful. Fortunately, synthetic biologist George Church of the Harvard Medical School offered to screen the parts personally to determine whether any parts were associated with pathogenicity. He found no problem with the parts. The absence of clear standards on the interpretation of Australia Group guidelines suggests the existence of a substantial practical gap in international oversight of trade in potentially pathogenic genetic materials. While George Church's generosity in screening the parts worked in this specific case, expert screening by Church is not scalable as a solution to this general problem in international biosecurity policy.

2-C. ASSESSMENT OF ADEQUACY OF RISK GOVERNANCE: LESSONS LEARNED, ADAPTATIONS MADE

Screening iGEM projects and parts began as a public service activity and evolved into a research project on adaptive risk management. From the outset, iGEM management and the Safety Committee viewed project screening as more than a simple enforcement mechanism. Information on how the technology of synthetic

biology is developing and diffusing is imperfect. Knowledge of how safety and security are understood by teams, advisors and regulatory agencies is limited. Data on how regulators and teams are acting to manage risks is incomplete. Project screening was set up as a means to learn about the technology of synthetic biology and about how humans are governing risks while enforcing iGEM safety standards.

What was learned? Three principal findings emerged.

- Biosafety competency and awareness of local biosafety oversight obligations should not be assumed. Other teams, not working with parts derived from pathogens, showed levels of competency and awareness on biosafety and biosecurity comparable to the team discussed in this case.
- Common perceptions of international variation in biosafety practices are well founded. The review of projects and safety questionnaires found more systematic attention to biosafety standards in Europe, the United States and Japan than in other parts of the world. Variations within regions were also striking, with higher standards in Hong Kong than other parts of China.
- Guidance from authorities on elements of the Australia Group guidelines was not forthcoming. While lists of organisms are self explanatory, the key expression "parts associated with pathenogicity" is ambiguous. In the absence of clearer operational definitions, this component of the international biosecurity regime will remain weak.

What adaptations have been based on what was learned? iGEM is now taking the following actions to address some of the weaknesses identified above.

- iGEM reaffirmed and expanded its commitment to continuing screening for safety and security. The members of the Safety Committee have agreed to serve in 2012, and the Safety Committee was expanded to ease workloads, to have a Safety Committee member in each of iGEM's regional competitions and to broaden its base of expertise.
- To address issues of basic biosafety competency and knowledge at the level of team members and faculty advisors, iGEM is now seeking access to the best web-based biosafety and biosecurity training packages used by nongovernmental organizations and commercial firms to train iGEM teams. The Safety Committee identified several good packages and is negotiating with owners over conditions of use.
- To address ambiguity in the interpretation of the Australia Group guidelines and to screen parts more efficiently for safety, the Safety Committee has been working with the developer of a software and database tool for design and screening under development. In a trial run, the software was used to re-screen the iGEM parts that had been evaluated by George Church. No red flags were raised and some unknowns were identified. iGEM is seeking access to this tool to screen all parts in the Registry.
- iGEM, NSF SynBERC, the FBI, U.S. Health and Human Services, the UN Biological Weapons Convention Implementation Support Unit, and other organizations are considering using this case as part of biosecurity and biosafety training workshops in advanced industrial countries, and in regional training centers in developing countries.

Typically, risks are addressed after the fact, after harms are manifest. In the synthetic biology cases, risks were addressed after warning signs but in advance of manifest harm. As noted in the first security case treated above, the U.S. Department of Health and Human Services (HHS) developed the "Screening Framework Guidance for Providers of Synthetic Double Stranded DNA" and synthesis providers formed the International Gene Synthesis Consortium (IGSC), the International Association of Synthetic Biology (IASB) and the International Consortium for Polynucleotide Synthesis (ICPS) after warning signs and adverse publicity. The iGEM screening measures represent proactive voluntary management of security and safety risks, in advance of demonstrated harms. iGEM accepted an obligation to protect students, publics and the environment through education and by establishing and enforcing screening procedures. The principal take away from the iGEM case is that organizations and individuals that may be generating potential risks should step up with proactive measures to address safety, security and environmental risks before rather than after problems arise.

