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Making Security Viral: Shifting Engineering Biology Culture and Publishing

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ABSTRACT: The ability to construct, synthesize, and edit genes and genomes at scale and with speed enables, in synergy with other tools of engineering biology, breakthrough applications with far-reaching implications for society. As SARS-CoV-2 spread around the world in early spring of 2020, researchers rapidly mobilized, using these tools in the development of diagnostics, therapeutics, and vaccines for COVID-19. The sharing of knowledge was crucial to making rapid progress. Several publications described the use of reverse genetics for the *de novo* construction of SARS-CoV-2 in the laboratory, one in the form of a protocol. Given the demonstrable harm caused by the virus, the unequal distribution of mitigating vaccines and therapeutics, their unknown efficacy against variants, and the interest in this research by laboratories unaccustomed to working with highly transmissible pandemic pathogens, there are risks associated with such publications, particularly as protocols. We describe considerations and offer suggestions for enhancing security in the publication of synthetic biology research and techniques. We recommend: (1) that protocol manuscripts for the *de novo* synthesis of certain pathogenic viruses undergo a mandatory safety and security review; (2) that if published, such papers include descriptions of the discussions or review processes that occurred regarding security considerations in the main text; and (3) the development of a governance framework for the inclusion of basic security screening during the publication process of engineering biology/synthetic biology manuscripts to build and support a safe and secure research enterprise that is able to maximize its positive impacts and minimize any negative outcomes.

KEYWORDS: *biosecurity, biosafety, SARS-CoV-2, synthetic biology, engineering biology*

INTRODUCTION

Engineering biology research is accelerating advances in health and medicine, food and agriculture, environmental sustainability, and the bioeconomy.[1] With the ability to build and engineer complex biological pathways, circuitry, and organisms comes an imperative to grapple with the potential negative uses and outcomes in addition to celebrating and sharing the good. The biological research community has long recognized the need to consider the safety and security aspects of research and innovation in publishing; however, addressing security while ensuring the fundamental values of open science and knowledge sharing has proved challenging. This issue came into focus during debates over publication of papers describing H5N1 variants with enhanced transmissibility.[2−7] There are currently no widely implemented guidelines for attending to security concerns in publishing.[8]

We, as members of the Engineering Biology Research Consortium (EBRC), offer the perspective of researchers working to build a scientific culture that supports the proactive identification and management of security issues emerging from biological research while recognizing and upholding the value of open science and the free flow of information as a driver of progress and innovation. Rarely, information or knowledge shared widely can pose significant risks. Evaluating the risks relative to the benefits of publication of some types of research or techniques—such as the *de novo* synthesis of viruses—is difficult and often subjective, and processes for doing so have not been widely adopted. Informed authors, editors, reviewers, researchers, and other stakeholders may, and do, reasonably come to different conclusions as to the levels of risk posed by research and how best to address and mitigate those risks.[9]

The publication in early 2021 of "Engineering SARS-CoV-2 using a reverse genetic system" in *Nature Protocols*[10] is a clear example of the need for such evaluative processes to be established, made transparent, and consistently implemented.[11] The detailed, step-by-step guide for the *de novo* construction of SARS-CoV-2 in the laboratory makes it feasible for individuals with minimal molecular biology or virology training, without

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access to appropriate biosafety facilities, and/or with ill-intent, to build and generate live virus from scratch along with variants with potentially higher transmissibility, decreased vaccine efficacy, and/or greater disease severity.[12,13]

Protocol papers explicitly lower the barriers for nonexperts to engage in new areas of research and are generally a great asset to the scientific community. However, in addition to the technical information provided in protocols, scientists new to an area of research or attempting a new method or approach need similarly detailed relevant safety and security information, particularly when the stakes associated with successfully completing the protocol are so high. Future iterations of security governance processes, standards, or guidelines should at a minimum identify protocol papers describing the synthesis and modification of viruses that cause serious disease as warranting further security review.

