Freedom and Responsibility in Synthetic Genomics: The Synthetic Yeast Project

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ABSTRACT First introduced in 2011, the Synthetic Yeast Genome (Sc2.0) Project is a large international synthetic genomics project that will culminate in the first eukaryotic cell (*Saccharomyces cerevisiae*) with a fully synthetic genome. With collaborators from across the globe and from a range of institutions spanning from do-it-yourself biology (DIYbio) to commercial enterprises, it is important that all scientists working on this project are cognizant of the ethical and policy issues associated with this field of research and operate under a common set of principles. In this commentary, we survey the current ethics and regulatory landscape of synthetic biology and present the Sc2.0 Statement of Ethics and Governance to which all members of the project adhere. This statement focuses on four aspects of the Sc2.0 Project: societal benefit, intellectual property, safety, and self-governance. We propose that such project-level agreements are an important, valuable, and flexible model of self-regulation for similar global, large-scale synthetic biology projects in order to maximize the benefits and minimize potential harms.

KEYWORDS synthetic biology; ethics; governance; oversight; yeast

AT the dawn of a new scientific field, it is incumbent on the scientists involved to consider not only the scientific challenges ahead but also the ethical and policy implications their work is likely to generate. Ideally, such consideration takes place in advance of the science; however, this is not always possible because new and unanticipated issues inevitably arise as a field develops, while other concerns fade away in the face of data and experience. Synthetic biology is on a continuum with the recombinant DNA (rDNA) research of the 1970s, and like the pioneers of rDNA, synthetic biologists are at the beginning of the process of dreaming of possibilities and forecasting risks without yet having the benefit of much data or experience. Synthetic biologists also echo their rDNA predecessors via a focus on ethical and policy issues. This focus is motivated by several of the features that are unique to synthetic biology, including the application of engineering principles to biology and the enthusiasm and participation of citizen scientists and the emerging do-it-yourself biology (DIYbio) laboratories. Concerns also have been raised regarding two particular types of synthetic biology experiments: those whose products are intended to benefit society but also hold the potential to cause harm (dual-use experiments) and those that aim to generate novel organisms for environmental release and use in medicine.

As with other emerging areas of science, synthetic biology has at times been ahead of not only the ethics but also the policy and often lies outside existing oversight mechanisms in academia and industry alike. In the case of synthetic biology, this is also true of DIYbio labs, which operate outside the standard academic and commercial oversight mechanisms. The potential—both good and bad—of synthetic biology has contributed to the field's mythos among the public as a source of both fascination and concern. Coupled with nascent oversight, this potential also suggests that scientists working in the field bear the unique responsibility of ensuring that the work they are contemplating or conducting is carried out in a way that maximizes the opportunity for benefit while minimizing the risk for harm.

In what follows we describe the efforts of one large international synthetic biology project [the Synthetic Yeast Genome 2.0 (Sc2.0) Project] to identify, anticipate, and

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mitigate potential risks associated with the work while maximizing potential benefits. Our approach to self-regulation is clearly on the continuum with the pioneers of rDNA technology and the Asilomar Conference that took place in 1975, which was arguably the birth of self-regulation in the biological sciences (Department of Health and Human Services 2012). We suggest that project-specific regulation similar to our approach should be an important component of oversight in synthetic biology moving forward.

Current Landscape

Synthetic biology is a young, dynamic field that is on the frontier of discoveries and developments in science and technology. As with other emerging fields, policy relevant to this area of science is not keeping pace with the science itself. Currently, the policy landscape is dominated by a few broad, voluntary guidelines. Further, technology assessment that might inform new policy is challenging because both risks and benefits are often difficult to predict (Carlson 2011). In this commentary, we summarize the current policy landscape governing synthetic biology and highlight several efforts to assess the policy and ethics implications of this field.