2.D AN EARLY REPORT ON EARLY ENGAGEMENT BY DARPA LIVING FOUNDRIES PROGRAM

The Defense Advanced Research Projects Administration (DARPA) has recognized the need for early engagement on ethical, legal, and social issues and security and safety risks associated with synthetic biology in its new Living

Foundries Program. The unclassified program aims to develop new tools, technologies and methodologies to decouple biological design from fabrication, yield design rules and tools, and manage biological complexity through abstraction and standardization. No biodefense work is conducted under the living foundries program.[xx]

In June 2011, the DARPA Director and Chief Consul asked the Living Foundries Program Director to establish an advisory committee on emerging ethical, legal and social issues. This top-down request came as Living Foundaries was being formed, and not as an after-the-fact response to crisis. The ELSI advisory group in the living foundries program was explicitly modeled after a Privacy Panel chaired by DARPA Chief Consul [xxi] The members of the ELSI Advisory Committee care leading authorities in diverse fields, including ethicist Arthur Kaplan of the University of Pennsylvania, biosecurity expert and NSABB member David Relman of Stanford University, intellectual property rights and commons expert Arti Rai of the Duke University Law School and the US Patent and Trademark Office, and public perceptions and risk assessment specialist David Rejeski of the Smithsonian Woodrow Wilson Center. These advisors serve as paid consultants to DARPA, and do not fall under the cumbersome provisions of the Federal Advisory Committee Act.

In 2012, the advisory committee was tasked to help shape requests for proposals, review all incoming proposals and flag potential areas of concern in advance, track research as it is conducted and flag emerging issues, assess how results to be released / publicized, and assess potential applications of research. The advisory committee kicked off with day long face to face meeting to orient on DARPA and living foundries, with subsequent consultations via teleconferences with all committee members, bilateral emails and phone calls with the program manager. The advisory committee will be joining in research retreats with performers. Feedback is to be provided through program manager to DARPA director and directly to performers. Advisory committee members are encouraged to discuss their work with anyone they chose in or out of DARPA. If the advisory committee flags a problem, no predetermined process has been set on how to respond. DARPA does not believe that one size is not likely to fit all and that variation from case to case and situation to situation

The key feature of this program is direct engagement of this exceptionally strong committee with incoming proposals and with projects conducted under the program. No specific instructions defining risks and methods of risk governance were established at the outset. Instead, like the iGEM safety committee, the DARPA ELSI committee was created with a mandate to learn from its reviews of projects and from continuing interaction with performers.

