A National Strategy for Synthetic Biology

Lt Col Marcus A. Cunningham, USAF
John P. Geis II

Abstract

We are experiencing a technical revolution in biotechnology that will change the way we live as much as any technological advance in human history.[1] Advances in gene sequencing, gene editing, and gene synthesis have shifted our relationship with the building blocks of life. This new science, synthetic biology, is in its early stages but has already created distinct threats and opportunities in US national security. It promises advances in materials science, manufacturing, logistics, sensor technology, medicine, health care, and human augmentation while simultaneously increasing the possibility and severity of man-made pandemics through unintended consequences in genetic experiments or improved bioweapons. This article proposes a National Strategy for Synthetic Biology (NSSB) to defend the homeland and promote American strength by building security into synthetic biology and by making synthetic biology an investment priority. The United States can achieve greater security by regulating and controlling synthetic biology to prevent unintended consequences while investing in people and industries to maintain a security advantage in the field.

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Futurist Klaus Schwab predicts in his book *The Fourth Industrial Revolution* "a technological revolution that will fundamentally alter the way we live, work, and relate to one another. In its scale, scope, and complexity, the transformation will be unlike anything humankind has experienced." This revolution builds on the Third Revolution based on electronics and information technology to blur "the lines between the physical, digital, and biological spheres."[2] Scientists have begun to use the term "synthetic biology" to describe the blurring of those lines by the convergence of genetic technologies powered by digital tools and engineering principles to create new physical substances and chemicals. Synthetic biology, advancing at rates exceeding Moore's Law, makes it possible to

develop unique solutions to some of the world's most difficult problems and improve the quality of life for billions of people.

The technological revolution brewing around synthetic biology creates two separate but related national security problems. First, synthetic biology enables people to develop—either deliberately or accidentally—pathogens with enhanced transmissibility or lethality, including entirely new kinds of biological agents and toxins.[3] This technology is becoming easier to access and to use. The second problem is that the United States finds itself in an era of global competition among great powers. China, in particular, is exploiting vulnerabilities in American academic and business institutions to erode US military and economic advantages. This creates the very real possibility that China will become the world leader in synthetic biology, with all the military, agricultural, medical, and industrial advantages that are conferred.

The question becomes how to address these problems. Existing strategies for defeating bioweapons and pandemics focus on deterrence and biologic incident response—two inherently public sector actions. The 2018 National Defense Strategy and the Department of State's Joint Strategic Plan focus almost exclusively on biodefense through traditional deterrence against states like North Korea.[4] Documents directly concerned with biodefense—defined as preparing for and responding to bioweapons and pandemics—such as the *National Biodefense Strategy* and the *National Health Security Strategy*, are too narrow because they do not address the public/private industrial and economic issues that would be required for a coherent technology strategy.[5] This matters because many of the steps needed to increase security in synthetic biology involve private industry and academia rather than governmental initiatives. Additionally, focusing on specific threats, whether those are states or viruses, creates the possibility that new actors or viruses will show up like black swans.

The United States should develop a separate, comprehensive, whole-of-government national strategy to address synthetic biology that supports efforts to provide general security and reduce the overall threat and risks. Our article explores this topic by providing background information on the technological innovations advancing synthetic biology, examining how these advances create the above-mentioned threats to national security, and discussing the declining American advantage in these technologies. It then presents the outline of a new National Strategy for Synthetic Biology (NSSB) to defend the homeland and promote American strength.

Technological Innovations Advancing Synthetic Biology

The ability to read DNA has grown exponentially since the first complete sequencing of the human genome and the discovery of a new class of gene-editing tools revolutionized the ability to manipulate DNA. Now, gene synthesis allows scientists to print DNA or biological material from a basic genetic sequence without modifying existing organisms or DNA. The umbrella term "synthetic biology" describes simultaneous advances in three separate genetic technologies: gene sequencing, gene editing, and gene synthesis. Individually, each area is a potential national security disruptor: gene sequencing creates the potential for very accurate individual identification and medical therapies, gene editing creates the potential to augment human performance, and gene synthesis creates the potential for designer pathogens. Understanding these disruptions requires some understanding of the underlying technological changes.

