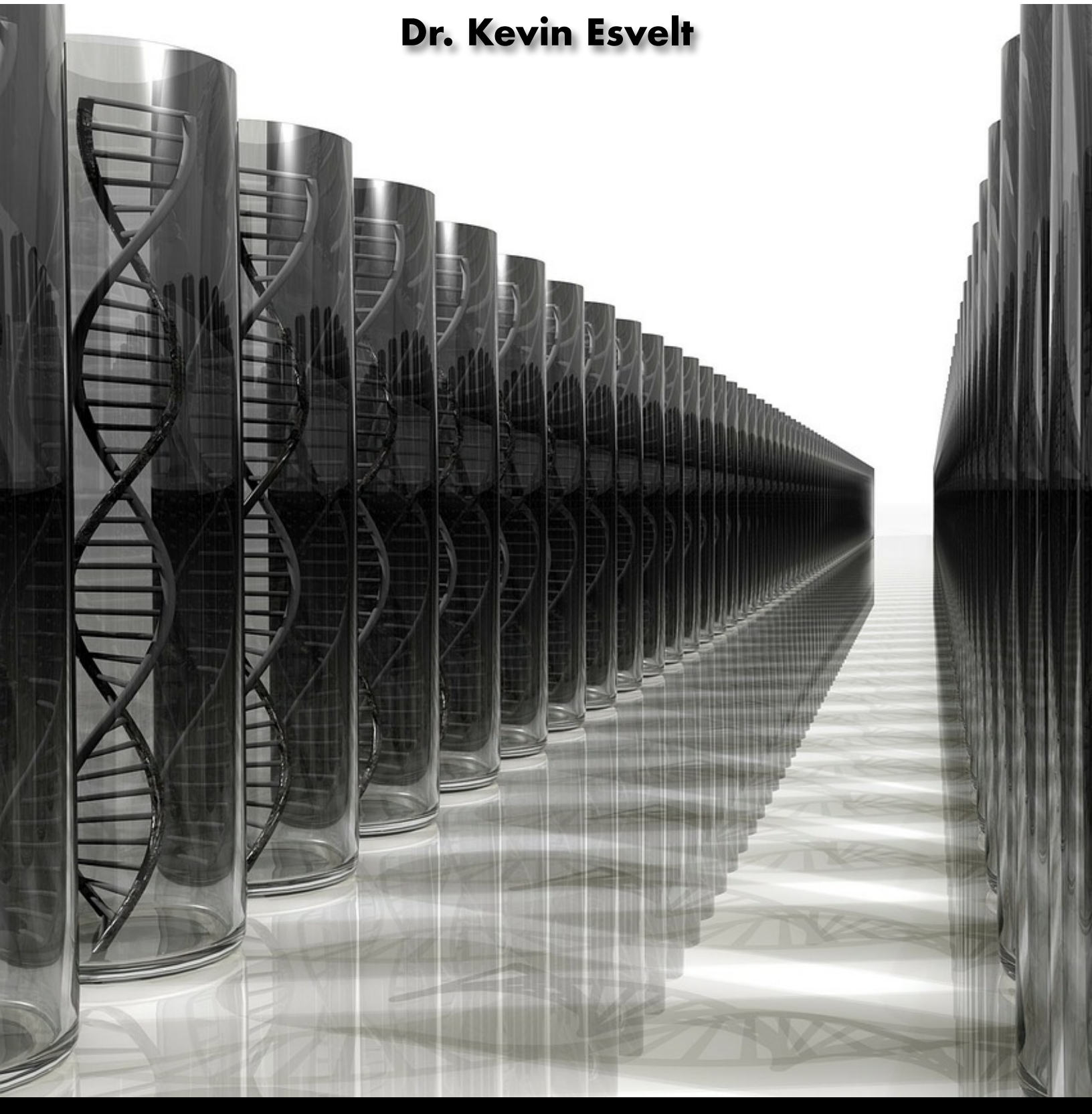
GENE DRIVE TECHNOLOGY: THE THING TO FEAR IS FEAR ITSELF

Dr. Kevin Esvelt



STUDY OVERVIEW

Researchers from George Mason University and Stanford University initiated a two-year multidisciplinary study, E*diting Biosecurity*, to explore critical biosecurity issues related to CRISPR and related genome editing technologies. The overarching goal of the study was to present policy options and recommendations to key stakeholders, and identify broader trends in the life sciences that may alter the security landscape. In the design of these options and recommendations, the research team focused on how to manage the often-competing demands of promoting innovation and preventing misuse, and how to adapt current, or create new, governance mechanisms to achieve these objectives.