To initiate meaningful discussion that yields actionable, widely adoptable guidelines, we offer preliminary recommendations for the publication of manuscripts with security implications in engineering biology. We call on researchers, journals, reviewers, and funders to collaboratively iterate upon these recommendations through further discussion with thoughtful input from stakeholders across the field.[14]

We recommend (1) that protocol manuscripts for the *de novo* synthesis of certain pathogenic viruses undergo a mandatory safety and security review; (2) that if published, such papers include descriptions of the discussions or review processes that occurred around security considerations in the main text; and (3) the development of a governance framework for the inclusion of basic security screening during the publication process of engineering biology/synthetic biology research to build and support a safe and secure research enterprise that is able to maximize its positive impacts and minimize any negative outcomes. We conclude by discussing potential processes for the adoption and implementation of these recommendations.

RECOMMENDATION 1: REVIEW OF PROTOCOLS FOR *DE NOVO* VIRAL SYNTHESIS

Protocols describing the *de novo* synthesis of human, animal, or plant viruses that are likely to be highly transmissible and have high mortality and/or morbidity (e.g., biosafety level 3 and 4 viruses) raise unique security concerns that deserve consideration in advance of publication. We recommend that editors incorporate security expertise into the peer review process before such protocols are published. Editors often invite peer review from individuals qualified to evaluate different aspects of a manuscript. Here, editors should invite security experts to review the manuscript in addition to technical reviewers. Ideally, a set of reviewers would include individuals with technical expertise who demonstrably incorporate security into their research and/or professional activities. We suggest the inclusion of three to five reviewers qualified to evaluate security considerations because experts often disagree about the extent of biological threats, so it is important that publication decisions that could have global implications not be made based on the views of one or two individuals.[9] There is, of course, a procedural burden of finding additional reviewers; however, the number of protocol papers describing synthesis of agents with transmissibility and high mortality and/or morbidity is low enough that this standard can be met if journals that publish protocols agree to do so.

In this review process, parties involved should consider the risks and the benefits of publishing the detailed protocol compared to letting previously published methods sections stand. (Generally, protocol papers elaborate on approaches previously published in research papers.) Reviewers should incorporate mitigating factors into their review considerations, including (1) a globally available vaccine with high efficacy against circulating variants and/or (2) established regulatory constraints around the distribution and availability of associated physical materials. At the time of publication of "Engineering SARS-CoV-2 using a reverse genetic system," vaccines were available only to the highest risk groups in the United States and widely inaccessible on a global scale. Early evidence in a preprint about Omicron (B.1.1.529) suggests they are less efficacious against some variants.[15] Efficacious therapeutics are now being approved but were unavailable even a few months ago. SARS-CoV-2 is not a Federal Select Agent, so its possession, use, and transfer are not regulated in the United States, although in November 2021, the CDC announced an Interim Final Rule placing SARS-CoV-2/SARS-CoV chimeras on the Federal Select Agent list.[16] If a nefarious actor was unable to access associated plasmids due to regulation or security practices of the repositories that might distribute them, that actor might be able to reconstruct the virus by ordering and assembling synthetic DNA. Some DNA synthesis companies screen for SARS-CoV-2 sequences, but they are not required to do so and, especially on an international scale, many do not. Those that do screen for SARS-CoV-2 sequences generally fulfill orders absent any other indicators of potential misuse.

Biodefense in the Age of Synthetic Biology, a 2018 consensus study report from the National Academies of Sciences, Engineering, and Medicine, provides a useful framework for evaluating research and capabilities for general usability, usability as a weapon, expertise and infrastructure required, and the potential for mitigation.[17] Derivatives of this framework that are expanded to evaluate safety and additional security considerations, developed through deliberation and consultation with the research community, journal editors, government agencies, and security experts, may be useful for security reviewers. If security reviews were divergent, a conversation between security reviewers and editorial staff could be considered to work toward a safe and secure outcome.

The most likely outcome of a review process that includes security-minded reviewers is that the authors be asked to make some revisions to their manuscript, for example, to incorporate explicit safety and security cautions in their paper and/or describe the necessity of appropriate laboratory conditions such as locked doors and freezers, appropriate air flow control, and biosafety cabinets. They may also be asked to provide a description of the security review process (see below). Security reviewers could possibly recommend that the journal decline to publish the protocol article or that it wait until the risks of doing so are decreased by greater availability of diagnostics, therapeutics, and/or vaccines, in which case previously published methods sections would still stand and enable direct communication between researchers as appropriate. Editors make decisions all the time about how manuscripts can be improved during review and whether or not manuscripts are appropriate for publication in their journal. Adding these reviewers to the process will better position editor(s) to make fully informed decisions about publication.