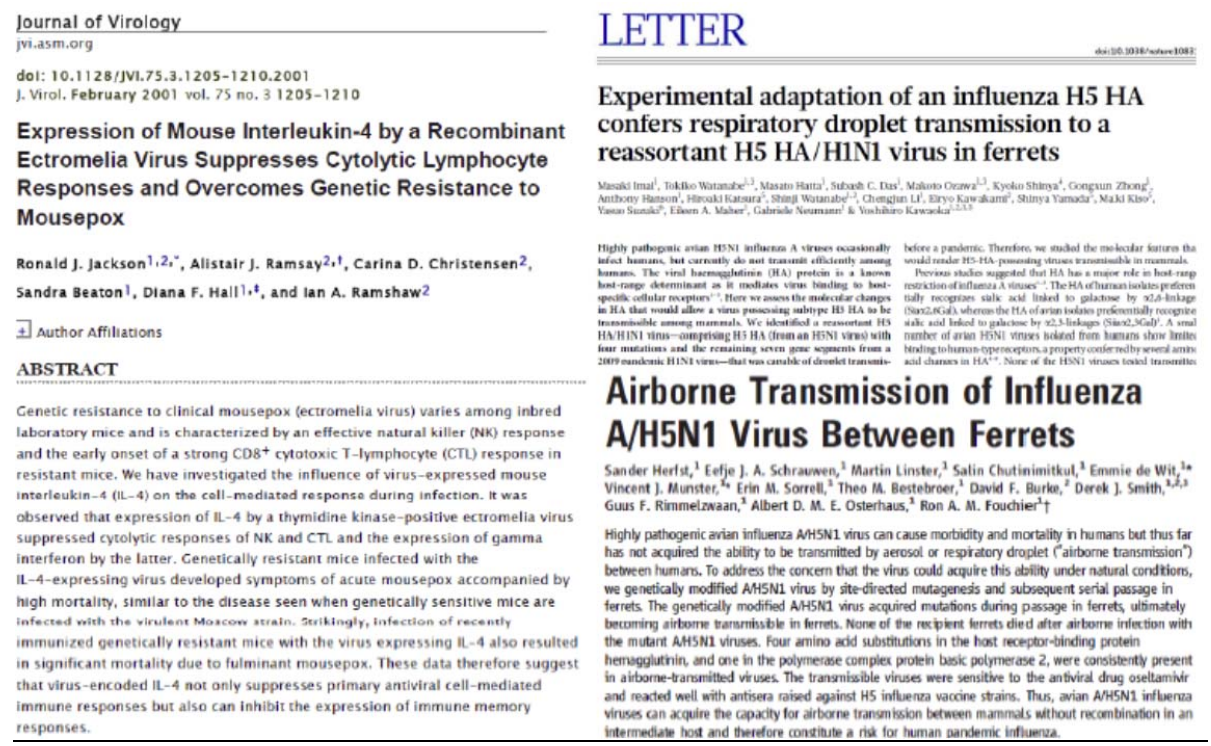
* * * * *

CASE 3. RISKS ASSOCIATED WITH RESEARCH AND PUBLICATION – MOUSEPOX AND H5N1

The most delicate area of security risk governance associated with synthetic biology cuts to the core of the scientific enterprise. Is there research that should not be conducted? Are there results that should not be published? This case discusses briefly the status of the ongoing debate over risk governance through controls on research and publication.

3-A. PROMPTS AND EMERGING RISKS

The emergence of risks in this domain may be divided into three sets of prompts. A paper on Australian mousepox was published in 2000, before 9-11 and the anthrax attacks. It remained a scientific curiosity rather than a prompt to reforms in risk governance. By contrast, the 2005 paper on reconstruction of the 1918 Spanish influenza discussed in Case 1 and the 2012 papers by University of Wisconsin and Erasmus Institute teams on modification of strains of H5N1 to foster mammal to mammal transmission have led to substantial initiatives on dual use research of concern.



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Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox

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Author Affiliations

ABSTRACT

Genetic resistance to clinical mousepox (ectromelia virus) varies among inbred laboratory mice and is characterized by an effective natural killer (NK) response and the early onset of a strong $CD8^+$ cytotoxic T-lymphocyte (CTL) response in resistant mice. We have investigated the influence of virus-expressed mouse interleukin-4 (IL-4) on the cell-mediated response during infection. It was observed that expression of IL-4 by a thymidine kinase-positive ectromelia virus suppressed cytolytic responses of NK and CTL and the expression of gamma interferon by the latter. Genetically resistant mice infected with the IL-4-expressing virus developed symptoms of acute mousepox accompanied by high mortality, similar to the disease seen when genetically sensitive mice are infected with the virulent Moscow strain. Strikingly, infection of recently immunized genetically resistant mice with the virus expressing IL-4 also resulted in significant mortality due to fulminant mousepox. These data therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses but also can inhibit the expression of immune memory responses.

LETTER

Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

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Highly pathogenic avian H5N1 influenza A viruses occasionally infect humans, but currently do not transmit efficiently among humans. The viral haemagglutinin (HA) protein is a known host-range determinant as it mediates virus binding to host-specific cellular receptors[1–7]. Here we assess the molecular changes in HA that would allow a virus possessing subtype H5 HA to be transmissible among mammals. We identified a reassortant H5 HA/H1N1 virus—comprising H5 HA (from an H5N1 virus) with four mutations and the remaining seven gene segments from a 2009 pandemic H1N1 virus—that was capable of droplet transmission before a pandemic. Therefore, we studied the molecular features that would render H5-HA-possessing viruses transmissible in mammals.

Previous studies suggested that HA has a major role in host-range restriction of influenza A viruses[1–7]. The HA of human isolates preferentially recognizes sialic acid linked to galactose by α2,6-linkage (Siaα2,6Gal), whereas the HA of avian isolates preferentially recognize sialic acid linked to galactose by α2,3-linkages (Siaα2,3Gal)[1]. A small number of avian H5N1 viruses isolated from humans show limited binding to human-type receptors, a property conferred by several amino acid changes in HA[1–4]. None of the H5N1 viruses tested transmitted

Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

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Highly pathogenic avian influenza A/H5N1 virus can cause morbidity and mortality in humans but thus far has not acquired the ability to be transmitted by aerosol or respiratory droplet ("airborne transmission") between humans. To address the concern that the virus could acquire this ability under natural conditions, we genetically modified A/H5N1 virus by site-directed mutagenesis and subsequent serial passage in ferrets. The genetically modified A/H5N1 virus acquired mutations during passage in ferrets, ultimately becoming airborne transmissible in ferrets. None of the recipient ferrets died after airborne infection with the mutant A/H5N1 viruses. Four amino acid substitutions in the host receptor-binding protein hemagglutinin, and one in the polymerase complex protein basic polymerase 2, were consistently present in airborne-transmitted viruses. The transmissible viruses were sensitive to the antiviral drug oseltamivir and reacted well with antisera raised against H5 influenza vaccine strains. Thus, avian A/H5N1 influenza viruses can acquire the capacity for airborne transmission between mammals without recombination in an intermediate host and therefore constitute a risk for human pandemic influenza.