Gene Sequencing

The most successful genetic technology so far has been gene sequencing. It is a process that reads the nucleotides in an individual strand of DNA. Techniques for decoding DNA have existed since the 1970s and vary widely in terms of expense and accuracy. As each person's DNA is unique, gene sequencing is a means of individual identification and may, if DNA databases are available, identify one's parents and children. There are currently no significant restraints on commercial genetic testing, and many public and private organizations have begun to compile massive databases of genetic information. The cost of genetic sequencing has decreased by six orders of magnitude in the past 18 years, creating massive public interest in genetics.[6] In 2015 alone, the cost of sequencing an entire human genome dropped from $4,000 to $1,500. Commercial services such as 23andMe and Ancestry.com offer tests in the range of $69 to $199 to provide consumers information on their genetic heritage. The market for direct-to-consumer genetic tests boomed in 2017–18, when bundled genealogy and health testing kits were an Amazon "Top 5" Black Friday bestseller.[7] An estimated 30 million Americans have now used a home test kit, and the current market is over $747 million.[8] People have put these data to some surprising uses, such as catching dog poop scofflaws and cold case murderers, and there is a potentially massive market for individually tailored medicines.[9] Sequencing, however, is most significant because it enables gene editing and synthesis at the level of the individual base pair.

Gene Editing

Most popularly known as genetic engineering, gene editing describes any process where scientists directly alter the information encoded in a strand of DNA. Gene editing was pioneered in the 1970s when scientists used viruses to insert, remove, or replace specific genes in various organisms, which are then known as genetically modified organisms (GMO). Applications range from scientific research to agriculture. The CRISPR (clustered, regularly interspaced short palindromic repeats) editing tool has been a watershed in allowing scientists to edit genes with ease and precision.[10] CRISPR describes a general class of gene editing tools based on a specific gene sequence within the immune system of bacteria, the most commonly used variant of which is CRISPR/Cas 9, where Cas 9 is the protein that does the actual editing.[11] These tools are most powerful when used on single-celled organisms or in sex cells because the changes are heritable, known as "germ line" edits. These germ line edits can also change genes in living multicelled organisms. CRISPR is revolutionary because it is precise, easy to use, and nonproprietary—its inventors decided to make it widely available as an academic product rather than a proprietary corporate process, as is the case with most GMOs.[12] In fact, it is so easy to use that companies are selling take-home gene editing kits. Those factors have inspired a boom in genetic engineering, with the number of CRISPR-related academic articles jumping from 100 in 2011 to 14,000 in 2015.[13]

While CRISPR is the most important innovation contributing to the speed of change, other advances continue to emerge. New editing techniques are being developed to overcome some of CRISPR's limitations, such as being too large to fit inside certain viruses and occasionally copying bacterial sequences into other DNA.[14] Beyond the actual editing tools, innovative approaches show great promise in defeating the traditional pitfalls caused by genetic complexity and expression. The 2018 Nobel Prize in Chemistry was awarded to scientists who pioneered "directed evolution" by randomly generating mutations in bacteria and then selecting only those mutations that produced useful or interesting effects—using evolution to replace iterative engineering—to "create antibodies, biofuels, drugs, and other important biological molecules."[15]