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RECOMMENDATION 2: PUBLICATION OF SECURITY REVIEW PROCESS ALONGSIDE MANUSCRIPTS

Publications describing the reconstruction of highly transmissible pathogenic viruses with high mortality and/or morbidity should be accompanied by a description of the safety and security review it underwent in advance of publication, including all efforts to engage with, understand, and mitigate security risks. Within the paper text itself, authors should briefly describe risks inherent in the research, detailed precautions that anyone using the protocol should take, mitigating actions, and any discourse undertaken with relevant experts or authorities during research or publication.

Journals could publish short commentaries accompanying such pieces describing how the security issues came to their attention, what (if any) steps they took to address these issues or to discuss the issues with the authors, and the journal's assessment of why the benefits of publication outweigh identified risks. While such statements may draw the attention of those wishing to cause harm, they can also draw the attention of relevant authorities positioned to monitor and intervene in nefarious activities. Protocols journals, in particular, often include concrete warnings about the safety risks of individual chemicals used in each protocol. These warnings show the journals take their role seriously in keeping practitioners safe, and we suggest that they extend this same attention to the security implications of published papers.

Security statements within a manuscript or accompanying articles with security implications may be seen as platitudes or boilerplate; however, their value is 4-fold as they (1) indicate that the authors have considered security issues associated with their work; (2) encourage authors to implement security best practices throughout the research lifecycle, as they know publishers will require a description of these practices; (3) help inform readers that evaluating the security implications of research is an important part of the scientific process; and (4) provide an empirical basis for future improvements of the security assessment process itself.

RECOMMENDATION 3: BROADER PREPUBLICATION SECURITY EVALUATION

The above recommendations pertain specifically to protocol papers describing the synthesis of highly transmissible viruses with high mortality and/or morbidity. There is, however, a broader scope to consider, including how security concerns can be identified and addressed more broadly in an engineering biology publication. More than other life science disciplines, engineering biology can be used to produce pathogenic biological agents, synthesize drugs and toxins, and have considerable environmental effects. Journals publishing engineering biology research should implement a standardized questionnaire or survey addressing security as part of the submission process. Some preliminary suggestions of information that journals should consider include (1) whether or not the authors identified any security concerns associated with the work they have submitted; (2) what, if any, security evaluation was done within the author's institution, the relevant funding organization, or a government-supported panel or review board; (3) whether the authors can cogently summarize whether (or, importantly, not) publication of the work poses substantive risk; (4) what mitigations they considered around this risk; (5) whether the submitted work has been previously rejected by any other journal due to security concerns; and (6) whether and how they plan to restrict access to materials required to reproduce their research and/or how they will promote their safe and secure use, particularly for research involving recently emerged viruses or organisms for which regulation on possession is still in development. Journals should make public the authors' answers to these questions in the same way and for the same reasons as answers to ethical and safety questionnaires are currently made public: to maximize transparency and opportunity for debate as to the boundaries of the publication of such research.

Questions for editors and reviewers should prompt them to consider if the work poses obvious security concerns, for example if it involves engineering of human or agricultural pathogens, synthesis of toxic compounds or narcotics, or could have serious environmental implications. Editors and reviewers should also be asked if the work has less obvious security implications, such as making an entire class of compounds significantly easier to synthesize (particularly if that class includes toxic chemicals or other controlled substances) or facilitating easier assembly of long DNA fragments. Given the limited security expertise and unpaid nature of journal editing and reviewing, questions for editors and reviewers should not be onerous.

The outcomes of author, reviewer, and editor surveys should be used as a basis for discussion on minimizing publication risks. In some cases, additional safety and/or security experts may need to be engaged, and it may be valuable for authors to discuss security concerns that may result from publication with research institutions, funders, and (rarely) appropriate governmental officials (e.g., in the United States, FBI WMD Coordinators).