The four study leads and seven research assistants for *Editing Biosecurity* were assisted by a core research group of fourteen subject-matter experts with backgrounds in security, the life sciences, policy, industry, and ethics. The centerpiece of the study was three invitation-only workshops that brought together the study leads and the core research group for structured discussions of the benefits, risks, and governance options for genome editing. To support these workshops and the final report, the study leads prepared two working papers on risk assessment and governance, respectively, and commissioned five issue briefs on key topics. The authors assume full responsibility for the report and any errors or omissions.

Issue Briefs and Working Papers

Perello E. *CRISPR Genome Editing: A Technical Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018.

Carter SR. *Genome Editing, the Bioeconomy, and Biosecurity*. Editing Biosecurity Issue Brief No 2. Arlington, VA: George Mason University; December 2018.

Watters K. *Genome Editing and Global Health Security*. Editing Biosecurity Issue Brief No 3. Arlington, VA: George Mason University; December 2018.

Esvelt K. *Gene Drive Technology: The Thing to Fear is Fear Itself*. Editing Biosecurity Issue Brief No 4. Arlington, VA: George Mason University; December 2018.

Vogel KM, Ouagrham-Gormley SB. Anticipating emerging biotechnology threats: A case study of CRISPR. *Politics and the Life Sciences*. 2018 Oct 23:1-7.

Koblentz GD, Kirkpatrick J, Palmer MJ, Denton SW, Tiu B, and Gloss K. *Biotechnology Risk Assessment: State of the Field*. Editing Biosecurity Working Paper No 1. Arlington, VA: George Mason University; December 2017.

Kirkpatrick J, Koblentz GD, Palmer M, Denton SW, and Tiu B, *Biotechnology Governance: Landscape and Options*. Editing Biosecurity Working Paper No. 2. Arlington, VA: George Mason University; March 2018.

All of the working papers, issue briefs, and a list of the project's participants are available at the project's website: https://editingbiosecurity.org/.

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KEVIN M. ESVELT BIOGRAPHY

Kevin M. Esvelt is an assistant professor of the MIT Media Lab, where he leads the Sculptin, Evolution Group in exploring evolutionary and ecological engineering.

Esvelt received his Ph.D. from Harvard University for inventing a synthetic microbial ecosystem to rapidly evolve useful biomolecules. He subsequently helped pioneer the development of CRISPR, a powerful new method of genome engineering.

In 2013, he was the first to identify the potential for CRISPR gene drive systems to alter wild populations of organisms. Recognizing the implications of an advance that could enable individual scientists to alter the shared environment, he and his colleagues chose to break with scientific tradition by revealing their findings and calling for open discussion and safeguards before they demonstrated the technology in the laboratory.

At MIT, Esvelt's laboratory develops safer daisy drives that only spread locally, as well as ways of restoring populations to their original genetics. Together with the communities of Nantucket and Martha's Vineyard, they are advancing the Mice Against Ticks project aiming to prevent tick-borne disease. Other research interests include unraveling the workings of molecular evolution, controlling the fitness of microbes in the gut, and reducing animal suffering. An outspoken advocate of freely sharing research plans to accelerate discovery and improve safety, Esvelt seeks to use gene drive as a catalyst to reform the scientific ecosystem.

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Abstract

CRISPR gene drive systems have raised concerns due to their ability to spread through wild populations over generations, but the technology is slow, easily detected by sequencing, and readily countered by overwriting unwanted changes. Populations of humans and other organisms with long generation times cannot be directly affected, agriculture is highly resistant thanks to seed farms and selective breeding programs, and population suppression drives that might affect wild ecosystems are the most trivial to counter. The primary hazard of gene drive technology is not physical, but social: that unethical closed-door research, overhyped fears, or an unauthorized release into a wild population will damage public trust in science and governance. Sunlight, in the form of new incentives favoring pre-registration of all proposed gene drive research, is the best way to dispel the clouds of fear and uncertainty. Ensuring that research is conducted in the open could lead to external scrutiny of research plans in other fields, potentially enabling nascent technological hazards to be identified early enough to intervene.