Gene Synthesis

Whereas CRISPR and other editing technologies modify existing DNA, it is also possible to manufacture complete strands of DNA from

sequences stored on computers. Gene synthesis refers to the process of creating DNA from scratch using chemical precursors. This "printed" DNA must be inserted into some form of host cell to come alive. Scientists conduct synthesis by dividing a DNA sequence into small chunks, "printing" them using strings of raw nucleotides, and then stitching the pieces together.[16] They sequence these, verify their accuracy, and then insert them into blank cells to check their function. Cells created this way can then reproduce normally. While progress has been slower, gene synthesis inspires the term "synthetic biology," which incorporates the idea of applying classic design-build-test-learn engineering principles to genetic manipulation. Synthetic biology has attracted significant interest and investment—the market for synthesis precursors grew from $5.5B in 2015 to an estimated $40B in 2020. Biologically derived chemical production made up only 2 percent of the $1.2T global chemical market in 2008, but that is estimated to rise to an estimated 22 percent in 2025, making the impact of synthetic biology to the chemical industry in the hundreds of billions of dollars.[17]

Threats to National Security

Technology now exists that allows malicious actors to enhance existing pathogens into more effective weapons and to create pathogens for which there is no natural defense. In May 2018, Johns Hopkins University conducted a tabletop pandemic exercise called "Clade X" to evaluate national and international responses to a bioengineered virus released by an Aum Shinrikyo–like cult whose goal was to save the world by eliminating humans.[18] At the conclusion of the exercise, after approximately 20 game months, nearly 150 million people were dead worldwide including 20 million in the United States. Without a vaccine, the game model predicted 900 million deaths worldwide—accompanied by civil disorder, governmental breakdown, riots, and additional deaths from starvation, lack of sanitation, and violence.[19] The military and government have long been aware of how badly pandemics can damage national structures and economies. The Covid-19 pandemic has vividly enacted these once esoteric tabletop scenarios for the whole world; engineered pathogens would cause significantly more harm.[20]

A keystone technology in the future of biomanufacturing is gene synthesis, creating organisms capable of producing advanced materials at scale. However, it also makes possible novel organisms, similar to viruses, engineered specifically to challenge the human immune system. Synthesis has advanced more slowly than sequencing and editing because the cost of

nucleotide precursors and reagents has stayed essentially the same over the past decade.[21] Still, this cost is relatively low. One can recreate smallpox in a private lab today for around $3 million; a similar effort in 2025 may cost as little as $100,000.[22]

Gene Drives and Unrestricted Warfare

Scientists have used CRISPR to develop gene drives. These are tools to "drive" a genetic modification through an entire population. By editing a small version of CRISPR into the gene itself, gene drives avoid the normal Mendelian inheritance process to guarantee a desired trait gets passed along.[23] This new trait is permanently dominant and is transmitted in each subsequent generation. In this way, scientists can genetically engineer whole species, though the process takes generations to achieve. Various nations and nongovernmental organizations are pursuing the use of gene drives to do things like eliminating the species of mosquitos that causes malaria and eradicating rats from the Galapagos by forcing rats to only produce males.[24] Gene drives spread generationally, meaning they are not suitable as direct weapons against human beings. However, when used in species that reproduce rapidly like bacteria and insects, they can eliminate entire species and collapse ecosystems. Because the delivery system of a gene drive can be as simple as a single introduced organism, gene drive effects are limited to a single trait, and the slow speed of propagation could provide anonymity, gene drives could become highly effective weapons in economic warfare. [25]

Dual-Use Technology

Synthetic biology is inherently dual use. From pharmaceutical companies to biohackers, the primary motivation of most is the desire to improve the human condition. Because these tools are "decidedly low-tech, inexpensive, and widely available," however, "life sciences research is now nearly borderless and is a global collaborative activity" that could just as easily cause harm.[26] In 2018, scientists at the University of Alberta used gene synthesis—"mail-order DNA"—to fabricate a sample of "living" horsepox, a relative of smallpox, without having any physical access to the virus.[27] They did this to make a case for reform. Others have conducted similar experiments to do pure viral research, like the team that synthesized the 1918 Spanish flu from frozen lung samples.[28] These efforts demonstrate both how well-meaning efforts can produce highly

dangerous outcomes and how few obstacles exist to the application of synthetic biology and gene synthesis.

