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Biosecurity at iGEM

Ensuring the Secure Advancement of Synthetic Biology by the Next Generation

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Executive Summary

This report recommends that the Department of Homeland Security (DHS) begin a dialogue with the iGEM Foundation addressing biosecurity and the trajectory of the competition before the increasing sophistication of student projects outpaces the International Genetically Engineered Machine (iGEM) competition's ability to identify, manage, and mitigate risks that could threaten the public.

Development in four key areas of the competition should be watched and influence DHS's biosecurity dialogue with iGEM:

- Materials – movement from biosafety level (BSL)-1 and -2 to BSL-3
- Security Culture – Diversified international backgrounds and experiences
- Oversight Implementation – Evolution of structures and adequacy of tools
- New Practitioners – Institutional affiliations and community-based norms

Pursuing this course of action will enable DHS to:

- Understand what small groups of highly motivated individuals with modest means, equipment, and background can produce with synthetic biology in a few months
- Develop a new pathway for engaging next generation synthetic biologists from around the world which will have long-term implications on norms development
- Positively influence the security culture of the competition and impress upon the iGEM Foundation their responsibilities, including as an online publisher
- Receive early warning on emerging threats that will provide valuable data for any future federal guidance and rulemaking on dual-use research and biological terrorism protection, preparedness, and risk mitigation
- Signal the synthetic biology community about the need to ensure that the field is advancing securely if it is to continue progressing in the absence of strict regulations

With these benefits in mind, DHS should consider the following policy recommendations:

- Do not pursue new regulations at this time

- Initiate a dialogue on biosecurity with the iGEM Foundation

- Offer a biosecurity prize at the iGEM World Championship

- Develop a specialized biosecurity sponsorship package with iGEM, perhaps including:
    - Introducing regional-level biosecurity officers as resources for the teams
    - Increasing attention to iGEM's responsibility as a publisher of novel synthetic biology material via the team wikis and Registry of Standard Biological Parts
    - Supplementing voluntary, graduate student human practice screeners and other volunteers with paid professionals
    - Rotating iGEM judges to different regional competitions to more equitably enhance biosecurity awareness at earlier stages of the competition

Introduction

This paper will focus on the potential homeland security implications from the U.S.-based annual international synthetic biology competition, International Genetically Engineered Machine (iGEM), and the policy actions that the Office of Policy at the Department of Homeland Security (DHS) should consider to mitigate them. Its findings are based on interviews with iGEM participants and volunteers, scholarly literature, governmental publications, news articles, and nongovernmental analyses. The iGEM Foundation declined involvement in this report.[1]

iGEM is a competition to build simple biological systems from standard, interchangeable parts that can operate in living cells. The competition allows participants to experiment with and build new biological systems in the rapidly evolving field of synthetic biology. iGEM began in January 2003 at Massachusetts Institute of Technology (MIT) as a month long course and has grown into an independent international competition involving summer projects conducted by nearly 200 teams.

Synthetic biology lacks a universal definition, but includes efforts to design and construct new biological parts, devices, and systems that strip away complexity and turn living organisms into modular building blocks for new and useful purposes.[2, 3, 4] Though synthetic biology is still a nascent discipline, it has advanced to the degree that a wide variety of gene sequences can be synthesized in a laboratory or ordered from a commercial company.

Manipulation of plants and animals to enhance desirable traits has a long history, but not at the scale and pace that synthetic biology now allows. In the 19th century, Gregor John Mendel studied why some traits were passed on from one generation to the next while others skipped a generation or randomly appeared. This work led to the formation of Mendel's Laws—the Law of Segregation and the Law of Independent Assortment—but they were largely unknown to the scientific community for decades. In contrast, the work done at the iGEM competition on synthetic biology is immediately and broadly shared through an online wiki and submissions to an open-source registry of biological parts. This allows community progress on a highly accelerated timeline, but it also introduces new challenges.

Advancements in genetically modifying organisms have increased in crop yield, reduced costs of food or drug production, lessened the need for pesticides, and enhanced nutrient composition and food quality.[5] The integration of new design techniques and construction capabilities gives researchers the potential for revolutionary advances with less training. Scientists and engineers can now focus on their goals without having to learn how to manipulate biological systems at a molecular level. The necessary equipment is inexpensive and readily available, and there are a growing number of companies with proprietary technologies that are able to synthesize gene and genome length DNA at rapidly reducing prices.[6] Bio Economic Research Associates estimated in a 2007 report that the global market for DNA reagents and services was nearly $1 billion and:

> [P]roductivity of DNA synthesis technologies has increased approximately 7,000 fold over the 15 years, doubling every 14 months. Costs of gene synthesis per base pair have fallen 50-fold, halving every 32 months. At the same time, the accuracy of gene synthesis technologies has improved significantly.[7]

Advances in synthetic biology and life sciences research have raised concerns about potential risks and complex legal, social, and ethical issues.[8, 9] Many countries have adopted policies and regulations for commercial companies and researchers in an attempt to address their safety and security needs. These policies are not uniform from country to country, but rather they were developed at different times and tailored to meet local concerns within the context of economic and political issues. In such an environment, regulatory gaps exist, as synthetic biology respects no national borders and many laws were not crafted with its unique attributes in mind.

The United States needs regulatory framework for synthetic biology that allows researchers sufficient freedom to ensure its continued growth while mitigating risk. Synthetic biology holds great promise to cure disease and change the world in many positive ways. Therefore, regulatory flexibility will be necessary as the science and associated risks become better understood. An adaptive and balanced approach to policy and regulation that allows for commercial growth and competitive research while ensuring proper risk mitigation is essential.

This paper aims to contribute to the ongoing development of such policies by assessing the benefits and risks of synthetic biology through the frame of the iGEM competition. First, it will define synthetic biology and describe the iGEM competition. Second, it will discuss biosecurity within the context of synthetic biology, including contrasting biosecurity with biosafety, examining the biosecurity risks and challenges associated with the field, and explaining the need for governance mechanisms that keep pace with its development. Third, the paper will examine the oversight structures in place at iGEM and how they are applied in practice. Then, it will describe four key areas that policymakers should monitor and consider when crafting new governance strategies. Finally, it concludes by examining policy opportunities, offering recommendations pertaining to engagement with the iGEM competition, and looking ahead to future research challenges.

