Synthetic Biology and Infectious Disease: Challenges and Opportunities**

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Summary

The tools of molecular biology (e.g., genetic engineering or synthetic biology) have advanced to the point where it is possible to synthesize the genomes of viruses and small organisms without nuclei (prokaryotes) *de novo*, and to carry out significant modifications of the genomes of larger microbes and higher organisms with nuclei (eukaryotes). There is also a potential to create novel organisms that have an origin largely independent of evolution. Our ability to predict the properties that genes, both new and old, will confer on organisms is incomplete. As a result, our understanding of how novel organisms will behave is to some extent unknown. The potential hazards associated with engineering organisms are inherently different from those of other fields because the agents involved have the potential to spread from small numbers, to proliferate outside of human control, and to evolve. These points notwithstanding, synthetic biology offers enormous opportunities to better human life, including preventing infectious disease. However, these same tools also offer opportunities for disease creation either by chance or as forms of economic sabotage or terrorism. The ability of engineered organisms to reproduce and to cross international borders, with potential effects on the environment and human health far from their site of origin, creates a unique set of scientific and regulatory issues that are just beginning to be considered. Research, regulation, and education are needed to promote beneficial uses of this technology in a responsible manner that limits opportunities for harm through ignorance, sloppiness, or design.

Current realities

It is now possible to synthesize large DNA molecules at low cost. These and other costs associated with genome engineering will continue to decrease, allowing us to rapidly determine the sequences of pathogens or potential pathogens, and to modify and create templates for entire organisms at will. Genome sequences, including those of known pathogens, are made available through publications and have been used to synthesize the genomes of known pathogens (e.g., 1918 influenza and polio). These synthetic genomes give rise to infectious viruses when introduced into cells, illustrating how information plus reagents can be used to create an infectious agent. The sophisticated genome manipulation and cell culture involved in bringing these pieces of DNA to life currently require a large amount of tacit knowledge, acquired through extended training in academic or industrial settings. However, there is a new community of individuals (the do-it-yourselfers) who conduct genetic engineering in private settings. This community will grow as costs decline and kits become available, making it easier for those with less specialized knowledge and funding to carry out sophisticated manipulations. A parallel increase in our ability to rapidly and cheaply sequence DNA provides a critical method for identifying known or unknown infectious diseases of plants, animals, and humans.

Synthetic biology is used to prevent infectious disease in many ways. First, engineered organisms are used as bioreactors to produce drugs or vaccines. In addition, disease agents that are identified via sequencing and direct isolation are synthesized and/or manipulated through genetic engineering to identify genes needed for essential pathogen functions such as entry, replication, and evasion of the immune system. It is important to note that, as part of this work, viruses have been created that were unexpectedly more harmful than the original virus, highlighting the potential for the creation of organisms with novel properties. Finally, synthetic biology is being used to engineer populations of disease vectors (e.g., mosquitoes), to make them unable to transmit disease or to bring about a vector population reduction, in either case

preventing disease transmission. Genes that prevent mosquitoes from transmitting disease have been identified or created, and genetic tricks for promoting the spread of these genes in wild mosquito populations are under development in the lab, but have not been tested in the field.

In the United States, synthetic biology is regulated through multiple federal agencies. DNA synthesis companies currently screen sequences for similarity to the genomes of known pathogens and the toxins they encode. When sequences of potential concern are identified, these companies also screen customers to confirm their identities, and ensure that customers have a legitimate use for the DNA and have considered safety/biosecurity issues. These actions are voluntary and subject to different levels of scrutiny depending on the company. The purchase of DNA synthesis machines themselves is not subject to regulation or monitoring. Transborder movements of genetically modified (GM) organisms are regulated through national and international mechanisms. Much of this is piecemeal, with different agencies involved depending on the organism. A number of countries, including the U.S., are not party to the Cartegena Protocol on Biosafety, an international agreement that regulates transboundary movement of GM organisms, and which would serve as an obvious framework within which to regulate the movement of other GM organisms. There is no clear, public resource that details regulations governing modified organisms or that outlines the principles and practices of risk analysis as they apply to different kinds of GM organisms.