In the 1970s, many scientists, as well as the general public, raised concern about the safety and direction of rDNA research. To address these issues, scientists enacted a voluntary moratorium on all rDNA research until they had considered the risks and risk-mitigation and oversight strategies. One important outcome from this process was the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Talbot 1980). These guidelines, along with the Recombinant DNA Advisory Committee (RAC), have governed NIH-funded recombinant DNA research in the United States for decades and have heavily influenced international policy. Today, the *NIH Guidelines* serve as the main document regulating U.S. synthetic biology research. The *NIH Guidelines*, now called the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, are reviewed and revised periodically to keep pace with current research. Institutional biosafety committees refer to these guidelines to determine the risk groups and biosafety levels of the organisms used in experiments, to ensure their proper handling and containment, and to minimize risk stemming from their use (Department of Health and Human Services 2013).

Recently, the U.S. Department of Health and Human Services (DHHS) issued a set of voluntary screening guidelines for companies producing and selling synthetic DNA (DHHS 2010). These DHHS guidelines focus mainly on confirming that the DNA sequence ordered does not code for harmful agents or toxins and on validating the identity and credibility of the individuals placing orders. The guidelines recommend further investigation as to whether either the nucleotide sequence or the customer raises a "red flag." If the DNA synthesis company cannot resolve DHHS concerns, the guidelines recommend that the company contact the nearest FBI Weapons of Mass Destruction Coordinator for further assistance. DNA sequence-matching software can help to flag sequences that correspond to agents or toxins on the Select Agents Regulations List or the Export Administration Regulations' Commerce Control List. Further, the DHHS guidelines advise each DNA synthesis company to develop its own evaluation system to help verify the authenticity and corporate identity of its customers, the validity of the primary user of the synthetic DNA sequence, and the intended end use of the product. The DHHS guidelines recommend that the DNA sequence companies refer to the Departments of Commerce, State, and Treasury lists of blocked entities to ensure that the customer or affiliated institution is not listed. The DHHS guidelines also stress the importance of maintaining order records, including those that were flagged but ultimately deemed acceptable, for at least 8 years.

On a global level, synthetic biology is regulated in broad terms by the multilateral treaty that was agreed to in 1992 at the United Nations Convention on Biological Diversity (the Biodiversity Convention) and signed by most countries (United Nations Environment Programme 1992). This convention focuses on the worldwide preservation of biological diversity, sustainable use of biological resources, and fair distribution of the benefits from genetic resources. The most recent UN Biodiversity Conference was held in October 2014, and the parties present were urged to preemptively establish regulations regarding the environmental release of synthetic biology products and to require appropriate risk assessments before authorizing a novel organism for field testing (Convention on Biological Diversity 2014). The Biodiversity Convention now also includes two supplements that address synthetic biology research and synthetic biology products: the Cartagena Protocol on Biosafety (Secretariat of the Convention on Biological Diversity 2000) and the Nagoya Protocol (Secretariat of the Convention on Biological Diversity 2010). The Cartagena Protocol focuses on biosafety aspects associated with biotechnology research, while the Nagoya Protocol focuses on the fair distribution of the benefits from biotechnology research throughout the world. Ultimately, each country is responsible for ensuring that its national laws are in accordance with this treaty.

In addition to regulatory action, there has been considerable academic and pragmatic interest in the governance of synthetic biology. Continuing in the tradition of rDNA scientists, Maurer, Lucas, and Terrell produced a white paper prior to the 2006 Second International Meeting on Synthetic Biology (2006 SB2.0 Meeting) outlining a plan of action for synthetic biology research with a focus on biosafety and biosecurity (Maurer *et al.* 2006). This paper and subsequent discussions emphasized measures that the synthetic biology community could take to complement the precautions taken by DNA synthesis companies. The recommendations focused on self-policing, insisting that all scientists working in synthetic biology should purchase DNA only from DNA synthesis companies that follow the DHHS guidelines.

Maurer *et al.* (2006) also emphasized that synthetic biologists should be equipped with the knowledge and tools necessary to address scientific "gray areas" and suggested that one approach could be the incorporation of ethics training into the synthetic biology curriculum. Finally, Maurer *et al.* (2006) proposed the establishment of a confidential hotline for reporting biosafety and biosecurity concerns.

As part of their ongoing efforts to minimize the risks and maximize the benefits of synthetic biology, the Woodrow Wilson International Center for Scholars runs the Maps Inventory project. Started in 2009, this project maintains an up-to-date world map highlighting the academic and commercial institutions where synthetic biology work is being done (Woodrow Wilson International Center for Scholars 2014a). The project also maintains the Synthetic Biology Applications Inventory, which lists notable commercial synthetic biology products (Woodrow Wilson International Center for Scholars 2014b).