Nature of Synthetic Biology

Synthetic biology is the modification of simple living systems so they enhance desirable traits or suppress undesirable ones through the design and construction of new biological parts, devices, and systems that strip away complexity and turn living organisms into modular building blocks for new and useful purposes.[10, 11, 12] Work often focuses on modifying simple organisms, such as Escherichia coli and Bacillus subtilis, to become the basic chasses for new organisms into which new functional parts from other organisms may be added.[13] Although great strides have been made and the cost of genetic sequencing and synthesis has dropped, there is still much that is unknown, and the functions of many genes in some of the simplest life forms remain unclear.[14]

Synthetic biology is distinguished from traditional molecular and cellular biology by its focus on the design and construction of core components that can be modeled, understood, and manipulated to meet desired performance criteria.[15,16] The assembly of the small parts and components can be integrated into larger systems to enhance or implant new desirable traits into biological systems. The goal is to dramatically decrease the amount of time needed to design, test, and build new and unique biological entities.[17]

Synthetic biology differs from genetic and metabolic engineering in the scale of change it envisions. Rather than modifying one gene at time, synthetic biologists are re-conceptualizing the genes themselves. Therefore, the field is more akin to engineering than biology in that it views biological materials as tools to be manipulated and remade for specialized purposes, rather than finished products to be understood and subtly improved.

Synthetic biology applies engineering methodologies to biological research and is sometimes referred to as "engineering biology." Synthetic biologists are striving to make artificial biological entities or "parts" programmable, self-referential, and simplified.[18] Their work constructing new enzymes, genetic circuits, and cells has immense transformative potential similar to how chemical synthesis revolutionized chemistry and integrated circuit design transformed computing.

Synthetic biologists have adopted the methods of engineers to share information and develop common standards and techniques. Like engineers, synthetic biologists have created standardized registries of parts, including the iGEM's Registry of Standardized Biological Parts (Registry). iGEM's Registry is modeled off of the electrical engineer's TTL Databook, which lists hundreds of standardized circuit components.[19] Rather than circuits, iGEM's Registry is composed of "BioBricks" which are descriptions of modified genes associated with specific traits that can be used to build new organisms. The iGEM Registry exists online to make the knowledge available to all. A username and password, obtained by registering with the iGEM Foundation, is necessary for editing the Registry, but a large variety of information is not password protected. The purpose of this open exchange is to allow individuals to examine the research from their own perspectives and apply what they learn in ways not foreseen by the original researchers.

Understanding the iGEM Competition

iGEM was designed to encourage students to develop new skills and advance the field of synthetic biology. It was founded in January 2003, beginning as a month long course at MIT, and has grown into an international competition with more than 3,000 participants comprising 190 teams from 34 different countries.[20] Competing teams are divided among three divisions: high school, collegiate, and entrepreneurial. Teams must advance through Regional Jamborees before competing at the World Championship Jamboree held in Cambridge, Massachusetts each fall. In 2012 the iGEM Foundation, an independent 501(c)(3) organization, was created to manage the iGEM competition. It is located on MIT's campus, despite no longer being affiliated with the school.

Students work at their own institutions during the summer to design new synthetic biological systems, and they maintain online wikis to detail their progress and findings. iGEM provides teams with wiki space, toolkits of BioBricks, and access to the Registry. New, functional parts designed by the student teams are contributed back to the Registry and built upon by future competitors and researchers. In 2004, five teams submitted approximately 50 new parts to the Registry, but in 2012, 190 teams contributed 1,708 new parts to it.[21]

The "get some, give some" principle of the Registry is expanding and defusing knowledge; it is helping to simplify the field of synthetic biology and allowing diverse practitioners the chance to

participate in its advancement. Unlike Mendel's work, which took decades to become influential, student competitors at iGEM are able to immediately impact the synthetic biology's progression.

In addition to disseminating knowledge, the iGEM competition generates excitement among the next generation of scientists and fuels the synthetic biology revolution by expanding the Registry. There are no monetary prizes associated with the competition. In fact, students surrender all rights to their creations when they contribute them to the Registry, whose contents are considered open-source, "freeware." The winning team simply takes home the "BioBrick" trophy and its associated prestige. This lack of a monetary incentive to win allows teams to pursue areas of intellectual interest rather than those offering financial gain. A wide array of impressive and useful products has been built by students, including:[22]

- Arsenic Biodetector: In 2006, a team from the University of Edinburgh built a biosensor that could cheaply detect arsenic in water. It was created with use in developing countries suffering from water quality issues, such as Bangladesh, in mind.
- BactoBlood: In 2007, a team from UC Berkeley built an affordable red blood cell substitute that could be stored for prolonged periods and transport oxygen into the bloodstream without inducing sepsis.
- TUM-Brew: In 2012, a team from TU Munich created the first SynoBio Beer which contained an anti-carcinogenic, a stimulant, lime flavor, and a protein sweetener to demonstrate the possibilities of synthetic food and beverage products.

Both the iGEM competition and student teams receive outside sponsorship. This includes funding from universities, private companies, and federal agencies. Student projects are reported to range in cost from a few thousand to $90,000.[23] The annual budget for the iGEM Foundation comes from several sponsors, including the Alfred P. Sloan Foundation, SynBERC, National Science Foundation (NSF), Agilent, Autodesk, MathWorks, Oil Sands Leadership Initiative, Integrated DNA Technologies, National Aeronautics and Space Administration (NASA) and Federal Bureau of Investigation (FBI).[24] However, its exact annual budget varies, and no one from the iGEM Foundation was willing to be interviewed for this paper that could provide more information on this.[25]

Biosecurity & Synthetic Biology

Biosafety vs. Biosecurity

Biosecurity is frequently conflated with or treated as a subset of biosafety. However, biosecurity is a distinct concept that communicates a different set of issues and concerns. Though biosafety and biosecurity are both relevant to scientists and policymakers, this paper focuses solely on biosecurity and strives to make the differences between the two issues clear in this section.