Proliferation and Unintended Consequences

With few regulatory hurdles, synthetic biology is proliferating wildly, including to high schools and amateur do-it-yourselfers. In 2018, biohacking became a major trend on the Gartner Hype Cycle as an emerging transformative technology, and it has since gone mainstream.[29] For $169, one can order a "DIY Bacterial Gene Engineering CRISPR Kit."[30] While many biohacking efforts can seem gimmicky, like glow-in-the-dark beer, much of this amateur work is serious. The International Genetically Engineered Machine (iGEM) competition is an annual MIT-sponsored event featuring 6,000 competitors from high school, college, and private industry seeking to produce the best synthetic biology designs. In 2018, the undergraduate grand prize went to Printeria, "a fully-equipped bioengineering device able to automate the process of printing genetic circuits in bacteria but made as simple and easy to operate as a domestic desktop printer."[31] These collaborative projects make synthetic biology easier and more accessible. While innovation drives economic expansion, each unregulated technical improvement decreases the expertise required for malicious actors to produce bioweapons and increases the likelihood of unintended consequences.

Unintended consequences have long been a part of the life sciences because biological systems are quintessentially complex. Genes are notoriously difficult to manipulate, often with negative or perverse outcomes. Gene therapy had its "defining moment" with the accidental death of one of its first subjects, 18-year-old Jesse Gelsinger, who had a bad reaction to a viral delivery agent designed to correct his genetic blood disorder.[32] The classic cautionary tale for genetic engineering is the Australian mousepox experiment in which scientists hoping to control an exploding mouse population introduced an infertility gene using the mousepox virus as a delivery vehicle.[33] Instead, they created a virus that was 100 percent lethal to mice within nine days of infection, even in mice bred to be resistant and in those immunized.[34] The episode was so frightening in its implications that an American effort to create countermeasures was widely condemned.[35] The obvious concern is an accidental release of a deadly pathogen resulting from some innocuous line of research—mousepox for humans.

Weak Regulation

Despite consequences on par with nuclear incidents, biotechnology is not controlled or regulated with nearly the same rigor as the nuclear industry. As a matter of international law, the Biological and Toxin Weapons Convention prohibits the development or production of agents or products that have no peaceful use. The United States applied that standard to develop the Dual Use Research of Concern policy, updated in 2014.[36] However, this policy is limited to "15 agents and toxins and 7 categories of experiments" that are under federal review and oversight. Having a highly selective list of prohibited materials might have made sense at one time, but it cannot keep up with the pace of innovation. Scientists can conduct limitless mutations on existing viruses with the specific intent to better understand or fight them and end up with a constant stream of novel pathogens.[37] So long as research is conducted with a legitimately peaceful research objective, it is permissible.

In the absence of strong regulation, the life sciences rely heavily on professional standards and norms to prevent bad behavior. The 2004 Fink Report outlined a moral duty of scientists to avoid experiments that could advance bioweapon technology, such as "rendering a vaccine ineffective or conferring resistance to available therapeutics, evading detection or diagnosis methods, enhancing or creating virulence, increasing a pathogen's transmissibility or altering its host range."[38] These concerns apply to both existing viruses tweaked to be deadlier or new classes of pathogens (engineered, for example, to evade the human immune system).[39] Under the current regulatory regime, the scientists who synthesized synthetic horsepox or the Spanish flu are doing nothing illegal.

The Declining American Advantage

Strategic competitors like China are working tirelessly to erode America's asymmetric technological advantage. In synthetic biology, this competition is fierce and stretches across economics, cyber, biosecurity, education, foreign investment, and control of genetic information. The context is one of a declining US advantage. Biotechnology is increasingly important in Chinese military doctrine, with the People's Liberation Army (PLA) designating biology as a separate war-fighting domain. Some of its most influential thinkers have described potential offsets including biomaterials, human enhancement, and "offensive capabilities" that may include ethnically targeted bioweapons.[40] Yet, as transformative as biotechnology will be in the future, American experts do not generally think of it as a transformative

military technology in the same class as "artificial intelligence, autonomous systems, ubiquitous sensors, advanced manufacturing, and quantum science."[41] This oversight creates an opportunity for China, with its closely linked security and economic structures. Seemingly trivial innovations, such as engineered hypermuscular "super dogs," will always have a military or security application.[42]