IMPLEMENTATION

Decisions as to when and how to publish research and protocols that pose safety and security concerns have caused debate in the past (see, e.g., refs 18−20). Moving beyond debate to the development of standards and practices that systematize biosecurity governance will take active participation and commitment from diverse members of the biological sciences research community. The vastness and diversity of this community make governance efforts by any single government difficult to develop and to implement and could not address the international nature of the field. The National Science Advisory Board for Biosecurity (NSABB) in the United States was formed to provide guidance and recommendations on biosecurity and dual use issues but has only met once since May 2017, and the US Department of Health and Human Service's Potential Pandemic Pathogens (PPP) Care and Oversight HHS department-level review groups review funding decisions on proposed PPP research.[21] International efforts, including those of The World Health Organization and the Nuclear Threat Initiative's Visibility Initiative for Responsible Science,[22] are developing experiments in the governance of security concerns across the research lifecycle, from funding to publication and beyond.[23] Given the challenges of universal implementation and international enforcement, this paper's recommendations are geared to journals that individually, or in concert with one another, can take steps to increase security. With the high number of biosecurity stakeholders with different experience and expertise, reaching consensus on governance is difficult. We suggest the development of a pilot governance mechanism,

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producing real-world data for iteration and broader implementation, similar to the approach taken in development of the Materials Design Analysis Reporting (MDAR) Framework.[24] A pilot program at one or more journals could be implemented at relatively low cost and the lessons learned from its outcomes may catalyze further NGO, philanthropic, and/or government investment.

A successful end state might have parallels with the practices of DNA synthesis providers. Government guidance has significantly impacted the screening practices of many DNA synthesis providers in the United States. Even without formal regulation, many companies still follow the Department of Health and Human Services "Screening Framework for Providers of Synthetic Double-Stranded DNA" to screen sequences and customers before filling orders. Similarly, government guidance could help journals implement appropriate publication standards for manuscripts with potential security concerns. Similarly to how DNA synthesis companies developed and have grown the International Gene Synthesis Consortium, which brings companies together to design and apply such screening steps, a consortium of journals could likewise come together to discuss security best practices. Of course, there are important ways that publication differs from gene synthesis; one significant challenge would be defining which journals ought to implement such processes, and how journals that publish research across a range of disciplines would determine when to implement security protocols.

Implementing these changes will support the development of a stronger culture of security in engineering biology research and publication. Other strategies for effecting such a cultural shift may draw on the findings of previous reports (e.g.,[25]). Adequate security training for undergraduate, graduate, and postdoctoral researchers can build a generation of community leaders equipped to incorporate security considerations into their work. Emphasis of the ethical, social, safety, and security issues in scientific research can be incorporated into undergraduate education, normalizing these as part of the research process and even highlighting career opportunities in these areas.[26] EBRC directly supports such training for graduate students and postdocs in engineering biology research through its "Malice Analysis" workshops (https://ebrc.org/malice-analysis). The workshops have been free to participate in and have facilitated the assessment of security considerations by trainees of their own work using a framework based on one developed by the National Academies of Sciences, Engineering, and Medicine in *Biodefense in the Age of Synthetic Biology*.[17]

Funders can also encourage a culture of security by requesting that proposers include precautions and/or mitigation strategies for work with security implications, and by tracking potential risks through the project lifecycle via progress reports for funded projects. They could incentivize or require publication of synthetic biology research or techniques in journals that have security screening. Additional fora for teaching and reinforcing security awareness should be identified, or built, and supported and should facilitate the building of professional networks such that researchers know with whom they can consult or collaborate when security issues arise.

Because EBRC advocates for and supports engineering biology, it also has an obligation to engage in discussions and development around security and responsible researcher conduct in the field. As members of EBRC, we took the publication of a detailed protocol for reconstructing SARS-CoV-2 as a call to catalyze dialogue around the guardrails for research with serious security and/or safety implications.[10] As capabilities within life science research grow, so too does the need for a culture that recognizes the concomitant security risks accompanying rapid development and dissemination.[27,28] Despite discussion around security in publishing, little concrete progress has been made toward establishing best practices across journals. We recommend the development of standards that give concrete guidance for authors and editors when evaluating whether to publish findings with safety and security implications. Such standards would need to be iterated upon and revisited over time but should be shaped by consensus built between the research community, the security community, publishers, and other stakeholders. We offer preliminary recommendations that can be built upon to support a research enterprise that incorporates security into its research, development, and publication practices.

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