Biosafety refers to containment principles, technologies, and practices that are employed to prevent the unintentional exposure to pathogens and toxins or their accidental release in a laboratory environment.[26] Researchers working in a laboratory are expected to follow professionally accepted practices when working with potentially harmful biological materials, pathogens, and toxins. Biosecurity concerns are much broader than biosafety issues and involve a higher degree of uncertainty.

Biosecurity involves the prevention of unauthorized access to high-consequence biological materials and information.[27] This includes protection, control, and accountability measures to prevent loss, theft, and misuse of organisms or data. The physical integrity of a laboratory is only one aspect of biosecurity; the security dual-use data is of equal concern. Dual-use research refers to the potential for legitimate research materials, data, and products to be used to benefit or harm the public and environment.

Biosafety is often emphasized in scientists' academic training there is much less focus on biosecurity. As iGEM's Security webpage acknowledges, "we are commonly taught how we should work safely, we are less often taught how to work securely."[28] Biosafety has a long tradition in the life science community while biosecurity issues have only recently begun to be publically debated. Some scientists fear that discussing biosecurity implications of their work will lead to the cessation of dual-use research or spur burdensome regulations. However, the potential misuse of biological knowledge and materials is a reality that must be addressed.

Though synthetic biology is still an emerging discipline, it has advanced to the degree that many viruses can be synthesized from scratch in a laboratory or their sequences ordered from a commercial company.[29] This argues for greater awareness of the potential risks associated with synthetic biology and steps to mitigate the potential for misuse. One example of how this is playing out in practice is with screening software. The U.S. government is working with domestic commercial gene sequencing companies to utilize software that identify orders for sequences of concern.[30]

Codes of conduct are also useful tools, but they primarily influence the behavior of responsible actors. Laws punishing irresponsible or malicious actions do not protect populations from accidents caused by negligence or misconduct. Policy actions that heighten among stakeholders about biosecurity may be the most effective means of developing norms and combating risk.

Risks and Challenges

Advances in synthetic biology are reducing the amount of knowledge necessary to produce new, artificial biological systems. The equipment necessary for genetic synthesis is readily available to anyone with a few thousand dollars, and a growing number of companies can supply genetic material at competitive prices. In 2007, there were estimated to be 24 commercial gene synthesis companies operating in the United States and 21 overseas, including in Germany, China, France, Russia, and South Africa.[31]

One of the primary goals of synthetic biology is to "deskill" the field by reducing the amount of time, and money necessary to create a biological system from scratch.[32] No longer are years of formal study combined with the tacit knowledge that can only be acquired from working with senior researchers in laboratories necessary for gaining the skills required to alter living systems using conventional recombinant DNA techniques. Projects like iGEM and its Registry play key roles in opening the field to a broader base of potential practitioners.

Synthetic biology is not necessarily practiced by biologists; those from outside of the life sciences are increasingly involved in the discipline. In fact, it was a small group of engineers

who pioneered iGEM's development. Such individuals bring a different set of perspectives, expectations, and skills to the field. In addition, non-academic individuals and those with little formal training or experience who may not be affiliated with any institutions are also contributing to the advancement of synthetic biology. This introduces new concerns about educational and ethical backgrounds as well as complicates outreach and norms development.

The sharing of knowledge to advance the sum and pace of science will always have risks and benefits. The free access and use of standardized biological parts and modular designs could enable someone seeking to do harm the ability to create biological weapons; however, it could also help create new, robust defenses against naturally occurring and artificial biological threats.[33] All contingencies cannot be anticipated, and the motivations of those seeking to do harm are infinite and even irrational. Further, the number of potential targets is nearly incalculable, and it is easier to attack with than defend against biological weapons. Ultimately, scientists in close collaboration with policymakers must regularly evaluate if the proper security culture, norms, incentives, and regulations are in place to ensure that the scientific value of the work outweighs risks it poses to the public. This will be an iterative process as knowledge increases and events unfold.

Governance Needs

There is a need for dynamic biosecurity incentive mechanisms, norms, guidance, and regulations to address the unique challenges of synthetic biology. These must strike a careful balance between access and control and be written with enough flexibility to be adapted as the field and technology progresses. They should facilitate the free exchange of ideas and information among the international research community while providing early warning about projects of concern so that their biosecurity implications may be thoroughly evaluated before the work progresses. Protection of the public and environment is critical, and these governance challenges are not unfamiliar or unique to synthetic biology.[34]

Protecting the American people from terrorist threats is among the founding principles of DHS. One of the Department's three primary goals is to "Prevent the unauthorized acquisition, importation, movement, or use of chemical, biological, radiological, and nuclear materials and capabilities within the United States."[35] Synthetic biology falls within this charge. According to leading researchers, synthetic biology appears to have minimal security implications in the near-term, create modest offensive advantages in the medium-term, and strengthens defensive capabilities against natural and engineered biological threats and enable novel potential offensive uses in the long-term.[36] DHS policymakers should be working to put in place flexible policy frameworks today that help make researchers cognizant of their biosecurity responsibilities to help risk mitigation strategies keep better pace with technology development.

Most existing laws and regulations for addressing biological risk were not developed with synthetic biology in mind. However, work is being done to update some existing guidance, such as the National Institutes of Health's (NIH) *Guidelines for Research Involving DNA Molecules* which was amended in March 2013 to *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.[37]

In its 2010 report, *Addressing Biosecurity Concerns Related to Synthetic Biology,* the National Science Advisory Board for Biosecurity (NSABB) stated, "there is currently no federal policy in place for the review and conduct of dual use research of concern."[38] The report proposes an oversight framework to help mitigate biosecurity risks and urges that such a federal policy be developed and implemented. In this regard, the NSABB offers four specific recommendations: [39]

1. Synthetic biology should be subject to institutional review and oversight since some aspects of this field pose biosecurity risks.
2. Oversight of dual use research should extend beyond the boundaries of life sciences and academia.
3. Outreach and education strategies should be developed that address dual use research issues and engage the research community that are most likely to undertake work under the umbrella of synthetic biology.
4. The US Government should include advances in synthetic biology and understanding of virulence/pathogenicity in efforts to monitor new scientific findings and technologies, such as "tech-watch" or "science-watch" endeavors.