Scientific challenges and opportunities

Dangers to human health from genetically modified or purely synthetic organisms are largely hypothetical. That said, it is important that rules be identified which can be used to predict the potential of an organism to spread and cause disease. Within this work, the synthesis of pathogens is challenging and controversial. While it involves altering known pathogens to make them less able to cause disease, it also mandates that we work to create novel potential disease agents as a way of understanding what the minimal requirements are to make an organism a pathogen. It is also important to study the evolution of engineered organisms. What are the forces that act to change these organisms over generations? How do these forces act on the genes we introduce to maintain, alter, or eliminate function? In a related vein, we must identify methods for engineering organisms that have built-in fail-safe devices that can limit their ability to survive and proliferate outside the relevant environment. It is particularly important to identify methods for making an organism's survival and/or proliferation dependent on laboratory reagents not found in the wild. Such technology, if incorporated into the design of engineered or purely synthetic organisms, would alleviate concerns about the chance creation of pathogens, though it would not prevent their deliberate creation.

Similar considerations apply when the goal is to alter a wild disease-vector population. We need to continue developing methods for spreading genes that prevent disease transmission into wild populations. We also need to identify genetic methods that will: (i) contain the spread of these genes within regions that support the use of genetically engineered organisms for disease prevention, and (ii) allow for elimination of transgenes from the wild, if necessary.

Policy issues

- Develop funding mechanisms through the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) that promote the identification, synthesis, and study of new and emerging pathogens, and the deposition of information relating to these pathogens in open databases. Private-sector funding is unlikely to be significant given the general lack of

perceived commercial opportunities. Promote the internationalization of this effort through WHO so that expertise in sampling and analysis is developed locally.

- Develop a harmonized, international regulatory structure that requires monitoring of all DNA synthesis orders for human, animal, and plant pathogens or toxins, as well as for customer identity. Information should be saved indefinitely. Sale of other technologies, including DNA synthesizers, sequencers, cell culture equipment, and bioreactors, should also be monitored because of their dual-use capability. In the U.S., the FBI is the lead agency in investigations of possible terrorist threats, including biological weapons.

- Given the specialized nature of the data being examined, a tiered system is needed. Agencies with greater expertise in biology (e.g., the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), CDC, and NIH) should coordinate archiving and analysis of sequences and consumer information from synthesis companies. It is more appropriate for only problematic cases to be referred to the FBI and international counterparts.

- At the international level, the International Health Regulations (IHR) structure should be used to mandate screening for pathogens and possible toxins. Other parties, such as the Food and Agricultural Organization (FAO) and the World Organisation for Animal Health (OIE) should take the lead in screening for agents that may damage the environment and/or plant and animal health. A mandate that synthesis orders be screened and archived for all customers will be challenging to implement since some orders will involve intellectual property; however, if an event occurs, it will be important to have all sequences immediately available to facilitate rapid identification of the pathogen and its creators.

- Develop regulatory guidelines that apply to all parties engaged in genetic engineering of organisms, regardless of funding source. This will require that those carrying out this work become licensed (e.g., requirements for driving, flying, amateur radio, or gun ownership) through training that serves to ensure minimal competency and acquaintance with relevant regulations and sanctions. These guidelines should be based, in part, on those for NIH-funded work, with input from federal agencies (e.g., the U.S. Department of Agriculture (USDA) and its Animal and Plant Health Inspection Service (APHIS), EPA, and FDA) and international organizations (e.g., WHO, FAO, and OIE). These guidelines should specifically address issues related to the potential consequences of release of engineered organisms into the environment. These guidelines should be regularly revisited and updated as new information comes in and risks are identified.

- Regulatory guidelines should be linked to a public clearinghouse that provides descriptions of regulations, contact information, and flow charts that detail paths through the regulatory process. This clearinghouse should also contain descriptions of risk analysis as applied to particular classes of agents, and be updated with information on potential or likely harms associated with genetic engineering using particular organisms and/or parts. It should also provide, or be linked to, unbiased information on the state of genetic engineering technology and regulatory oversight.