Also in 2009, the Hastings Center launched a project to study ethical issues in synthetic biology (Kaebnick *et al.* 2014) to identify the potential benefits and risks of synthetic biology and survey its effects on humankind. The project leaders stress that it is important to consider these factors in deliberations concerning governance of synthetic biology. Project materials are available online, including recorded lectures and presentations and a series of articles and commentaries (http://www.thehastingscenter.org/Research/Archive.aspx?id=1548).

In 2010, the U.S. Presidential Commission for the Study of Bioethical Issues published a report on synthetic biology in response to Craig Venter's publication of the first cell with a fully synthesized genome (Presidential Commission for the Study of Bioethical Issues 2010). The commission found no reason to halt synthetic biology research, nor to enact new laws governing the science, at that time. Instead, the commission stressed the importance of ongoing dialogue between synthetic biologists and the general public, recommending "prudent vigilance" as technology moves forward (Presidential Commission for the Study of Bioethical Issues 2010). The Woodrow Wilson Synthetic Biology Scorecard Project was established to comprehensively survey how researchers, industry, policy makers, and other stakeholders function in the context of each of the 18 recommendations outlined in the commission's report. The information gathered from the Woodrow Wilson Project will be used to help ensure that the field moves forward responsibly (Woodrow Wilson International Center for Scholars 2014c).

The International Risk Governance Council (IRGC) also published a set of guidelines for the science in 2010, recognizing that today's policies and regulations will shape the future of synthetic biology (IRGC 2010). The IRGC guidelines address three main topics: biosafety and biosecurity, engagement of the public and other stakeholders, and ongoing interdisciplinary dialogue to inform policy. The guidelines call for the establishment of an internationally uniform method for DNA synthesis companies to screen requests, the conduct of regular audits to ensure that laboratories are following the appropriate safety precautions, and continued development of built-in safeguards (*i.e.*, engineered fragility) that can mitigate risks in the event of accidental release.

Finally, a recent expert workshop report (Jefferson *et al.* 2014) identified an interesting and important tension in synthetic biology that bears directly on the ethics and policy response to the science. This group noted that when synthetic biologists focus on the transformative application of engineering principles to biology and the de-skilling of the science that makes it more accessible to nonscientists in their public discussions of the science, the perceived risk of dual-use applications by criminals and combatants is higher. In contrast, if scientists acknowledge that tacit knowledge remains important and that the science is thus less accessible to nonscientists, the perceived risk of dual-use applications is lower. The group calls this the "synthetic biology/engineering conundrum." Clarity regarding where the science is on the spectrum of tacit knowledge to de-skilling is critical for accurate risk assessment and ethical and policy response.

Regulatory Leverage Points

One aspect of the current landscape deserves particular attention: the lack of good leverage points for regulation and oversight. Synthetic biology is fundamentally interdisciplinary, with members trained in fields from biology to computing to engineering and with applications from biomining to human health, making it difficult to define (Kronberger 2012). Definitional challenges, in turn, can make it difficult to regulate. For example, the International Genetically Engineered Machine (iGEM) competition is a worldwide annual competition that started in 2003. iGEM projects range from engineering novel proteins to designing novel cellular pathways. iGEM participants are required to deposit any building blocks, or "BioBricks," they design into a public BioBricks database. BioBricks are standardized DNA widgets that can ostensibly be used in downstream applications.

Beyond widgets, synthetic biology also includes systems incorporated into entire organisms. In 2013, a group raised more than seven times their fund-raising goal on Kickstarter (www.kickstarter.com) for the development of bioluminescent plants, controversially promising seeds of the final product to donors in return for their contributions (Drinkwater *et al.* 2014). This new category of organisms created through synthetic biology methods falls outside the scope of existing regulations and raises questions about how it ought be regulated (Carter *et al.* 2014). Additionally, although the Environmental Protection Agency has so far successfully reviewed new applications, Carter *et al.* (2014) have suggested that applications that include microbes stemming from synthetic biology will dramatically increase over time and that the existing review system may not be sufficient for the increased volume. Further, others stress the importance

of ongoing public dialogue regarding the benefits, risks, and governance of gene-drive and similar experiments during both design and conduct of the research (Oye *et al.* 2014).