In February 2013, the White House Office of Science and Technology Policy released for public comment a policy for minimizing the risks of dual-use research of concern while maximizing the benefits of life science research.[40] The proposed policy complements internal federal guidance released in March 2012 by extending new oversight responsibilities to institutions working with select agents that receiving federal funding. It is posted on the U.S. Department of Health and Human Services' Science Safety Security website and is reaching the end of the 60-day comment period.[41] It focuses on dual-use research involving 15 agents and toxins and seven categories of experiments. The proposed policy was a collaborative, multi-agency effort and applies to federal departments and agencies that fund life sciences research and institutions within and outside of the United States that that receive federal research funding. Penalties for non-compliances with it would include the suspension of funding and the loss of future funding opportunities. While iGEM is a recipient of federal funding, it is unlikely to be impacted by this guidance due to the nature of the agents and experiments with which it is involved.

Biosecurity at iGEM

Synthetic biology is value neutral; how it is used determines if the outcome will be positive or negative for public welfare. The oversight policies and structures employed at iGEM relevant to biosecurity have evolved during the last decade, but it is not clear if they are maturing at pace with the scale, scope, and science of the competition. Further, the biosecurity guidance that is offered on the iGEM website is incomplete and not contextualized for teams' needs. However, there was a tangible sense of stewardship and concern among all those interviewed for this report who are involved with iGEM that the competition must continue to progress safely, securely, and unencumbered.

Policies and Oversight Structures

Much like synthetic biology, the iGEM competition grew out of the interdisciplinary cooperation of biologists, engineers, chemists, and computer scientists. It generates enthusiasm among the next generation of scientists and is very successful as an educational tool. For many students, the

competition is the first time they have the chance to work with microorganisms and genetic engineering techniques. It also may be the first time they are exposed to biosecurity issues.

iGEM encourages teams to think through the biosecurity implications of their work; however, it does not provide specific policy documentation that addresses biosecurity within the context of the competition. Rather, it relies on international law, local regulation, and institutional guidelines to guide competitors' work. International treaties prohibit the use of biology for hostile or harmful purposes, and most countries have national laws criminalizing the use of biology in this way. Institutions where research is conducted also maintain their own regulations and guidelines relevant to the day-to-day functioning of their laboratories, and some large institutions may have dedicated biosecurity officers and review boards. Consistent with federal guidance, iGEM encourages teams to familiarize themselves with and follow the local rules applicable to their work.

iGEM is a growing organization with increasing international participation. From 2004 to 2012, the number of teams increased from 5 to 190; the number of participants increased from 50 to 3,000; and the number of countries increased from 1 to 34.[42] Regional competitions were introduced in 2011 to cull the number of competitors. In 2012, five regional jamborees were held in Hong Kong, Amsterdam, Bogotá, Pittsburgh, and Palo Alto to narrow the field for the World Championship Jamboree in held in Cambridge, MA.[43] iGEM has played an important role in helping synthetic biology become well-established around the world, highlighted by its 2006 international ambassador initiative that helped further diversify its competitors as well as the recent victories of teams from England in 2009, Slovenia in the 2010, and the Netherlands in 2012.[4445] These figures and activities demonstrate the quickening pace, growing complexity, and increasing international reach of the competition.

The NSABB's review of potential gaps in synthetic biology oversight identifies the large, diverse synthetic biology practitioner base that lacks formal institutional affiliations and is not trained in the life sciences as a principle concern.[46] While iGEM has a diverse, somewhat nontraditional participant base, at present none of its competitors lack an institutional affiliation. In fact, this affiliation may be the most stringent of requirements that iGEM imposes on competitors. It stems from iGEM's roots at MIT and reliance on local control mechanisms to oversee project development.

On its webpage dedicated to security, iGEM explicitly states that its lists of national and international legal guidelines are incomplete and requests that students submit additional information about their home countries. It is not clear if this has ever been done.[47] The Security webpage also offers the following resources:[48]

- Links to biosecurity reports relevant to synthetic biology, including:
    - *Biorisk Management – Laboratory Biosecurity Guidance* (2006), World Health Organization (WHO)
    - *Responsible Life Science Research for Global Health Security* (2010), WHO
    - *Understanding Biosecurity* (2009) by the National Research Council

- Contact information for Dr. Piers Millet, a safety and security expert and the Deputy Head of the Implementation Support Unit (ISU), Biological Weapons Convention (BWC), United Nations (UN) Office for Disarmament Affairs
- Discussion of the biosecurity implications of publishing the "Spanish Flu" gene sequence and citations for three cases studies for further reading
- Descriptions of two previous biosecurity-related iGEM projects developed by the VT-ENSIMAG team in 2010 and the PKU Beijing team in 2009
- A Code of Conduct to which they encourage students to contribute and refine
- Links to international regulations, national laws, and guidelines for five countries

Further, iGEM's Security webpage tells students that there are three specific things they can do to help secure the science: [49]

- Fully answer the *safety* questions that demonstrates that you have thought about how others could misuse your work [emphasis added]
- Contribute to community discussions on what needs to go into a code against the use of our science for hostile purposes
- Look into what security provisions, such as laws and regulations, are already in place in your country

The information provided on iGEM's Security webpage relies on the initiative of competitor teams to access it, and it is not user-friendly. In fact, the long list of legal information that the Security webpage links to may even discourage participants from investigating these issues further. For example, each link in the "Working Within the Law" section leads to the UN BWC website which details national export regulations, executive orders, laws and code, public health strategies, proliferation control initiatives, mail service regulations, arms trafficking regulations, hazardous material transport guidance, and export control restrictions. While exhaustive, this list does not include specific guidance on biosecurity, nor does it link to particular local governmental websites or policies. It is difficult to see how a student competitor would be able to use this information in practice. It is not at all contextualized for their needs.