Mousepox: In the view of most biosecurity specialists, the Australian mousepox research posed more serious security risks than the better known and more recent Spanish influenza and H5N1 cases. In 2000, an Australian research team inserted the gene for interleukin-4 (IL-4) expression into mousepox in an attempt to stimulate the production of antibodies to render the mice infertile. Instead of the intended effect, the researchers discovered that this engineered mousepox suppressed immune response to viral infections. Normal mousepox usually causes only mild symptoms in the type of mice used in the study. The engineered mousepox, however, killed all unvaccinated mice in nine days and killed half of the mice vaccinated against mousepox. The researchers believe that performing the experiment on smallpox would have the same results in humans.[xxii]

Perhaps the most significant aspect of this experiment is the unexpectedness of the result. Before these results were reported, most researchers had believed that modification of viruses would tend to make them less, not more, dangerous.[xxiii] This unpredictability would be a significant handicap for an organization with limited resources attempting to create genetically modified harmful biological agents. Most attempts to modify naturally occurring pathogenic agents have no dangerous implications and so never come to the attention of those outside the research community. Thus most observers are likely to overestimate the likelihood of such experiments having biowarfare implications. A sub-state actor, or even a state with limited resources, may have considerable difficulty using conventional genetic engineering techniques to change or enhance the effects of natural biological agents.

Although the Australian Mousepox experiment presents what is in retrospect perhaps the most vivid demonstration of security and safety risks associated with advanced biological engineering, this event did not prompt significant action. Attention to bio-safety and bio-security concerns remained low without larger scale events that crossed thresholds of public recognition.

H5N1 Modification to Enable Mammal-to-Mammal Transmission: In 2011, research groups led by Yoshihiro Kawaoka at the University of Wisconsin and by Ron Fouchier of the Erasmus Medical Center submitted manuscripts to *Nature* and *Science* on their modification of the H5N1 virus to enable airborne transmission between mammals. This research had been funded by NIH to evaluate the potential for a human pandemic and to provide an animal model that could be used to develop ways of preventing and controlling outbreaks in humans. The research demonstrated that the H5N1 strain had the potential to mutate in a manner that could threaten human health and offered insights into complex factors associated with host switching and transmission of influenza viruses. NIH funded this "gain of function" research on the premise that characteristics of a virus

associated with mammal-to-mammal transmissibility could aid in surveillance should wild type strains mutate toward a genomic signature predictive of transmissibility and could provide a head start on production of vaccines against such strains. The research and its publication also created security and safety risks. Inadvertent release of the redesigned strains of H5N1 could directly threaten human health, while publication of research results might enable others to synthesize and express an H5N1 strain with mammal-to-mammal airborne transmissibility.

3-B. RISK GOVERNANCE – PRECAUTIONARY CONTROLS ON KNOWLEDGE

What measures to assess and govern risks associated with H5N1 research have been taken? In November 2011, the Kawaoka and Fouchier manuscripts were submitted to the National Science Advisory Board for Biosecurity (NSABB), triggering a cascade of risk governance measures. To date, the H5N1 case has prompted a January 2012 NSABB recommendations for pre-publication controls, a voluntary 60 day moratorium on dual use H5N1 research of concern by the influenza research community, a debate in the Netherlands over use of export controls to block publication, issuance of US guidelines governing dual use experiments of concern, and, ultimately, an NSABB split decision reversing initial recommendations for controls.

1. In January of 2012, the NSABB concluded that the security risks associated with publication of research on the altered H5N1 strains exceeded the benefits of unrestricted publication, and recommended that the authors redact their manuscripts to reduce the risk of inadvertent or malevolent misuse of the information. In the face of mounting criticisms of the H5N1 research and prospective publication, 39 H5N1 researchers opted for a pause. In a statement published in Science and Nature, "We recognize that we and the rest of the scientific community need to clearly explain the benefits of this important research and the measures taken to minimize its possible risks. To provide time for these discussions, we have agreed on a voluntary pause of 60 days on any research involving highly pathogenic avian influenza H5N1 viruses leading to the generation of viruses that are more transmissible in mammals."