This diversity of research questions, applications, actors, and institutions complicates regulation: to whom and in what contexts does oversight apply? One common, though not universal, feature is the use of synthetic DNA sequences purchased from DNA synthesis companies. As noted earlier, these companies have been a focus of synthetic biology policy to date. However, as the cost per nucleotide of synthetic DNA continues to drop over time, the general public—largely the DIY community—is increasingly able to pursue personal synthetic biology projects (Boldt 2010). Importantly, the risks posed by these groups have thus far proven to be very low (Grushkin *et al.* 2013); nonetheless, it is important to consider what constitutes appropriate oversight of experiments that take place in settings outside the traditional sphere. For example, there is currently no policy in place that would prevent an individual with malicious intent from purchasing his or her own DNA synthesizer and synthesizing potentially harmful DNA segments (Garfinkel *et al.* 2007). Garfinkel *et al.* (2007) proposed that this policy gap could be addressed by requiring the owners of DNA synthesizers to register their machines and to hold valid licenses to own the machines as well as to purchase related reagents and services. Regulation is also complicated by transnational collaboration between investigators from countries with different laws and governance structures, some of which directly affect the flow of products and resources generated by synthetic biology research. For example, variation in import and export laws complicate both research and its regulation (Bar-Yam *et al.* 2012). Already there have been cases where concerns about dual-use research and its potential misuse have affected the dissemination of knowledge (Kuhlau *et al.* 2013). In a recent incident, the Dutch government asked Ron Fouchier to obtain an export permit before he published his work on mammal-to-mammal transmission of H5N1 influenza virus (Herfst *et al.* 2012). Fouchier complied; however, his home institution is now suing on the basis that there is a European Council regulation clause that excludes the need for such a permit for basic scientific research (Palù 2014). In the United States, there is currently a "pause" on federal funding for gain-of-function research, which aims to introduce novel functions into existing pathogens, increasing their transmissibility, virulence, or number of target hosts.

Finally, there are emerging concerns about how to accurately classify novel organisms made by synthetic biology according to biosafety level (BSL). Currently, the *NIH Guidelines* assign BSLs to hybrid novel organisms based on the BSL of the organism in the higher risk group until experiments have been performed demonstrating that the DNA that was transferred into the new nonpathogenic host is "only a totally and irreversibly defective fraction of the agent's genome," after which the BSL can be lowered to BSL2 (Bar-Yam *et al.* 2012). While this guideline is adequate for a subset of synthetic biology experiments, other synthetic biology projects transcend the scope of this guideline. For example, this guideline fails to address synthetic biology projects that aim to synthesize proteins with completely novel functions.

Given the unique characteristics of synthetic biology, it can be difficult to find good leverage points for regulation and oversight. One possible approach, with which the field is well familiar, is self-regulation. In the next section we describe our approach to self-regulation in the context of the Sc2.0 Project.

The Sc2.0 Project

The Sc2.0 Project was first introduced in 2011 (Dymond *et al.* 2011) and aims to synthesize the complete *Saccharomyces cerevisiae* genome. This project is expected to culminate in the first eukaryotic organism with a genome fully assembled from synthetic DNA. The genome of *Sc2.0* was designed *in silico* and is based on the wild-type *S. cerevisiae*; however, a number of new genetic features have been included in its design. These engineered features will be used as tools to answer a number of age-old biological questions. Two of these genome-wide genetic tools are (1) symmetrical loxP sites, introduced throughout the genome, which will be used in genome structure/evolution experiments, and (2) the swapping out of all TAG with TAA stop codons in order to free up a codon. Once *Sc2.0* is complete, the TAG codon will be available for reassignment with a nonnative twenty-first amino acid that will allow for studies of expansion of the genetic code, as was recently reported for *Escherichia coli* (Lajoie *et al.* 2013). Recently, completion of the first fully synthetic yeast chromosome, *synIII*, was published (Annaluru *et al.* 2014), which, among other findings, demonstrates the usefulness of the system for studying evolutionary variation under defined laboratory conditions.