There is a strong feeling among those involved with iGEM, as well as the broader synthetic biology community "that the work done should be used only for the benefit of humankind. It should not be used to do harm or to make weapons."[50] While steps have been taken to address biosecurity at iGEM, its organizer's direct role has been somewhat passive. There appears to be little formal communication to students about biosecurity from the iGEM Foundation, and many of those involved with iGEM describe the issues of biosafety and biosecurity as intimately intertwined. [51, 52, 53] Though there are good reasons for addressing these issues together, it is important to avoid subjugating one to the other, and iGEM appears to prioritize safety.

Biosecurity Oversight in Practice

The Registry and iGEM competition materials are open-source, and the gene sequences used in the competition can be bought from commercial synthesizers. Only the data in each team's wikis is truly unique and may not be catalogued anywhere else. These wikis are viewable by the public, however, like the Registry, a username and password are required for editing them.

iGEM employs an "adaptive oversight framework" that is adjusted as the competition and field progresses for flexibility and fairness.[54] It relies on international and local laws and each institution's regulations and requirements for oversight and expects teams to know and follow those guidelines. iGEM emphasizes local control and uses professional networks and largely unpaid volunteers to screen.

Teams competing in iGEM apply at the beginning of the calendar year, work through the summer, and compete in the fall. When teams register for iGEM, they fill out a form where they describe their intended project, which includes stating what organisms they are working with and explaining how they are mitigating any associated risks. BioBrick kits are sent to teams once their applications have been processed. However, teams typically do not wait for these kits to arrive before beginning work and may not use them at all.

The iGEM Foundation is not selective about what projects are entered into the competition. Projects also are typically underway by the time teams fill out the safety form in the registration package, which does not include a separate biosecurity form.[55] Graduate student screeners look for and flag any human practice concerns (i.e. safety and security issues) they notice in the forms. These reviewers may contact the team with questions about what they have submitted. However, the work is already underway, and as long as a team is able to fund their project, submit the proper forms, and justify their choices, they will likely be allowed to participate.

In the early years of the competition, the organizers focused on improving the logistical operations of the event to deal with the influx of teams, but as the competition has evolved, more attention has been paid to its oversight structures. In 2008, the iGEM organizers made addressing biosafety issues a mandatory requirement for participation.[56] Every iGEM team must now complete a safety questionnaire that is reviewed by the iGEM Safety Committee. Any team that does not complete the safety requirements is disqualified from the competition, while teams with notable attention to issues of biosafety can be awarded a safety commendation.[57] While this progress is important, it is mainly focused on biosafety issues.

Though iGEM's website clearly delineates biosafety and biosecurity, in practice they are jointly dealt with under the category of human practices. Human practices scores at Regional and World Championship Jamborees are given equal weight to other judging categories. However, human practice judges are given wide latitude in what they ask competitors about laboratory safety and the dual-use implications of their work. Some teams may even go through their regional competitions without ever being asked a tough biosecurity-focused question; however, at the World Championship, this issue is always addressed.[58]

Some teams at iGEM have taken a special interest in the biosecurity risks associated with synthetic biology. For instance, a team of students from Virginia Tech's Virginia Bioinformatics Institute created GenoTHREAT software to supplement their wet lab project in the 2010 competition. This software identifies sequences of concern, specifically select agent pathogens and toxins.[59] It follows the algorithm given by the federal guidelines and uses the BLAST software for sequence alignment. It was used to analyze the iGEM Registry in 2010 and identified one BioBrick as derived from a toxin.[60] The circumstance of this part's introduction

was not known by those interviewed, but its organism of origin was clearly labeled. [61] GenoTHREAT, and other projects like it, are important in that they enhance how iGEM participants think about biosecurity.

Additionally, iGEM partners with its sponsors to integrate biosecurity education into the competition. Most notably, the FBI has given a highly popular presentation and maintained an outreach booth at the competition for several years as part of their efforts to raise biosecurity awareness among young researchers.[62] It has conducted workshops promoting responsible research and worked with iGEM to incorporate security in the judging process.[63] The FBI also collaborates with the BWC ISU on poster exhibits and dual-use research presentation at iGEM to accomplish its goals. These efforts are part of the FBI's work to establish an ongoing dialogue between law enforcement and life science research communities, highlighting the importance of communicating research concerns with local field agents.[64] Sponsorship of iGEM has allowed the FBI to raise awareness and begin to instill a culture of security in the next generation of researchers and entrepreneurs.

Policy Development

The DHS Office of Policy should begin a dialogue with the iGEM Foundation addressing biosecurity and the trajectory of the competition before the increasing sophistication of student project outpaces iGEM's ability to identify, manage, and mitigate biosecurity risks that could threaten the public. A chief goal of this dialogue should be to assist iGEM in scaling up its oversight structures and tools to keep on pace with the growing complexity and international reach of the competition. DHS should work to build a collaborative relationship and use voluntary incentives to raise the priority of biosecurity issues with the iGEM Foundation and at the competition, rather than pursuing formalized regulation at this stage.

There are several ways in which DHS could positively influence the iGEM competition on biosecurity matters. For instance, DHS could offer a prize to a team at iGEM for the most significant contribution to biosecurity. This could be a trophy presented at the World Championship by a high-level official from DHS, perhaps even the Secretary. The prize does not need to include a monetary reward or even be given every year. It could be reserved for new and significant contributions to heighten awareness and encourage students to be effective stewards of biosecurity. This would align with iGEM's focus on reputational, community-derived accolades, rather than monetization of achievements. It also fits with iGEM's practice of using partner institutions to supplement its programming.

DHS should consider becoming a sponsor of the competition. It could work with the iGEM Foundation to develop a specialized sponsorship package that focuses on capacity building that addresses long-term biosecurity concerns, not on having DHS's name on iGEM signage. DHS sponsorship could largely play a behind-the-scenes role, offering support for such things as: introducing regional-level biosecurity officers as resources for the teams; increasing attention to iGEM's responsibility as a publisher of novel synthetic biology material via the team wikis and Registry; supplementing voluntary, graduate student human practice screeners and other volunteers with paid professionals; and supporting the rotation of iGEM judges at regional

competitions to more equitably enhance biosecurity awareness at earlier stages of the competition.