Introduction

Gene drive is a ubiquitous natural phenomenon in which a genetic element reliably spreads through a population even if it does not help individual organisms reproduce (Burt, Trivers, and Burt 2009). The advent of CRISPR-based genome editing in 2013 enabled the construction of gene drive systems that use CRISPR to replace the original version of a gene with the edited version in successive generations of descendants (K. M. Esvelt et al. 2014). The technology is broadly restricted to species that exclusively reproduce sexually, that have a short generation time of roughly two years or less, and in which delivery of DNA into the germline is feasible. The difficulty of germline delivery is the primary barrier limiting accessibility in most species.

History

Austin Burt first detailed the potential to harness natural homing-based self-propagating gene drive systems in 2003 (Burt 2003), but technical limitations largely precluded their use (Windbichler et al. 2011). My collaborators and I independently realized CRISPR could be used to accomplish gene drive shortly after its development, and published a detailed description of likely capabilities and call for discussion prior to demonstrating the technology in the laboratory (K. M. Esvelt et al. 2014; Oye et al. 2014). Our intent was to set a precedent of open disclosure of research plans in advance of gene drive experiments, enabling people to voice their opinions in advance of experimental decisions that could affect them. Before publishing, we consulted with experts from a variety of fields to identify potential negative consequences, including those related to security (Drinkwater et al. 2014). Misuse was an obvious possibility, as any technology capable of ensuring that mosquitoes do not spread disease could do the opposite.

However, slow spread over generations, easy detection via sequencing, and the potential to overwrite harmful changes renders renders gene drive comparatively harmless relative to other technologies. Even the deadliest blade poses little threat if the only possible attacks are slow, obvious, and easily blocked.

On the other hand, any unauthorized or accidental release of a gene drive system, even if ecologically harmless, could severely damage public trust in science and governance. Raising awareness of the hazard and of available safeguards was judged a high priority.

Our assertion that gene drive poses little security risk relative to other technologies was challenged by a letter in *Science*, which drew an analogy to nuclear weapons in arguing that the technical details involved in making specific gene drive systems should remain classified (Gurwitz 2014). In our response, we noted that the technology was biased towards defense, that open research will benefit security by aiding environmental monitoring of at-risk populations, and that the greater risk was to public perception of biotechnology and the potential benefits thereof (Oye and Esvelt 2014). The first laboratory tests in yeast, which were described in January 2015, verified that CRISPR-based gene drive was highly efficient and that it was possible to overwrite and undo the effects of an existing drive system (DiCarlo et al. 2015). Subsequent experiments demonstrated efficacy in flies and multiple species of mosquitoes (Gantz and Bier 2015; Gantz et al. 2015; Hammond et al. 2016).

Since then, the perception that gene drive may pose a security risk has arguably grown over time, aided by inflammatory and ill-informed articles in the popular press as well as increasing awareness of biotechnology on the part of the security establishment (Clapper 2016). Because the primary danger arises from unwarranted fears, this perception is dangerous. Unfortunately, very few researchers are deeply familiar with both the technical capabilities and limitations of CRISPR as well as its application to gene drive; neither alone suffices. While our assessment of the security implications has been public for years, it is not widely known or understood ("FAQ - Sculpting Evolution" n.d.). Here I outline the limitations of CRISPR-based gene drive, describe the actions needed to ensure the technology will not present a security threat, and outline a greater concern.

Constraints Limiting Misuse

Slow

Gene drive systems spread from parents to offspring over generations, meaning only fast-reproducing species are susceptible. A perfect self-propagating gene drive system in a population with randomly mating individuals can almost double in frequency with each generation, with the rate of increase slowing as the number of potential mates that are not already carriers declines. No actual populations meet these criteria. Even in the fruit fly *Drosophila melanogaster*, which can reproduce roughly every 10 days and benefited from inadvertent human transport, the natural P-element gene drive system required over 50 years to spread to every population in the world (Burt, Trivers, and Burt 2009). To spread much faster, large numbers of carrier organisms would

need to be distributed evenly across the existing population. Any such release program would be obtrusive.