- Work with other countries (perhaps through WHO, FAO, OIE) to craft similar regulations and outreach programs. For GM vectors of disease, work with countries with significant levels of vector-borne diseases to create a regulatory structure that promotes the possible use of these tools to enhance human health while minimizing risk and respecting divergent views on the acceptability of GM organisms. These regulatory

structures should be separate from those — such as the Cartagena Protocol — designed around GM crops, because they may not be applicable to all GM organisms.

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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. Bruce Hay (see above). Dr. Hay 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. Hay. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Hay, 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

- Rapid technological advances in the field of synthetic biology (e.g., developments in recombinant DNA technology and genomics) have led to many new discoveries applicable to the prevention and control of infectious diseases. Technological progress and decreased costs have facilitated a substantial increase in the number of amateur scientists, known as "do-it-yourselfers" (DIYers), who design, redesign, and fabricate biological components and systems. Although DIY scientists have made and will continue to make critical discoveries in the field, it is important that this community adheres to the same regulations and receives the same training as professional scientists.

- Because synthetic biology utilizes living organisms that can replicate on their own and evolve, it is critical for potential risks to be identified and addressed. Deliberate or accidental harm to humans (i.e., stemming from bioerror or the unpredicted evolution of designed organisms) may be caused by the engineering or re-engineering of organisms. The potential for harm must be limited through improved biosafety measures, including expanded regulation (mandatory and/or voluntary), as well as training in areas of biosafety, biosecurity, codes of conduct, and ethics.

- While intentional harm (e.g., caused by "lone rangers," rogue DIYers, or coordinated bioterrorists) is a significant concern, it is impossible to entirely eliminate this risk. Mandatory regulations (e.g., licensure requirements and the creation of a centralized intelligence database) will, to some degree, decrease the likelihood of successful illicit conduct, but there will always be ways for individuals to work around such rules. Mandatory regulations are accordingly better for tracing negative events to their source after the fact. Self-regulation should accordingly be employed in concert with mandatory regulation to promote positive practices and to increase the relaying of intelligence knowledge from scientists themselves to law enforcement. Given concerns that over-regulation will stifle innovation, a balance between mandatory and voluntary regulation is needed.

- Training of both professional and DIY scientists currently takes place. In the United States, this is exemplified by the training courses offered and promoted by the Federal Bureau of Investigation (FBI). However, there is a lack of awareness of existing training opportunities among both groups of synthetic biologists. Awareness of existing training programs must be raised through expanded outreach efforts. Additionally, increased training programs are needed.

Current realities

In the last decade, there have been significant scientific advances in the burgeoning field of synthetic biology (i.e., in sequencing and manipulating DNA in existing and simple organisms to create novel organisms). It was recognized that such developments have been produced both by highly trained scientists (primarily micro- and molecular biologists) within established academic and private institutions and by DIY scientists. While conventional scientists conduct synthetic biology research in highly supervised, well-resourced laboratories, DIYers commonly conduct their research in makeshift, unsupervised labs set up in kitchens, garages, and small storefronts. Additionally, DIYers do not typically have the same formal training as their conventional counterparts. The emergence of the DIY synthetic biology community has been accelerated by its members' ability to access equipment and materials at affordable costs (e.g., by purchasing secondhand DNA sequencers, synthesizers, or construct incubators online or at garage sales), as well as the online availability of genetic code and sequence data. It was noted that some DIYers will evolve to become registered commercial entities, but others will remain under the radar and avoid corporate registration and legal business formalities.

Advances in synthetic biology have been used for health promotion efforts, including infectious disease prevention, treatment, and control. While much enthusiasm was expressed for the positive discoveries that synthetic biology could produce for health, it was strongly emphasized that there are potentially dangerous elements associated with research in this area. Technologies that have both beneficial and potentially harmful applications are known as "dual use" technologies. There was substantial discussion of individuals whose goals are to use synthetic biology for nefarious purposes. It was noted that these individuals fall into three primary groups: (i) lone rangers who are highly trained biologists, work in established labs, and pose an insider threat, (ii) a handful of rogue DIYers, and (iii) coordinated bioterrorists who work in groups and possess varying degrees of formal training.