Even if DHS chooses not to become an official sponsor, its Office of Policy should pay attention to developments in the following four areas at the iGEM competition: materials, security culture, oversight implementation, and new practitioners. The level of sophistication required to win the iGEM competition is increasing each year. Teams build off of the work of previous competitors contained in the Registry and the tacit knowledge passed down to new university teammates, and many schools are repeat competitors. While this growth is beneficial for the field of synthetic biology, it argues for a similar maturation of the oversight policies and procedures throughout the competition to ensure that projects are being conducted in a secure manner.

Materials

There are currently few genetic parts that iGEM competitors need that cannot be found in BSL-1 and -2 organisms, but as their work is built upon over time, the winning teams at iGEM will be those with the most unique organisms.[65] This likely will lead to projects using parts from BSL-3 organisms.[66] Students are not prohibited from using BSL-3 or higher organisms now, but their inclusion in a project would be flagged and heavily questioned with the aim of discouraging use.[67] It is not clear, but seems unlikely, that the iGEM Foundation intends to transition from this soft rule of discouragement to a formalized exclusion of particular materials. It seems most probable that iGEM will continue to rely on local and national laws and regulations to guide which materials student competitors may use. In short, if teams can buy a sequence from a commercial company, justify its use in their project, and have the skills necessary to advance through the competition, the iGEM Foundation is unlikely to object.

DHS should closely monitor, but not intervene, in this material evolution. It provides a unique window into what is both possible and being done in synthetic biology – not from the most advanced scientists in the field, but rather – from a small group of highly motivated individuals with modest means, equipment, and knowledge to execute their design. Such knowledge is of direct interest to DHS in fulfilling its anti-terrorism mission related to biological organisms.

Further, while the inclusion of the BSL-3 derived parts in the Registry will contribute to the lowering of knowledge barriers of entry into this field, work on these parts is likely to take place regardless of iGEM's policy on it. It is in DHS's interest to have this work openly shared, reviewed, questioned, and refined, rather than taking place below the radar in obscure projects by unknown individuals for unknown purposes.

Security Culture

iGEM is increasingly integrating competitors from new countries with less robust security cultures than the United States. Communicating the differences between safety and security can be a challenge, even on a simple linguistics level as some languages may commonly translate "safety" and "security" interchangeably. This is not a challenge unique to iGEM or synthetic biology, but one that must be addressed nonetheless to ensure that scientists are not unintentionally neglecting to consider the biosecurity implications of their work.

Though information on safety and security is separate on the iGEM website, on a practical level, they are addressed together at iGEM through its human practices focus. Experience has shown that some regions pay less attention to the security angle of their work than others. According to one human practices judge, European teams tend to be the most thoughtful about these issues, followed by the Americans, and least of all the Asian teams.[68] Currently, only one team is from Africa and none are from Middle Eastern universities, but this could soon change.

At present, some teams make it to the international competition without having to answer any hard questions about the security implications of their work at the regional level.[69] Judges for regional competitions are sourced locally and have discretion in what they ask. Scrambling the judges from different regions to judge the regional competitions would be helpful.[70] This possibility is currently precluded due to travel costs that are borne by iGEM's volunteer judges or their affiliated institutions. This is an area where DHS assistance in building biosecurity-focused capacity at iGEM through a specialized sponsorship package could be valuable. DHS could work with those judges whose travel they fund to ensure they are equipped with the latest information and are asking practical security questions. Judges could brief DHS upon their return from the regional competitions.

Oversight Implementation

The explosive growth in scale and scope of the iGEM competition does not appear to be abating. The recent spin-off of the iGEM Foundation from MIT to manage the competition full-time suggests that iGEM's organizers share this view. This raises the question of whether the oversight structures of the competition are evolving at pace with its overall development. Many scientists are quick to point out—and many policymakers also recognize—the difficulty that governments have creating adaptive and appropriate rules and regulations to govern emerging technologies. In terms of the iGEM competition, it will ultimately be up to its organizers to ensure that its practitioner-focused, community-centric ideal of personal responsibility is sufficiently advanced to preclude the need for government intervention to protect public welfare.

It is important to note that the resources that iGEM provides on its website are useful and communicate a concern for the impacts and potentially negative consequences of the work they are inspiring students to perform. However, online resources are no substitute for human-to-human interaction, even if that interaction is over a digital platform. There is currently no guarantee that student competitors ever visit the Security webpage or review their national legal frameworks.

The iGEM competition appears to be outgrowing its largely volunteer-based organizational model and reliance on professional networks. The individuals who serve as volunteer screeners and judges are well-educated, enthusiastic, and distinguished graduate students and other professionals of a very high caliber. Graduate students obtain valuable experience through their involvement with iGEM, and professionals with other careers report that the iGEM experience is incredibly rewarding and inspiring for them. However, it is unclear that either group's necessarily part-time, divided attention to the iGEM competition will be sufficient to ensure it continues to operate securely as it grows in scope and scale over the long-term. The iGEM Foundation has a staff of six, but this report cannot confirm that they all work full-time at iGEM.

Volunteer, student screeners already appear to be having difficulty keeping pace with the amount of material produced by iGEM teams. For instance, a team made it all the way to presenting their work at the World Championship Jamboree in 2012 before a part in their project that should have been flagged and questioned by iGEM screeners was identified. This part was added to the team's project after human practice screeners had reviewed their wiki and after the team qualified for the World Championship at the regional level. The team's presentation was abruptly stopped by iGEM organizers and its work disqualified. This example illustrates the need to begin integrating more robust monitoring of the student projects throughout the competition to avoid future surprises that could be of larger consequence as the materials used and complexity of organisms grows.