Methods

Sc2.0 is a massive, collaborative synthetic biology project that is unprecedented in many respects. The Sc2.0 team is international and includes scientists from diverse academic and commercial institutions. Notably, the Sc2.0 team includes a group of DIY scientists at LA Biohackers (http://www.biohackers.la) and a dedicated class of high school students in New York City. In all, over 300 individuals from five countries are contributing to the Sc2.0 Project. Each team is assigned to assemble one or more chromosomes depending on capacity and interest. Each chromosome is centrally redesigned *in silico*, with the changes conforming to a global standard. Next, the teams pursue various methods of building the chromosomes. One bottom-up approach has been to start with oligonucelotides of 60–70 bp, ordered from DNA synthesis companies and assembled into building blocks (~750 bp) *in vitro* by PCR and subsequently molecularly cloned in bacteria. The building blocks are stitched

together first into minichunks (~3 kb) and then into larger chunks (~10 kb) by the method of *in vivo* yeast assembly followed by bacterial plasmid recovery for sequence verification. Finally, the chunks are ligated *in vitro*, and the resulting megachunks (30–50 kb) are integrated into the yeast genome, replacing endogenous chromosomal material with the new synthetic version. However, teams are encouraged to pursue new strategies that further optimize the chromosome-building strategy.

The Sc2.0 team consists of scientists from different backgrounds, diverse settings, and many nations who have come together to work on a single project. With team members from such diverse backgrounds, it is essential that all are well informed and conscientious of the ethics and policy issues in synthetic biology in the context of this project. As such, a discussion was sparked at the First International Meeting on Synthetic Biology by one of us (H.Y.), and following substantial debate, the Sc2.0 team agreed that a document outlining the major ethics and policy issues of synthetic biology as they relate to the project and the team's collective response to these issues would be useful and important. After reviewing the current literature on the ethics and policy challenges raised by synthetic biology research and evaluating the current regulatory landscape in the United States and abroad, an ethics and governance document for the Sc2.0 Project was drafted. The first draft of the governance document was presented to all scientists working on the Sc2.0 Project at the Second International Synthetic Yeast Genome Meeting in July 2013. Feedback both at the meeting and via subsequent e-mail correspondence was incorporated, and a revised draft was produced. The resulting Sc2.0 ethics and governance document was finalized and circulated to all project scientists in November 2013. The document is now incorporated into the agreement that team members at each participating site must sign prior to joining the project and is being added as an amendment to all previously executed partnership agreements.

Sc2.0 Statement of Ethics and Governance

The ethics and governance document contains 11 statements to which all Sc2.0 participants must adhere (Table 1). These statements can be further grouped under four main categories: societal benefit, intellectual property, safety, and governance.

Societal Benefit

As scientists and human beings, our goal and desire are for our work on the Sc2.0 Project to benefit society and not to bring harm. This work will be done only in service to "peaceful purposes." Further, individual participants and the Sc2.0 Executive Committee (described later) will make efforts to ensure that all the benefits from *Sc2.0* are maximized and any potential harms of *Sc2.0* are minimized (see *Safety* section). Our efforts to maximize the benefits stemming from this project include a commitment to transparency and public engagement. The Sc2.0 Project Web site is the public-engagement venue with the broadest capture of updated project information and has the most extensive reach to individuals outside the project. Sc2.0 Project participants regularly contribute information and data to this resource, which includes updates about science, ethics, governance, and funding. All participant laboratories hold public lectures annually and receive support for these activities from the Boeke Laboratory. Additionally, members of the public are directly involved in the project through partnerships with the LA Biohackers and students at New York City's private Dalton High School. Outreach will continue throughout the duration of the project and is expected to expand in the coming year with a free online course on synthetic biology, ethics, and governance. Finally, all Sc2.0 Project participants are encouraged to publicize both the potential and actual benefits (along with the potential risks) of *Sc2.0* and other synthetic biology projects in a manner that is accessible to the public.