Some of the individuals who aim to cause harm may simply be testing the system to see what boundaries they can cross (both legally and scientifically), while others may intend to genetically engineer agents for harmful purposes. One way that synthetic biology could be exploited would be to recreate known pathogens in a lab to circumvent the legal and physical controls that currently limit access to select agents (i.e., agents flagged by the U.S. government as posing a biological risk). Yet, it was also noted that because synthetic biology is an intellectually difficult enterprise, the threat of bioterrorist activities is partially mitigated by the fact that it would be challenging for even the most highly skilled scientists to produce in large quantities and spread the engineered organisms that can cause damage to humans.

It was contended that since the inception of bioengineering in the 1970s, there have been no significant, adverse human events related to the release of genetically modified organisms (GMOs). Although adverse events have not been identified, a large portion of the debate focused on the increased potential for intentional or unintentional harm. Intentional harm was primarily discussed in terms of potential terrorist activities. It was suggested that since much of the genomic data are stored in digital form, and genomic synthesis is now computer driven, the potential for individual- and country-level illicit activity has significantly increased. Terrorists, it

was noted, also have access to much of the same information for gene synthesis as established scientists (e.g., from scientific articles and in publicly available Web sites such as PubMed). However, concerns related to potential harm that could be caused by legitimate synthetic biology-related activities were also expressed. For example, it was questioned what would happen if the deliberate release of genetically modified mosquitoes (for malaria prevention) has unexpected negative side effects. It was argued that credible synthetic biologists should always build fail-safe measures into their work so that it is possible to reverse any new organisms that have been released.

In addition to biosecurity, biosafety (i.e., the safe transfer, handling, and use of any living modified organism) was highlighted as a major concern. It was noted that biosafety efforts related to synthetic biology are globally diverse. Although some countries have implemented national regulations and monitoring efforts (e.g., lab inspections) for work related to GMOs, there is a lack of uniformity in their regulatory approaches (e.g., mandatory regulations that apply to both professional and amateur scientists, mandatory regulations that apply only to professional scientists, and/or voluntary regulations). There was no agreement on which method is most effective. Proponents of a mandatory approach cited a need for improved oversight, while advocates for a voluntary approach argued that laws would need to change too frequently to be useful for this rapidly evolving technology.

Although mandatory and voluntary regulatory efforts do exist, there was general agreement that many researchers, as well as some government agencies, are not aware of these initiatives. To illustrate this point, it was contended that 85% of researchers are not familiar with the U.S. National Science Advisory Board for Biosecurity (NSABB). The NSABB is charged with speaking on behalf of and guiding scientific researchers on biosecurity issues. Also of note, data are currently collected and screened in the context of commercial trade of manufactured genomic sequence building blocks. The data include the contents of purchase orders, as well as the identity of sellers and purchasers (i.e., the individuals, academic institutions, and private companies procuring genomic information). Yet, there was a general lack of understanding as to who currently collects the data and how they are subsequently used to investigate potential terrorist threats.

It was noted that most existing data collection and screening efforts are based on self-regulation in the field, are voluntary, and solely focus on select agents or parts of select agents. Several international consortia, composed of research and commercial biotech companies, have been organized to address bioethics, biosafety, and security concerns associated with synthetic biology and develop best practices and codes of conduct. Specifically, the Germany-based International Association Synthetic Biology (IASB) and the U.S.-based International Gene Synthesis Consortium (IGSC) address issues related to the creation of databases to assess the validity of clients, recordkeeping of purchasers for tracking purposes, and the development of contacts with law enforcement.

Using examples and hypothetical situations, the debate clarified the procedures used by U.S. law enforcement for monitoring, investigating, and prosecuting the potentially illicit purchase and use of biological material. The process combines voluntary measures with governmental oversight. U.S. companies are expected to contact their local FBI Weapons of Mass Destruction (WMD) coordinator if they receive suspicious orders (e.g., neurotoxin genes from a dubious point of origin) from other companies or individuals based in the U.S. The case may also be referred to the U.S. Department of Commerce. Questionable requests from a suspicious country and threats on the control list are referred to the U.S. Department of Commerce. Other relevant agencies (e.g., Centers for Disease Control and Prevention [CDC] and U.S. Food and Drug Administration [FDA]) may also be consulted to provide an assessment. If the assessment determines that a pathogen or biological agent is on the “select agents” control list, the Department of State may be brought in to investigate the case. Concern

was expressed that this process may cost businesses time and money. However, it was pointed out that the FBI has an expedited process for legitimate orders (i.e., they can clear the order by next business day). If everything meets the requirements, the individuals are informed of necessary import/export documentation.