As part of its dialogue with iGEM, DHS could encourage the work of volunteers to be supplemented by paid, full-time screeners during the summer. These could include additional human practice screeners and the introduction of regional-level, virtual biosecurity officers to interact with the teams. The biosecurity officers would not be present at the teams' institutions, as is normally the case with such personnel, but they could intermittently reach out through the internet during the course of the project to the teams to ask questions and offer advice. These positions would increase the attention paid to biosecurity throughout the competition, and their funding could be part of DHS's sponsorship package. Those receiving this funding could also report back to DHS about their experiences and provide early warning of potential threats. DHS may wish to team up with the other federal agencies that sponsor the competition, including the FBI, NASA, and NSF to share costs and expand the paid professionals' focus to safety and other governmental concerns.

New Practitioners

Teams without institutional affiliations are not allowed to compete in iGEM, but this too could evolve with time. iGEM avoids potential liabilities for student projects by leaving most of the basic, practical oversight to their affiliated institutions. It is not advisable or feasible for iGEM to exercise direct control over laboratory practices, and this fact is highly unlikely to change as the competition grows in scope and scale. However, this fact should not preclude the thoughtful consideration of eventually including unaffiliated teams in the iGEM competition.

The NSABB points to these individuals—those dabbling in synthetic biology outside of institutional confines and without academic training typical in the life science fields—as the most difficult to reach and where oversight gaps are most pronounced.[71] *The National Strategy for Countering Biological Threats* encourages community-based approaches for developing behavioral norms, identifying and addressing irresponsible conduct, and sharing experiences and best practices for risk management of dual-use information of concern.[72] The iGEM competitions may offer an opportunity for engaging with these individuals in an open and transparent manner.

DHS's dialogue with the iGEM Foundation should address the pros and cons of allowing unaffiliated teams to enter the iGEM competition. There may be homeland security benefits and educational opportunities from having unaffiliated synthetic biology practitioners discussing their work in collegial competitions and on monitored wikis. There may also be serious risks to

providing encouragement to unaffiliated teams to work in this field with minimal on-site oversight and regulation. These are issues that DHS and iGEM staff can share ideas on and parse out together in an open exchange whose outcome is not prejudged by either side. This is also an area where the judgment rendered could evolve as synthetic biology and iGEM's oversight structures progress.

Conclusions

Timeline for Policy Development

DHS should begin a dialogue with the iGEM Foundation now to address the mitigation of biosecurity concerns at the competition. This would help DHS fulfill its charges of protection, preparedness, and risk mitigation from biological terrorism. DHS and iGEM have a shared interest in scaling up the biosecurity oversight structures and tools at the competition before the increasing complexity of the organisms being modified by student teams from around the world outpaces iGEM's ability to identify, mange, and mitigate their security risks.

DHS's goal should be to positively influence the security culture of the competition and impress upon the iGEM Foundation their responsibility to establish strong biosecurity norms within the community and take their responsibilities as an online publisher seriously. A successful dialogue would provide DHS with a new pathway for influencing how iGEM's international student researchers incorporate biosecurity into their work which will have long-term implications on the field's development.

There does not presently appear to be a biosecurity risk at iGEM to which DHS should respond to with formalized rule making and regulation. However, much like the field of synthetic biology itself, the scale and scope of the iGEM competition is quickly evolving. The growth trajectory that it has experienced over the last decade does not appear to be slowing. Initiating a dialogue now will help avoid a surprise that could threaten homeland security later. The FBI has opened the door to this type of engagement with iGEM and DHS should work with them to leverage that inroad.

A relationship of trust must be gradually built between the DHS and the iGEM Foundation around their shared interest in avoiding a biosecurity incident resulting from work done for the competition. From this common ground, a mutually beneficial relationship should be established that will help DHS fulfill its mission and the Foundation to continue its work. DHS would benefit from a closer relationship with iGEM by being privy to information produced by it about emerging trends and over-the-horizon challenges and opportunities in synthetic biology. iGEM would benefit from a closer relationship with DHS by obtaining support in fortifying the biosecurity aspect of its activities and having a strong, trusted partner to turn to if a potential incident appears to be brewing. Finally, a partnership between DHS and iGEM would send a strong signal to the synthetic biology community about the need to ensure the field is advancing securely if it is to continue to progress in the absence of stricter regulations.

Policy Recommendations

The iGEM competition provides a unique window into the field synthetic biology and demonstrates what small groups of highly motivated individuals with modest means, equipment, and education are capable of producing in a matter of months. The advancement of synthetic biology will likely increase risks in the medium-term by making it easier to engineer a modified pathogen for an offensive weapon, but over the long-term, it may lead to more novel, robust ways to defend and mitigate natural and man-made threats.[73] DHS has direct interest in understanding the state of the field's development and how it impacts homeland security today and in the future to fulfill its anti-terrorism mission. The following recommendations should be considered:

- **Do not pursue new regulations at this time**. The work conducted by iGEM competitors does not appear to pose a risk to homeland security in the short-term. But due to the potential for transformative breakthroughs, the risk level could change over the medium- to long-term. Building a relationship of trust with iGEM now will offer better insights on the field's progression and more effectively provide early warning on over-the-horizon threats than formal rulemaking and regulation could at this stage.

- **Initiate a dialogue on biosecurity with the iGEM Foundation.** DHS should begin a dialogue with the iGEM Foundation about biosecurity and the trajectory of the competition before the increasing sophistication of student project outpaces iGEM's ability to identify, manage, and mitigate biosecurity risks that could threaten the public. The FBI could be a valuable partner in initiating this dialogue.

- **Offer a biosecurity prize at the iGEM World Championship**. A high-level DHS official should award a trophy to an iGEM team that makes a significant contribution to biosecurity through their project. The prize need not be monetary, or even awarded every year. It would align with iGEM's focus on reputational, community-derived accolades, rather than monetization of achievements.