2. In March of 2012, the NSABB conducted closed door meetings with the authors of the manuscripts, and heard new information on the likely transmissibility of the altered strains in ferrets and in humans. The NSABB then voted unanimously to allow publication in Nature of a revised version of the Kawaoka paper and voted by 12-6 to allow publication of the data, methods and conclusions presented in a revised version of the Fouchier paper. The NSABB Findings and Recommendations of March 29-30 provide a summary of the axes of disagreement within the Board. The entire Board noted that information that would enable the construction of an H5N1 virus that is highly pathogenic and transmissible between mammals through the air should not be included in manuscripts on security grounds. The majority of the Board found that the Fouchier manuscript, as revised, did not provide such information. The minority of the Board found that the revised Fouchier manuscript provided information that would enable near term misuse of highly virulent strains, while noting that the data in the Kawaoka paper were less dangerous because that team used less virulent viral strains. The minority also concluded that the data in the two manuscripts was not directly relevant or immediately helpful to current public health and surveillance. Both the majority and the minority called for development of mechanisms for disseminating sensitive scientific information to subsets of the scientific community in a controlled manner without specifying how such controls might be enacted. The government of the Netherlands had considered using its authority under export control laws to restrict the shipment of information from the Erasmus group to the journal Science. It dropped consideration of this approach when the majority of NSABB accepted publication of the revised version of the Erasmus article.

3. In March of 2012, the US government issued “Policy for Oversight of Life Sciences Dual Use Research of Concern.”[xxiv] The policy requires formal risk assessment and regular review of federally funded life sciences dual use research of concern.

Under this Policy, review will focus on research that involves agents or toxins which pose the greatest risk of deliberate misuse with most significant potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence. The policy document lists agents and toxins of concern including: a) Avian influenza virus; b) *Bacillus anthracis;* c) Botulinum neurotoxin; d) *Burkholderia mallei;* e) *Burkholderia pseudomallei;* f) Ebola virus; g) Foot-and-mouth disease virus; h) *Francisella tularensis;* i) Marburg virus; j) Reconstructed 1918 Influenza virus; k) Rinderpest virus; l) Toxin-producing strains of *Clostridium botulinum;* m) Variola major virus; n) Variola minor virus; and o) *Yersinia pestis.*

The new policy listed specific categories of experiments of concern. These include any experiment that: a) Enhances the harmful consequences of the agent or toxin; b) Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification; c) Confers to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies; d) Increases the stability, transmissibility, or the ability to disseminate the agent or toxin; e) Alters the host range or tropism of the agent or toxin; f) Enhances the susceptibility of a host population to the agent or toxin; or g) Generates or reconstitutes an eradicated or extinct listed agent or toxin.

Implementation of these requirements will be modeled after the traditional NSABB/RAC system, with local IRBs conducting assessments of proposed research as a part of the grants submission and oversight process. As is the case with traditional NSABB/RAC guidelines, practices affecting recipiants of Federal funds are expected to define norms and expectations more broadly.

4. The journal *Science* embraced the controversy by including extensive commentary on pros and cons of the H5N1 research and publication in the June 23, 2012 issue in which revised Fouchier piece was ultimately published and by granting open access without fees to that issue. External technical assessments of the NSABB risk assessments mirror the disagreements within the board. However, there is near unanimity in external recommendations on process, with critics and supporters of the NSABB decision concurring on the need to engage civil society in dialogue early on. For example, Fauci and Collins note that the intensity of disagreements within the scientific community on risks and benefits of the H5N1 research underscores the need for a rational and transparent explanation of how decisions on research funding and publication are made. They call for a social contract among the scientific community, policy-makers and the general public that builds trust, albeit without specifying how such a social contract might be developed. There is also near unanimity among critics and supporters of the publication decision on the need to fill gaps in technical knowledge on influenza risks on fundamental issues such as the extrapolation of data on virus transmission and pathogenesis from the ferret model to humans, and the need to improve turnaround times between virus isolation and sequencing to provide for real time surveillance. However, there is intense disagreement within the scientific community over the practical value of the Fouchier H5N1 gain-of-function research. [xxv]

3-C. ASSESSMENT OF ADEQUACY OF RISK GOVERNANCE

First, to what extent were mechanisms for precautionary management of potential risks in place? The controversial H5N1 projects were reviewed by specialized review boards at national levels and by traditional local institutional review boards. In the local reviews, it appears that the dual use nature of the research was recognized by boards, but local institutional reviews focused on near term risks associated with research procedures, containment measures, and protective devices that would affect risks to laboratory personnel. Local review boards did not believe that they were competent to treat the possible dual use character of the research and the implications of finding. Under the new US policy on dual use research of concern, local institutional review boards are now charged with responsibility of evaluating the dual use character of the research. It is not clear that the local review boards have the expertise to conduct such assessments.