Economic Competition

Synthetic biology has become a major area of Sino-US economic competition as well. The United States is struggling to respond to what the White House Office of Trade and Manufacturing Policy describes as "economic aggression." The White House estimates China's human infiltration and cyber espionage efforts cost the United States economy between $180 and $540 billion per year as China seeks to "capture the emerging high-technology industries that will drive future economic growth."[43] Biotechnology is a favorite target for Chinese exploitation as one of the top 10 focus areas of the "Made in China 2025" plan, with a target to reach four percent of the country's GDP by 2020.[44] Further, China wants to ensure that it not only catches up to the United States technologically but surpasses and dominates it. Biotechnology was prominent in the Chinese Communist Party's recently launched initiative to become the world leader in relevant military technologies, with $20.9 billion in direct investment in 2019.[45] China's tightly intertwined civilian and military institutions blur any distinction between private and public sectors, guaranteeing the inevitable transfer of superficially nondefense investments to the military-security apparatus.[46]

China's espionage and investment activities reflect the vulnerability of the American synthetic biology industry. Weiqiang Zhang, a former lead scientist at Ventria Bioscience, was recently convicted of trying to steal a technique that uses rice to produce customized proteins for medical research and therapies (with potential revenues of $1 billion per year).[47] Others have been caught smuggling genetically modified corn and cancer cells for genetic research from the United States to China.[48] When not stealing intellectual property, the Chinese are buying it outright. The Beijing Genomics Institute (BGI) recently purchased California-based Complete Genomics and used that acquisition to help build a new generation of genomic sequencing machines capable of cutting 40 percent off the market price.[49]

Cyberbiosecurity

China's renowned hacking abilities present a unique threat to synthetic biology, which relies heavily on information technology. Cyberbiosecurity, which fuses ideas from cybersecurity and biosecurity into a multidisciplinary approach to mitigating those vulnerabilities, has emerged to grapple with the vulnerability of biotechnology-related information systems and laboratory equipment.[50] The digital infrastructure that supports synthetic biology includes data (base pairs or bits), data storage (DNA or silicon), laboratory equipment, communication networks, and supply chains. Most cyberbiosecurity efforts are mundane, such as encrypting medical records and genetic profiles. However, one unique concern is the interface between digital and genetic data. In 2017, researchers at the University of Washington were able to encode malicious "software" into a string of DNA that, when sequenced, allowed them to take control of the underlying computer system.[51] This vulnerability provides a sophisticated attack vector into academic and commercial operating systems, enabling traditional cyber threats such as data exfiltration or industrial sabotage. Facilities and equipment for genetic sequencing and gene synthesis are often colocated, and genetic malware potentially allows bad actors a covert and nonattributional way to synthesize artificial pathogens by hijacking automated laboratory equipment. DNA-based malware then can spread computer viruses that create real viruses.

Education

For decades, the United States' university system brought the world's best and brightest to study, and many of them stayed to work in its technical industries. China, through recruitment initiatives like its "Thousand Talents" program, is trying to take advantage of the US research system based on trust, good faith collaboration, and the free exchange of ideas to build a rival higher education system.[52] When these scholars come to China to build research centers, they often bring cutting-edge or proprietary knowledge with them. Simultaneously, American universities have built their business plans on having a continuous stream of foreign students as full-tuition-paying graduate students who contribute billions of dollars to universities through tuition and on-campus spending. Now, a sharp decline in Chinese students poses a potentially "existential" threat to many science, technology, engineering, and mathematics (STEM) graduate programs that fuel the American innovation base.[53] Although staying in the United States was never part of the "deal" for foreign students, the

current administration's policies increasingly discourage immigration. The State Department has imposed visa limitations for Chinese scholars as "non-traditional information collectors," especially in fields with national security implications.[54] These restrictions simultaneously fail to discourage actual spies, who can jump the bureaucratic hurdles necessary to stay in the United States and damage the institutions they are designed to protect. International student enrollment has flattened over the past two years, with the US economy losing an estimated $5.5 billion. American universities started taking out insurance policies, while international student enrollment has increased as much as 20 percent in countries like Australia and Canada.[55]