- **Develop a specialized biosecurity sponsorship package with iGEM.** DHS should work with the iGEM Foundation to develop a biosecurity-focused sponsorship package that focuses on capacity building and security culture enhancement at iGEM. Elements of that package could include:
    - Introducing regional-level biosecurity officers as resources for the teams
    - Increasing attention to iGEM's responsibility as a publisher of novel synthetic biology material via the team wikis and Registry
    - Supplementing voluntary, graduate student human practice screeners and other volunteers with paid professionals
    - Rotating iGEM judges at regional competitions to more equitably enhance biosecurity awareness at earlier stages of the competition

Implementing some or all of these policy recommendations will provide DHS with two immediate benefits. First, they will help foster a friendly relationship between DHS and the iGEM Foundation. This will allow DHS to have fuller information about synthetic biology and

its practitioners if future regulation is developed. For now, DHS should make clear that its efforts to engage iGEM stem from a desire to gain a greater understanding of what is happening in synthetic biology to better fulfill its missions, not because it suspects iGEM of wrongdoing, incompetence, or negligence or plans to regulate it.

Second, these recommendations could help fundamentally change the way biosecurity is perceived by iGEM competitors. They could help make biosecurity a more explicit element of the "good stewards" role that many competitors appear to embrace. Every individual interviewed for this paper spoke about iGEM with passion and enthusiastically touted the humanitarian benefits of synthetic biology. Engaging directly with iGEM could help it avoid becoming a victim of its own success by encouraging brilliant young people to build new biological systems that may not be clearly understood by the builder. Young people also take risks without fully weighing the consequences. The biosecurity risk associated with iGEM is not necessarily from the nefarious character, but rather the well-intentioned competitor seeking to do something good. Expanding the opportunities that they have to discuss the implications of their work will help address this challenge.

Future Challenges and Research

The policy recommendations in this report are completely reliant on DHS's ability to connect with the iGEM Foundation. This was something that the authors of this report were unable to do. The professional networks with which the iGEM Foundation interacts is a tightly knit group. Many of iGEM's key actors have long-standing collegial relationships with each other. DHS should work with the FBI and leverage other relationships that its staff has with individuals involved with iGEM to informally introduce the idea of engagement and then formally initiate a biosecurity dialogue.

DHS must avoid giving the impression that it is an interloper that does not truly understand the science and is merely interested in regulation and intervention. Suspicion of its motives is likely and resistance from the life science community to direct regulation is strong. The authors of this report believe that the nature of their research into iGEM and the transparency offered about who would be reviewing the findings of this graduate student project hampered their ability to connect with the iGEM Foundation. If DHS staff reaches out to the iGEM Foundation, they must present themselves as a helpful potential partner and resources, not investigators. They should ask for help from iGEM in maintaining a safe and *secure* culture within the synthetic biology community and directly acknowledge the limitations that federal regulation would have on the vibrancy of this fast moving, international competition.

If a relationship of trust can be built with the iGEM Foundation, it could have a meaningful impact on the maturation of iGEM's biosecurity structures. While the iGEM competition began nearly a decade ago, the iGEM Foundation is relatively new. Though its staff is experienced, they are likely still finding their footing as an independent organization. DHS must recognize that the iGEM Foundation needs to remain nimble and flexible to meet new challenges, seize opportunities, and cope with the liabilities of managing a highly dynamic, cutting-edge international synthetic biology competition.

The FBI and other outside contributors have already laid a foundation for interactive dialogue on biosecurity responsibility with iGEM that DHS can build upon. DHS should not do this alone, as there are members from within the federal government already represented within the process with which DHS can usefully collaborate. However, ensuring that all federal partners have clearly defined roles and responsibilities will be necessary to avoiding interagency disputes and maintain credibility. Avoiding conflict with the FBI will be critical.

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[1] Attempts to reach iGEM Foundation staff by phone and email were unsuccessful. Two emails were sent to iGEM Foundation president, Randy Rettberg, in February 2013 describing the nature of this project and requesting an interview. These emails expressed interest in speaking with him or someone from his staff by phone, Skype, or at their offices about when, why, and how biosecurity is addressed at the iGEM. Both emails went unreturned. In March 2013, two phone calls were made to the iGEM Foundation. No one answered on the first attempt, but a junior staff volunteer took a message on the second call. She had no knowledge of the project and was happy to pass on a message to senior staff members about interview requests. No one returned this message. Additionally, requests submitted through the iGEM website by the authors to the iGEM Foundation for user names and passwords that would provide full access to iGEM's website pages were ignored.

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[47] This statement is based on the inability of all interviewees to answer this question.

[48] "Security," <http://igem.org/Security>.

[49] Ibid.

[50] "Security," <http://igem.org/Security>.

[51] "Interview with Megan Palmer." Telephone interview. 19 Mar. 2013.

[52] "Interview with Ralph Turlington." Skype interview. 27 Feb. 2013.

[53] "Interview with Laura Adam." Skype interview. 26 Feb. 2013.

[54] "Interview with Ralph Turlington." Skype interview. 27 Feb. 2013.

[55] "Interview with Laura Adam." Skype interview. 26 Feb. 2013.

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[58] "Interview with Ralph Turlington." Skype interview. 27 Feb. 2013.

[59] "Security," http://igem.org/Security <http://2010.igem.org/Team:VT-ENSIMAG/Genothreat>.

[60] "Interview with Laura Adam." Skype interview. 26 Feb. 2013.

[61] Ibid.

[62] The FBI declined to speak with us, however materials from previous years were found as well as Ken Oye speaking of their popularity at competitions.

[63] Kwinn, Laura, Ph. D, ed. "FBI Connects Science and Security Communities." *Science, Safety, Security Quarterly* (May 2012): 1. *phe.gov*. Public Health Emergency, May 2012. Web. Mar. 2013. <https://www.phe.gov/s3/Documents/s3newsletter-may2012.pdf>.

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[65] According to interviewees the complexity of organisms used as chassis at the competition has been steadily evolving since its inception. While early projects focused on E.coli, students quickly moved to developing parts based on bacillus subtilis, an organism that is closely related to and provides usable knowledge for working with anthrax. Projects are now more commonly using yeast, and some experts expect viruses as chassis to be next introduced, citing the use of parts from the adenovirus already having appeared at the competition.

[66] "Interview with Ralph Turlington." Skype interview. 27 Feb. 2013.

[67] Ibid.

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