Second, to what extent was alarm over potential security implications of the H5N1 research justified? On this point, opinion remains divided. Within the medical research community, there is disagreement over the benefits and risks associated with H5N1 gain-of-function research among medical researchers, between NIH and US defense and law enforcement agencies. Biosecurity issues are less salient to civil society than environmental issues and views are divided. Some suggest that the biosecurity risks have been understated by individuals and agencies seeking to protect research areas, to avoid oversight and to defend the quality of past regulatory oversight. Others warn of biases toward exaggeration of security threats by individuals and agencies wanting to move more biological research into the classified realm of National Laboratories. This is a case where expert knowledge may be required to evaluate risks, yet those with expert knowledge are divided on the substance of the issue and are mistrusted by others because material and intellectual interests may be motives for distortion and bias. Assessment of claims by third parties may be advised.

Third, the H5N1 controversy has raised once again the conflict between national security based controls over sensitive information and the scientific and public interest in access to information. The government of the Netherlands had considered blocking publication of details of the H5N1 research by invoking export control laws. Unlike Wikileaks, the Pentagon Papers and other cases, there is no issue of classification in this instance. The research in question was based on open sources and the principals did not make use of classified sources. Within the US, a near analog on restricting access to unclassified information on national security grounds is the US patent secrecy order, where DTRA and the US Patent and Trademark Office screen patent applications and block publication and use of patents deemed to pose a threat to the security of the US. Other near analogues would include US "Deemed Exports" provisions that bar transfer of sensitive knowledge to foreign nationals working in US laboratories. "Exporters" are exempted from this requirement if the technology transfer occurs in the course of "fundamental research" that is pursued without a specific practical aim or with the intention of publication in the scientific or academic literature. However, research and development conducted by private corporations, or funded by corporations, in which the findings are reviewed with the intent of controlling the results to be released in the open literature are considered proprietary and are subject to the licensing requirement. The law governing dual-use exports under Commerce control expired in August 2001 and the regulations are being governed by an Emergency Powers Act. [xxvi]

Note that the second and third points above may be difficult to reconcile. A limit on publication and secrecy by its very nature forecloses open inquiry on the merits and demerits of research. One cannot reach credible outcomes on the merits of arguments on threats to national security and benefits for medical research without access to information.

PART III. ON IMPLICATIONS FOR RISK GOVERNANCE IN OTHER DOMAINS

This section draws general lessons for more effective governance of emerging risks from these cases. Security risks associated with synthetic biology research are now assessed and addressed by diverse public and private sector initiatives. Our three cases treated public/private consortial DNA synthesis screening to back up controls potentially dangerous pathogenic materials, voluntary iGEM screening of projects and parts to shape the diffusion of skills and materials, DARPA formation of an ELSI advisory committee as a proactive component of its Living Foundries Program, and NSABB and HHS regulation of dual use research and publications of concern. In addition to these cases, other measures engaging with synthesis and synthetic biology risks include NSF sponsorship of work on security and environmental risks in its Synthetic Biology Engineering Research Center, and FBI, DTRA and UN educational programs to mitigate security risks. This unusual variation in risk governance approaches is appropriate to an emerging technology whose risks and benefits are imperfectly understood.

A. How to obtain, process and use data where early information is unclear and unreliable

* Breed canaries -- fund research and observation to improve early detection of risks
* Engage broadly – draw in diverse stakeholders from disciplines as a check on ignorance and bias

The NSABB, HHS, NSF and DARPA have all played key roles in promoting engagement with risks in the field of synthetic biology at an early stage, albeit with somewhat different methods and results.

HHS worked with synthesis houses, security agencies and the NSABB to obtain and to update information on synthesis technologies, on screening technologies, on the number and location of customers placing orders for synthesized DNA, and on the number and location of firms providing synthesis services. HHS convened a series of consultative meetings as it formulated the framework guidance on synthesis and worked with security agencies and the screening consortia at the Heidelberg meeting. Synthesis firms provided privately held data to screening consortia and to public agencies with the explicit intent of improving the efficiency and effectiveness of screening guidelines and procedures.

NSF added funding to SynBERC to promote research on safety and security issues within SynBERC, the SynBERC sponsored iGEM program, and within synthetic biology more broadly. This funding was used, in part, to conduct the multidisciplinary safety screening of iGEM projects and parts and to evaluate the practical importance of institutional review boards in areas beyond the most advanced industrial countries.