In addition to providing oversight, it was highlighted that the FBI is heavily engaged in training activities within the synthetic biology community. The FBI provides training to scientists within academia, the private sector, and the DIY communities to explain the laws and regulations that govern synthetic biology practice, provide education on performing research safely and securely, and identify opportunities for improving biosecurity by working with stakeholders to determine risks.

Scientific opportunities and challenges

There was general consensus that the scientific advances in DNA sequencing and manipulation of existing organisms that have transpired during the past decade have created new opportunities for health promotion by allowing agents to be created much more easily than in the past. Such advances have not only enhanced the synthetic biology research opportunities for professional scientists, but have also facilitated the growth of ideas generated within the DIY scientific community. Recognition of DIYers as accepted players in the field is rapidly growing. However, it was also noted that the disparate training and oversight levels among these amateur researchers have intensified the need for a balance between safety and scientific discovery within synthetic biology.

Global protection against the malicious use of DNA sequences (e.g., bioterrorism and experiments by “mad geniuses”) was recognized as a significant challenge during the debate. It was argued that laws and regulations are imperfect solutions because individuals with harmful intentions may either completely disregard such rules or work around them (e.g., employing genetic elements that are not on the select agents lists). It was also noted that it is often difficult for the intelligence community to identify groups such as lone rangers, rogue DIYers, and coordinated terrorists. Detecting lone rangers is problematic because they frequently work under the auspices of credible research in established universities or institutions. As such, they have the ability to purchase dual-use equipment and other materials through unsuspected channels. DIYers, on the other hand, pose a challenge because they often work in isolation. Both DIYers and coordinated terrorists conduct their research without oversight from universities or corporations.

It was contended that it is also extremely difficult to protect against potential biological mistakes that endanger public health and human safety (i.e., bioerror). Such unintentional harm could be caused by the *accidental* release of genetically-engineered plant, animal, or human organisms. Inadvertent damage may also result from the *purposeful* release of freely reproducing, novel modified organisms when unforeseen (or even unimaginable) outcomes occur. Although few major bioerror problems have been reported to date, it was argued that minimizing risk through improved biosafety mechanisms will be of critical importance.

It was proposed that a centralized intelligence database should be created to catalog the purchase and sale of genetic material at national and international levels. The primary purpose of such a database would be to protect against individuals who intend to produce modified organisms for intentional harm. However, numerous obstacles and prerequisites to the success of such a database were outlined during the debate: (i) it would be challenging to keep a centralized database up to date, especially in real time; (ii) currently, formal channels to collect data on non-select agents do not exist and cunning individuals who intend to cause harm may try to stay under the radar by genetically engineering non-select agents; (iii) if data on non-

select agents were included in such a database, the size of the database might make it too difficult to detect red flags (it was also argued that the size of the database does not matter and therefore there was no agreement on this point); (iv) intelligence databases may be able to more accurately trace the chain of events leading to a realized event than they can predict insider threats or other bioterrorist activities, and thus, the end-goal of a database should be clarified from the outset; and (v) it would be imperative for such a database to be screened on a regular basis by an agency assigned this responsibility. These issues must be reconciled before efforts to create a centralized intelligence database can move forward.

There was general agreement that regulating synthetic biology without stifling innovation is a tremendously difficult task. Different viewpoints on the intersection of regulation and scientific discovery were expressed. Some argued that loosening mandatory regulatory controls (e.g., fewer limitations on select agents) would help ensure that opportunities for biological advancement are not overly constrained. Proponents of limiting the scope and number of formal mandates contended that increased self-regulation should be encouraged instead. Conversely, those in favor of formal oversight maintained that conducting synthetic biology research is a privilege and not a right. They further asserted that compulsory regulations related to licensure and continuing educational credentialing would not counter innovation and that there are successful models (e.g., Australia) that can be emulated.