Foreign Investment

China has leveraged its newfound economic might to take advantage of the United States' open markets to obtain technology through foreign direct investment. By supporting or buying struggling companies or through venture capital, Chinese investment firms gain legitimate access to business and technical information. In 2018, Congress passed the Foreign Investment Risk Review Modernization Act (FIRRMA) to strengthen the Committee on Foreign Investment in the United States (CFIUS). Originally created to prevent foreign investors from acquiring national security–sensitive companies, both the Obama and Trump administrations used the power of the FIRRMA much more frequently than in the past.[56] The most important update to the CFIUS is that it can now review noncontrolling investments, giving investors certain rights including accessing nonpublic proprietary information, observing the board of directors, or having nonvoting decision-making input.[57] Although biotechnology was a broadly covered industry under FIRRMA's pilot program, critical technologies are included in one of five existing control categories, such as arms control treaties and nuclear dual-use restrictions that do not generally apply to synthetic biology.[58] During the public comment period for regulation under the Export Control Act of 2018, the industry lobbied hard and succeeded in preventing any biotechnologies from making the revised Commerce Control List.[59] Biotech firms also led the way in lobbying to narrow the definition of "sensitive personal information" to protect companies that collect genetic information.[60]

Genetic Information

The foreign sale of genetic data may provide other nations with an information advantage. China has amassed the world's largest genetic database

and prohibited its export to preserve its intrinsic economic and security value. The proliferation of genetic information creates some concerns for privacy and anonymity. In America, enough people have publicly shared their genetic information that 90 percent of European-Americans will be genealogically identifiable within three years. Foreign agencies can obtain DNA from a variety of sources and use profiles either available freely online or obtained through espionage to identify spies, soldiers, and their families—who then become vulnerable to threats, attacks, or exploitation.[61] The DOD is aware of this vulnerability and in 2019 circulated a memo discouraging members from purchasing or using at-home genetic tests.[62] Additionally, genetic information could indirectly provide intelligence agencies with potentially powerful information about individuals' genetic predispositions that could be used to compromise officials or operatives.

A National Strategy for Synthetic Biology

America's bioeconomy relies on openness, transparency, globalized supply chains, and a worldwide customer base to foster innovation and economic growth. This creates inherent vulnerabilities within the biotechnology industry that often go unaddressed.[63] Synthetic biology has too few touch points within the national security structure to rely on existing strategies to address its vulnerabilities and opportunities. It is similar to computer technology in that the private sector's production and consumption far exceeds the public sector's, making the technology difficult to secure by focusing on public initiatives.

There have been several attempts to create national-level frameworks to address the public/private divide in synthetic biology, including the 2018 *Biodefense in the Age of Synthetic Biology* and the 2020 *Safeguarding the Bioeconomy* reports from the National Academies.[64] However, these academic reports fail to provide a strategy to drive priorities and spending. This simultaneously allows them to be quite expansive in terms of describing problems and risks while avoiding concrete solutions. These documents repeatedly point out that any successful strategy will require a broad-based and interdepartmental approach with many public and private stakeholders, which makes their findings incompatible with existing strategy documents.

Defending the Homeland

A national strategy for synthetic biology can defend the homeland by regulating synthetic biology activities. Five key lines of effort include im-

plementing a framework to prioritize threats, regulating synthetic biology processes to guard against accidents and nefarious acts, controlling our technology exports to guard against leaks that threaten our security, building international cooperation to restrain unauthorized synthetic biology activities, and conducting horizon scanning to maintain awareness of and prepare for future threats. Each of these will require an interdepartmental regulatory effort, public-private partnership, or both.