Obvious

Gene drive systems require microbial CRISPR genes to be expressed in the germline cells of sexually reproducing multicellular organisms in order to function. The combination of a eukaryotic expression signal and a microbial CRISPR system component does not occur naturally and cannot be hidden from modern sequencing methods, especially those that sequence thousands of bases at a stretch. Any sequencing read that detects such a junction is an telltale indication of human engineering. Using current technology, populations deemed at risk can be monitored by sequencing individual organisms. As the cost of sequencing continues to fall, it may be possible for environmental metagenomic sequencing to detect any gene drive organism in a watershed. Because monitoring efforts will benefit from a clear understanding of the current state of the art in potentially relevant species, open gene drive research will enhance active monitoring and therefore security.

Easily Blocked

Changes made by one gene drive system can be overwritten by another. Due to the availability of CRISPR systems with diverse targeting requirements, it is not currently possible to construct a functional sequence that does not have any accessible target sites. This challenge will only grow more difficult with time as new nuclease variants are characterized, engineered, and evolved. Constructing an immunizing reversal drive system that can overwrite a rogue gene drive system involves taking the original sequence, removing any harmful elements, and adding guide RNAs that target the original sequence (K. M. Esvelt et al. 2014). The resulting gene drive system will spread through and immunize the unaffected population at least as quickly as the rogue drive can spread because it relies on the same expression conditions and target sites. Whenever the two are present in the same organism, the rogue drive system will be overwritten in the germline. Overwriting was demonstrated in the first report of CRISPR-based gene drive in yeast (DiCarlo et al. 2015), but should be confirmed in diverse other species. Gene drive systems in r-selected organisms such as mosquitoes should be more readily countered due to the rapid population expansion of immunizing reversal drive carriers afforded by the large number of offspring.

Current Constraints

The difficulty of detecting and countering rogue gene drive systems will depend on the accessibility of the technology. Design and construction are straightforward and require only readily available supplies: most molecular biology laboratories have access to CRISPR, and the unique targeting sequences can be obtained from any number of synthesis companies. These sequences are virtually identical to those required for legitimate CRISPR-based research.

In contrast, few individuals have the technical ability to deliver DNA into the reproductive cells of sexually reproducing organisms, although this varies tremendously by

species. Over ten thousand people possess this capability in fruit flies, whereas the number is likely fewer than a hundred in mosquitoes. Thousands of facilities can engineer mice, but projects in mammals tend to be very closely scrutinized due to animal welfare laws, and few if any individuals or small groups could generate transgenics without the facility's equipment.

Only extremely well-funded groups or governments are likely to be capable of accessing gene drive technology in organisms other than fruit flies for a number of years and possibly even decades, but only if the transgenesis bottleneck remains in place.

Given the rate of advancement in the life sciences, this appears quite unlikely; there are strong incentives for scientists to develop easier approaches, and few of them are aware of the likely consequences for gene drive. If future methods are not species-specific and/or do not require expensive equipments and teams of experts analogous to current approaches in mice, gene drive in other organisms will become much more accessible. The best way to prevent this scenario is to encourage the development of transgenesis methods that would ease the bottleneck for legitimate science without increasing the accessibility of gene drive.

(Non)-Candidate Species and Misuse

Humans

The collective human germline cannot be effectively altered by gene drive systems. This cannot be overemphasized. Our generation time is far too long for any meaningful number of people to be affected in a timeframe of less than centuries, even if future generations for some reason chose not to sequence their genomes and undo the changes. Engineered gene drive systems could only affect the human gene pool following the collapse of civilization.

Agriculture

Many analysts have speculated that agriculture might be threatened by gene drive, but the genetics of key agricultural species are tightly monitored and controlled for economic reasons. As a rule, farmers in the developed world purchase their seeds to access new traits and benefit from hybrid vigor rather than save and plant their own (Birchler, Yao, and Chudalayandi 2006). The advantage conferred by hybrid vigor is substantial enough that farmers in the developing world are rapidly transitioning towards commercial seed production. A similar situation holds for livestock and even honeybees. Because gene drive systems cannot spread through populations whose genetics are monitored and controlled, agriculture is mostly immune to potential misuse and rapidly becoming more so. Wild-caught marine organisms are a noteworthy exception.