Policy issues

A large part of the discussion centered on the need to limit intentional or unintentional harm that may be caused by the design/redesign and construction of biological parts, devices, and systems through synthetic biology. There was general agreement that enhanced training of professional scientists and DIYers engaging in synthetic biology is necessary. It was asserted that training is essential for laws to be effective. There is currently a lack of clarity concerning legal demarcations in what activities are permissible within synthetic biology research, as well as in the proper protocols that must be followed. Moreover, it was contended that training also benefits self-regulation by teaching professional and DIY scientists how to deter bioterrorist activities. Specifically, it was suggested that education, training, and outreach are needed in the areas of biosafety, biosecurity, codes of conduct, and ethical aspects of genetic engineering. It was cautioned, however, that training programs will need to be regularly updated because of the rapid evolution of synthetic biology technologies and regulations.

It was asserted that, in the U.S., training is already being conducted: The FBI plays a large role in training efforts aimed at both the professional and DIY synthetic biology communities. It was generally agreed, however, that many scientists are not aware of existing training. Although it was noted that the FBI has made a concerted effort to raise awareness of its training programs (e.g., via outreach at the International Genetically Engineered Machine (iGEM) competition), it was strongly recommended that additional outreach and advertising is needed by all agencies conducting training.

It was suggested that solutions for addressing potential harm caused by the misuse of synthetic biology also need to take into account the possibility of insider threat (i.e., professional scientists in academic institutions or private companies who aim to use synthetic biology for injurious purposes). It was generally agreed that there is no fail-safe solution to insider threat, and that zero risk is impossible to achieve. For example, proposed solutions, such as a central intelligence database, were believed to be unable to ensure the detection of insider threats before the execution of a harmful event. However, despite limitations to insider threat prevention, certain activities should nevertheless be performed. In particular, promotion of self-governance and the existence of codes of conduct were stressed as areas where improvements are needed. This form of threat should be countered by intelligence activities, such as

interviews by FBI agents, who are heavily engaged in averting insider threats and engaged in surveillance oversight and biosecurity outreach to specifically address this issue (e.g., ethics training and scientist education on how to identify and report suspected insider threats).

It was proposed that governments should implement knowledge-based licensing of all scientists who genetically manipulate organisms that could accidentally or purposefully be released. Synthetic biology licensing should be akin to other forms of professional licensing (e.g., medicine and law) or operational licenses (e.g. motor vehicles) and only licensed individuals could obtain reagents to conduct their work. To further induce licensure, it was suggested that patent offices could be advised to recognize only the ideas of those who are licensed. Synthetic biology licensing could be carried out by the government, professional associations (e.g., American Medical Association), or through community self-regulation. The development of acceptable licensing standards would facilitate the work of law enforcement, and accordingly, threat prevention. There was no agreement, however, over whether such licensing is necessary, and some argued that it could be counterproductive.

It was suggested that over-regulation may stifle innovation. Some questioned why those engaging in synthetic biology activities should be singled out for restrictive regulations (e.g., licensing or mandates to register in a database). Other fields, such as computer programming, may also pose significant threats to individuals and societies (e.g., via computer hacking). It was counter argued, however, that because this unique aspect of biology deals with living organisms that can replicate on their own and evolve, it constitutes a special case and necessitates such measures.

Although it was stated that the regulation of synthetic biology is a subject of recent concern, it was countered that the Organization of Economic Cooperation and Development (OECD) has been engaged in efforts to regulate genetically modified foods since 1985. Furthermore, it was noted that the Cartagena Protocol on Biosafety is an existing international agreement that is focused on addressing the risks posed by genetically modified organisms. Approximately 30 countries have not ratified the Cartagena Protocol, including the U.S. It was accordingly questioned why the U.S. is unwilling to become a party to the Protocol as a policy-level solution to some of these regulatory issues. There was agreement that trade implications are the reason that the U.S has yet to ratify the Cartagena Protocol, which therefore is unlikely to be a realistic policy solution.