Intellectual Property

The Sc2.0 Project is committed to facilitating innovation and maximizing the beneficial use of *Sc2.0*. The project has benefited from substantial public funding, and the founders of the Sc2.0 Project emphasize that the project is about the creation of a public resource—a platform—for asking questions about evolutionary biology and developing solutions to global problems, such as the need for sustainable energy sources and alternatives for the diverse small molecules that are currently obtained from petroleum. Members of the project agree that no intellectual property rights or restrictions on data and materials sharing should be exercised on the clones used to generate novel strains, intermediary strains, or the final *Sc2.0* strain. These strains will be available to the broader community at cost through a central repository.

Safety

As noted earlier, because of the nature of synthetic biology and the general lack of good leverage points for regulation, individual projects and scientists must exercise a degree of self-regulation. While we believe that our experiments do not currently involve significant risks for either the members of our laboratories or the broader community, the Sc2.0 Project embraces and employs rigorous safety practices. Although we currently have no plans to intentionally release *Sc2.0* nor any intermediaries into the environment, all strains contain a number of auxotrophic mutations, rendering them unlikely to be fit for long-term survival outside the laboratory (Mortimer 2000). Indeed, in previous studies, commercial laboratory–generated winemaking strains used in wineries were observed among (but did not dominate over) the natural yeast flora in the vineyards directly adjacent to the wineries. Further, the commercial strains did not appear to have a growth advantage but rather followed the same appearance and disappearance cycles seen for natural wild yeast strains (Valero *et al.* 2005). However, we acknowledge that it is formally possible that streamlining the genome and making it less likely to undergo rearrangement could

Table 1 Sc2.0 ethics and governance statement

Societal benefits
1. We will conduct and promote our work on *Sc2.0* for the benefit of humankind.
2. We will participate with the project's efforts to engage with the public and be transparent and open about our work on *Sc2.0*.
Intellectual property
3. Intellectual property rights will not be taken on *Sc2.0* once created, nor on the intermediary clones and strains generated as part of the project.
4. Data and materials generated by this project will be made available to other researchers.
Safety
5. All sequence providers generating sequences for use in *Sc2.0* shall be in compliance with the U.S. Department of Health and Human Services' *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*.
6. Members of the Sc2.0 Project will assess individuals requesting Sc2.0 Project data/materials prior to shipment of any such materials to help reduce the chance that we are distributing materials to those with nefarious intent.
7. Our laboratories, practices, and methods will have at their core an ethos of safety for both laboratory workers and the communities outside our institutions.
8. All personnel will receive training in biosafety, dual-use concerns, and other ethics issues, as appropriate.
9. Our work on *Sc2.0* is in compliance with national and local laws.
Governance
10. The Sc2.0 Executive Committee will address any issues that may arise with regard to safety or compliance with this agreement.
11. We will revisit this agreement as the project and the technologies it uses develop to ensure that any risk posed by this work is appropriately matched to the oversight it receives.

confer a growth advantage relative to wild-type yeast, at least under specific laboratory conditions. In an effort to address these concerns and to minimize the chance of harm should there be an accidental release, we are exploring the possibility of including additional engineered vulnerabilities to further decrease the likelihood of viability outside the laboratory.

In addition to the systematic scientific design, the Sc2.0 Project also addresses safety concerns through faculty and staff training. Even though biosafety training is generally not required for individuals or laboratories working with organisms such as *S. cerevisiae* that are generally regarded as safe by the U.S. Food and Drug Administration, individuals working on *Sc2.0* receive training on the risks of dual-use technologies through lecture, the use of the National Science Advisory Board for Biosecurity's educational module for individual learning, and group discussions. Additionally, we are developing a massive open online course, Engineering Life: Synbio, Bioethics, and Public Policy (https://www.coursera.org/course/synbioethics), that will be available not only to members of the Sc2.0 Project but also to anyone with the time and interest and an Internet connection. This course will draw on both the Sc2.0 Project and its descendant, the Induced Evolution of Synthetic Yeast genomes (IESY) Project, and will be available in late 2015.

Sc2.0 Project members also agree only to order DNA from synthesis companies that abide by the U.S. DHHS guidelines for screening of all orders. While companies are encouraged, but not required, by the U.S. federal government to follow the guidelines, we feel that they are reasonable, prudent, and critical to efforts to maximize benefit and minimize harm stemming from synthetic biology. Therefore, we support only the companies that follow these guidelines, even in cases where this increases cost. While we acknowledge that such screening cannot guarantee against every potentially harmful sequence being shipped, this is a valuable effort and represents current best practice in the field.