Ecology

In the absence of monitoring, gene drive systems targeting keystone species that are central to ecosystem function could conceivably cause harm. Notably, population suppression drive systems that impose a genetic load are predicted to cause sharp declines in the target population with few obvious early warning signs save detection by sequencing (Deredec, Burt,

and Godfray 2008). However, suppression drive systems are more difficult to construct, more likely to be blocked by natural resistance, and are even more easily countered than alteration drive systems by releasing organisms with mutations that prevent the target gene(s) from being cut (Burt 2003; K. M. Esvelt et al. 2014).

Misuse could also be accidental rather than deliberate. Ecological side-effects from authorized or unauthorized self-propagating gene drive systems that spread beyond their intended target population could potentially cause harm to local areas. Preventing this outcome will require thoughtfully designed field trials using local drive systems on the one hand, and careful monitoring on the other. Technologies that would render transgenesis widely accessible should be regarded warily, not because any particular unauthorized drive system is likely to cause harm, but because widespread access will make unauthorized releases more likely, greatly increasing the total economic and social cost of monitoring, overwriting, and cleanup.

Preventing misuse will require active monitoring and defense

Overall, gene drive poses comparatively little risk of misuse, but only if defense agencies invest in active monitoring and response capabilities. Sequencing-based monitoring may focus on particular species deemed at-risk or whole environments, but will require substantial and ongoing investments as well as up-to-date knowledge of which species are amenable to gene drive. Monitoring need not go into effect immediately due to the currently limited state of CRISPR-based gene drive technology, but research programs to identify key species and superior methodologies are needed. Similarly, efforts to verify that overwriting drive systems function in other organisms as well as they do in yeast and test their efficacy in large, structured populations will be required. Active research programs including FELIX (IARPA) and Safe Genes (DARPA) are designed to meet these needs, but still greater investments will be required to support indefinite operational costs.

Openness should promote defense

As a defense-biased technology, gene drive monitoring and security will benefit if the current technological state of the art is well-known. Knowing which species are at-risk will facilitate monitoring and the ability of governments to readily create countermeasures in the event that a rogue drive system is detected. Hence, ensuring that research involving relevant technologies is open will effectively guard against misuse.

Social, Economic, and Diplomatic Hazards

The primary danger posed by CRISPR-based gene drive is social. Given widespread skepticism of genetic engineering, any unauthorized release of a gene drive system could lead to a strong social backlash and serious damage to public trust in science and governance when society can least afford it. In addition to the institutional damage, any such backlash would almost certainly delay efforts to use gene drive to prevent vector-borne and parasitic diseases such as malaria and schistosomiasis, possibly resulting in millions of otherwise preventable deaths.

Economically, the 'contamination' of foodstuffs with trace amounts of genetically engineered products or radiation can justify the imposition of trade restrictions desired for unrelated economic reasons. The release of a completely harmless but unauthorized gene drive system could lead to more profound economic disruption, particularly if widespread alarm leads to demands for draconian transport controls intended to keep the rogue gene drive out at all costs. Such costs could prove quite severe, and the controls that would incur them currently appear to be entirely legitimate under the SPS Agreement of the World Trade Organization.

Finally, the unilateral release of a gene drive system, even if objectively beneficial, could precipitate a diplomatic crisis or even war. Many antagonistic countries share ecosystems, meaning that a self-propagating gene drive released to remedy a local health or environmental problem is highly likely to spread across the border, with unpredictable diplomatic consequences.

Mitigating Social Risks

The most immediate concern for policymakers is the potential damage that may result from the release of a rogue gene drive system impacting fruit flies. Because so many individuals could build drive systems in these organisms, there is a correspondingly nontrivial likelihood of potential accidental or deliberate release in the near term. A fruit fly drive system will almost certainly have zero physical or ecological effects, so the damage resulting from misuse will be primarily social, economic, and diplomatic. It may be wise to take preemptive steps to mitigate this damage through public engagement and through the creation of institutional barriers to preclude hasty diplomatic and trade decisions, especially by politicians under adverse incentives.