NSF is now in discussions with the Woodrow Wilson Center and MIT on creation of what might be termed a canary breeding program. This experimental initiative would reduce policy relevant sources of uncertainty on security, safety and environmental risks of synthetic biology. If funded, mixed teams of synthetic biologists, environmental microbiologists, regulators and others would identify areas where early information is unclear or unreliable, and then develop requests for proposals for research that would fill critical gaps in knowledge. NSF would then provide funding for some of the RFPs.

The NSABB sought to evaluate risks associated with H5N1 publication on the basis of manifestly unclear and unreliable early information. At one level, the NSABB relied on the velvet glove of consultation within its membership, authors of the reports and external consultants. At one level, the NSABB relied on the mailed fist, by initially restricting publication and then placing the burden of proof on actors seeking reversal of initial decisions.

The DARPA and iGEM cases illustrates mechanisms for obtaining clearer and more reliable early stage information on human practices as well as narrowly scientific and technical issues. The iGEM project screening approach generated information on the scope and extent of compliance with safety and security standards, on the adequacy of institutional review and on the state of knowledge within national authorities designated to administer Australia group guidelines. The DARPA ELSI advisory group is tasked with early identification of emerging ethical, legal and social problems as well as security and safety risks. The key source of information on emerging risks will be the mixture of proposals and projects that the advisory group will filter and as the conferences with providers.

B. How to make decisions with limited information in situations of complexity and uncertainty

* Use public private partnerships with voluntary guidelines and consortia in early stages
* Encourage majority and minority reports, not consensus

The DNA synthesis screening case is exemplary, with HHS voluntary guidelines and private consortia making and updating decisions with limited initial information. The combination of the informality and flexibility of such

arrangements with explicit commitments to updating and revising responses in the face of new information may be particularly appropriate to the governance of emerging risks. It is important to note that public and private actors in the screening case shared strong mutual interests in improving the effectiveness of screening. Michele Garfinkel, then of the J. Craig Venter Institute, observed that leaders in the synthetic biology community "have definitely expressed concern that one thing is going to go wrong and that thing is going to shut down the industry completely."[xxvii] This strong interest in addressing risks is a fundamental requisite of effective voluntary action.

We also recommend not seeking consensus, but rather fostering assessment and decision making processes with open acceptance of majority and minority reports. Under conditions of complexity and uncertainty, the pursuit of consensus is likely to suppress good analysis and discussion. The NSABB 12-6 split on assessment of risks associated with publication of the revised Erasmus Medical Center H5N1 article should be viewed, not as a problem, but as a step toward better decision making under conditions of limited information. Sources on the NSABB have told me that the highly publicized disagreement over risks was personally painful, but also yielded better assessments of assumptions, analysis of biases and distortions in data, and evaluations of the validity of inferences than would have been the case if a premium had been placed on consensus. In the H5N1 case, different schools of thought emerged naturally as the NSABB deliberated. In other instances, managers of risk governance processes may wish to consider the deliberate introduction of critical perspectives by creating devil's advocates or red teams with the task of challenging accepted truths.

C. How to communicate clearly and effectively with higher management and publics

* Develop briefing materials for higher management and publics but vetted by scientists
* Communicate uncertainty as distinct from risk and benefit.

Clear and effective communication on risks and uncertainty is a particular challenge for synthetic biology - more difficult than communication in fields such as nuclear engineering, pharmaceuticals, air traffic safety. The complexity of advanced biological engineering is daunting. In preparing the Framework Guidance for Providers of Synthesized Double Stranded DNA, Jessica Matthews understood the need to write passages on technical issues to be understood by public officials, lay citizens, nongovernmental organizations and business leaders. The clarity of the Framework Guidance may have contributed to its broad acceptance. For joint MIT-Wilson Center exercises on security, safety and environmental risks of synthetic biology, our MIT group prepared primers on risks intended for the scientifically uninitiated but written to pass muster with field specific experts. To convey degrees of uncertainty, as distinct from risk, primers included information on the evidentiary base for claims and on inferential fights over how to read evidence.

What process was used to produce primers? Leaders of civil society and regulators asked our group to create briefing documents on horizontal gene flow and genetic stability to help them prepare for an upcoming meeting on potential environmental effects of inadvertent release of applications of synthetic biology. We prepared materials through a process of writing and re-writing by mixed teams of scientific experts and nontechnical social scientists. The results of this iterative process were then subjected to review by an environmental activist, an official in the US government, an expert on environmental toxicology from a major firm and a technologist heading a synthetic biology program. The primers were then revised to take account of their suggestions and a glossary was added to define recurring technical terms. Although this process was time consuming and relied on participation of unusually strong writers and reviewers, it may provide a model for communication on other emerging risks.