Finally, prior to sharing Sc2.0 Project data and materials, members of the project agree to make reasonable efforts to ensure that individuals requesting *Sc2.0* materials are motivated by legitimate goals and have the appropriate training and infrastructure to safely handle the requested data/materials. We wish the fruits of our research to be used only in efforts that are "reasonably justified by a prophylactic, protective, *bona fide* research, or other peaceful purpose" (National Research Council 2009), and we feel that it is our collective responsibility to help ensure that this is the case.

Governance

The implementation and any necessary revisions of the Statement of Ethics and Governance are the responsibility of the Sc2.0 Project Executive Committee. The committee consists of individuals who are internal and external to the project and have scientific, ethics, and policy expertise. The composition of the committee may be modified over time to include additional individuals from the same or neighboring disciplines. The committee is in charge of addressing any issues that might arise with regard to safety or compliance with the statement. Members of the project are expected to discuss any concerns they have about the project with the Executive Committee. Individuals outside the project are also encouraged to raise concerns. The committee has the authority to remove from the Sc2.0 Project any partner who violates the statement.

Understanding that science advances very quickly and that local and national policies may change over time, the Executive Committee will regularly review the statement to

ensure that the project policies appropriately reflect the risks and regulatory status of the project. If the risks increase, so will oversight.

Implementation

As mentioned earlier, the Sc2.0 Statement of Ethics and Governance is an integral component of the agreement that each partner signs on joining the Sc2.0 Project. Each new participant receives a copy of the statement, and the statement is also posted on the project Web site. Compliance with the statement is assessed on an annual basis, including monitoring compliance with training requirements and tracking data and materials requests, screening procedures followed, and any DNA sequence providers that were used. Finally, each site is required to complete and report one public engagement activity annually. A selection of these activities will be shared not only with other members of the project but also with the public via the project Web site. The Governance Committee is responsible for reviewing the annual reports and managing compliance.

Conclusions

While project-level accountability does not suffice as the means to regulate all of synthetic biology, we believe that the Sc2.0 Statement of Ethics and Governance holds value as a model for regulation in the field. Further, we believe that large, publicly funded projects such as the Sc2.0 Project have the responsibility to help fill in the gaps in current oversight mechanisms through measures of voluntary self-regulation. In a field with broad societal and environmental implications that generates substantial public interest and concern, especially when the research is publicly funded, investigators must take extra precautions to ensure that their work is not only scientifically justifiable but also ethically sound. Self-regulation has the benefit that the scientists at the forefront, who are conducting the research, can assess and identify sources for concern. However, as synthetic biology advances, institutional and governmental oversight as well as self-regulation will continue to be important because these two distinct forms of regulation function to mutually inform and benefit from one another (Maurer 2012).

In the wake of recent events such as the anthrax exposure following 9/11, the Centers for Disease Control and Prevention reports of biosafety violations in 2014, and the accidental shipment of live anthrax in 2015, it is clear that national security and safety in related biotechnology research will continue to be important issues. As seen with the recent work done by Fouchier on H5N1, opinions as to whether particular research topics should be pursued sometimes vary, and synthetic biology research is no exception to this. In the H5N1 case, some see the research being done as essential preparation for a possible epidemic in the future, while others view work with the virus as an unnecessary risk to the public (Tu 2012). These strongly opposing perspectives led to a brief voluntary moratorium on the research in January 2012, which was later reversed. More recently, the NIH has instituted a funding pause for gain-of-function research while it assesses the risks and benefits of the science. Self-governance of the sort described here, at the 1975 Asilomar Conference, and by Maurer *et al.* (2006) will continue to play an important role as the field of synthetic biology and the related oversight matures. In such a broad and diverse field, it is important to match the risk of different classes of experiments to appropriate oversight rather than apply the same approach to all of synthetic biology. As data on risks and benefits accrue, it will be important for scientists and the public alike to periodically reevaluate research in this field and determine whether governance is appropriately matched to risks. These assessments will be particularly important—and complex—when navigating cultural and legal differences in large international research projects.

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