Ideally, technical advances will come to the rescue. If engineered genes are viewed in the popular imagination as likely to remain in the population for centuries, gene drive will be perceived as a form of lasting genetic pollution. But if it is widely understood that all engineered genes can be readily removed, no matter their source, then even an unauthorized self-propagating gene drive is no longer *dangerous contamination*. It becomes *graffiti*: annoying, the right treatment will wash it right off. Hence, developing and publicizing a pressure-washer for gene drive is a high priority.

To date, only one still-theoretical approach could completely eliminate all engineered components of a rogue self-propagating gene drive (Min et al. 2017). Research to realize this system and develop alternative approaches capable of the same outcome should be a correspondingly high priority.

Traditional Closeted Research May Pose a Major Security Risk

While active monitoring can minimize the security risks posed by gene drive technology, the story of its development highlights a greater peril.

First, the advent of CRISPR-based gene drive demonstrates that technological capabilities can rapidly grow in unanticipated directions. In 2012, no one imagined that a typical scientist might be able to alter entire populations, however slowly. The concept does not seem to appear in science fiction. Now, self-propagating CRISPR-based gene drive appears feasible in several species (DiCarlo et al. 2015; Gantz and Bier 2015; Gantz et al. 2015; Hammond et al. 2016). If not countered, even some of the least effective proof-of-principle systems are predicted to spread through multiple populations (Noble et al. 2018).

Second, even brilliant and well-meaning researchers cannot reliably anticipate the consequences of their work. In 2013, we were concerned that other researchers unaware of the concept of gene drive might develop the technology as a laboratory genetics tool without considering its potential to impact wild populations. These concerns proved well-founded (Gantz and Bier 2015).

Finally, the closed-door nature of academic science prevents others from identifying and warning them. Even the extensive coverage of CRISPR-based gene drive in the scientific literature and popular press in 2014 failed to alert researchers who independently invented the technique for laboratory use.

These events highlight major flaws inherent to the current system of closed-door research: technologies never before imagined can be developed and disseminated by small groups of similarly trained specialists who cannot reliably anticipate consequences, nor be identified and warned by any who do.

Suppose there exists a technology within humanity's future discovery space that would pose a major security risk if discovered and made accessible. The story of CRISPR-based gene drive suggests that the current scientific enterprise will discover and disseminate it. Hence, the discovery of unanticipated hazardous technologies arguably constitutes a form of global catastrophic risk.

While there are no easy ways to address this problem, the scrutiny of research plans by outside experts would provide many more opportunities to intervene than are available under the present closed-door system. Changing the scientific incentives governing gene drive research to favor pre-registration of experiments would be a small but crucial step towards some form of collective scrutiny for other nascent technologies.

Discussion

Because gene drive systems are slow, obvious, and easily countered, major security risks are likely avoidable if at-risk populations are actively monitored by defense establishments. Current IARPA- and DARPA-sponsored research programs aim to ensure that early detection and rapid response are feasible. Open gene drive research and continued investments will be needed to identify and monitor at-risk populations for the foreseeable future. Institutional changes to limit the economic, social, and diplomatic damage resulting from the unauthorized release and international spread of a gene drive system would seem prudent.

Transitioning the gene drive field to an open research model will require leveraging some combination of intellectual property, national regulations, and publication and funding requirements to encourage or require experiments to be pre-registered (K. Esvelt 2016; K. M. Esvelt 2017). In addition to the security benefits, openness is arguably morally required to ensure that people have a voice in decisions intended to affect them. Last but not least, the current system of closed-door technology development by small groups of similarly trained specialists poses a global catastrophic risk. Changing scientific incentives to favor pre-registration of gene drive experiments would set a precedent for the collective scrutiny of technology development that could be extended to other fields.

Conflicts of Interest

The author is an inventor on patents filed by Harvard University and MIT on various forms of gene drive systems. Opinions are those of the author only. The author's research on gene drive systems is supported by the Burroughs Wellcome Fund, NIH, and DARPA Safe Genes.

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