D. How to increase accountability of people and organizations to address complex, uncertain long range risks

* Punish bad behavior -- need fear of litigation, adverse publicity and regulation to encourage accountability
* Reward exemplary behavior – need concrete benefits from engaging proactively with risks
* Provide solutions – if cannot address complex uncertain long range risks, then actors shed accountability

In many areas of risk governance, actors seek to avoid accountability by not seeking credible information on potential emerging risks. For example, the USDA deliberately used the wrong antibodies in its confirmatory immunehistochemistry tests for BSE, Kraft and other manufacturers opposed NIH funding for research on adverse effects of transfats, and NASA rejected recommendations for more active dynamic testing programs for its shuttle. Synthetic biology is an exception to this generalization of too common willful blindness.

What mechanisms may encourage acceptance of accountability and incentivize actions to engage with emerging risks? Past or prospective penalties for not engaging effectively with risks have been the keys to successes in addressing synthetic biology security risks. The synthesis consortia accepted responsibility because the Guardian humiliated them when they filled orders without screening and because compliance costs were low and because firms feared that mandatory standards would displace voluntary guidelines. The iGEM case of proactive engagement was encouraged, in part, by iGEM management fears of the adverse effects of unsafe behavior on perceptions of the field of synthetic biology. The NSF funded work to address safety and security risks associated with the technologies that it was developing as part of SynBERC and DARPA created an ELSI advisory committee because they believed they would be held accountable for adverse effects.

E. How to address tradeoffs across risk aversion and risk taking

* Improve terms of tradeoffs across risk aversion and risk taking, improve the power curve.
* Promote proactive and adaptive risk governance as alternative to precautionary moratoria and laissez faire.

Too often, approaches to risk governance are defined in terms of a choice between two alternatives. Either accept the precautionary principle but in so doing choke off development of potentially promising technologies, or go with laissez faire and in so doing accept potentially irreversible harms. To improve tradeoffs across risk aversion and risk taking, reduce initial risks by going with initial applications with strong priors on safety and security benefits and by observing early applications with care, then modify the terms of engagement and the range of applications in light of what is observed. In synthetic biology, NSF and DARPA initial support has been directed toward projects with substantial potential benefits and initial risks, with more attention to observation of the effects of early stage experimentation needed.

Adaptive approaches to risk governance are required more often than they are followed. In a survey of 32 US environmental, health and safety cases that all required adaptive approaches to risk management, McCray, Oye and Petersen found only 4 cases where adaption defined in terms of both sensing and feedback took place. In 18 cases, insufficient information was available. In 3 cases, policies changed without an empirical basis for adjustment. In 7 cases, sensing and assessment took place, but policies were static.[xxviii]

In areas beyond synthetic biology, a proactive and adaptive approach to risk governance has taken hold most clearly in the area of pharmaceuticals licensing. Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted safe and efficacious therapy. By contrast, adaptive drug licensing approaches are based on stepwise learning under conditions of acknowledged uncertainty, with initial limits on use, iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. Proposals for adaptive approaches to licensing have been advanced by Health Canada under the term “progressive licensing” and by the European Medicines Agency as “staggered approval.”[xxix]

Relative to other emerging technologies at comparable stages of maturity, potential risks associated with synthetic biology have been the object of more early stage risk assessment, more public and private sector collaboration in formulating risk governance strategies, more systematic efforts at risk communication, and greater acceptance of accountability. After reflecting on lessons learned for other emerging risks from thse synthesis and synthetic biology cases, we should note that many of the best practices from synthetic biology may not transfer easily to other domains. The conjunction of 9-11, the anthrax attacks, rapid advances in synthesis and synthetic biology, the mail order experiment by resourceful Guardian reporters, and an exceptionally intense debate over H5N1 have prompted the actions described in this piece. Absent the strong stimuli that prompted engagement with potential risks associated with synthesis and synthetic biology, academic technologists, commercial bioindustry, and regulators would not have developed and refined the risk governance practices for synthesis and synthetic biology.

[i] Note: This primer is an updated and revised version of a section of Gautam Mukunda, Kenneth Oye and Scott Mohr, “The Rough Beast: Synthetic Biology and the Future of Biosecurity,” *Politics and the Life Sciences* 2009.

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