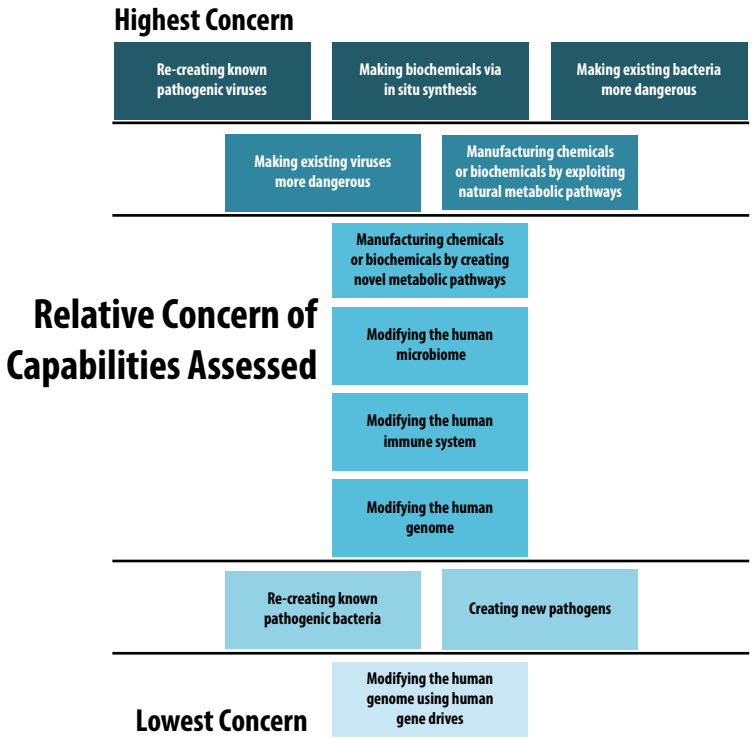

Figure 1. Threat hierarchy. This prioritization of threats was achieved by using the Imperiale Framework. (Reproduced from National Academies of Sciences, Engineering, and Medicine, *Biodefense in the Age of Synthetic Biology* [Washington, DC: National Academies Press, 2018], 5, http://nap.edu/24890.)

Adopt a framework to prioritize actions. The Imperiale Framework introduced by the National Academies in 2018 provides a context for prioritizing actions to mitigate hazards created by synthetic biology. This framework uses the following criteria to establish a hierarchy of concern for potential misuse of synthetic biology: usability of the technology, usability as a weapon, requirements of actors, and potential for mitigation.[65] The resulting threat hierarchy (fig.1, above) shows that the most pressing security concerns include the re-creation of known viruses and toxins and the modification of existing viruses and bacteria. This suggests that actions

should focus on preventing the use of synthesis to manufacture viruses and monitoring and restricting research that could modify existing viruses and bacteria in dangerous ways. The current regulatory structure makes these steps all but impossible without drastically rethinking America's approach to regulating biotechnology, which focuses on products and not process.

Regulate process, not product. Regulation in synthetic biology focuses almost exclusively on consumer safety instead of biosecurity. The nation's regulatory baseline, called the Coordinated Framework for the Regulation of Biotechnology, establishes regulatory agencies responsible for different product groupings but explicitly avoids interfering with production processes.[66] President Trump reinforced that focus with an Executive Order on Modernizing the Regulatory Framework for Agricultural Biotechnology Products in 2019, which further eased regulations.[67] For example, the FDA regulates genetically modified animals but only when a developer decides to sell an innovation.[68] It allows noncommercial experiments to continue without supervision.[69]

To effectively regulate synthetic biology, the government must take an approach to synthetic biology that reduces the possibility of dual use, similar to the way it regulates supply chains in the nuclear industry. Done properly, an agency such as the National Institutes of Health (NIH) would monitor research and development in real time to update the Dual Use Research of Concern policy at the pace of technology, regardless of whether synthetic biology is used by university researchers, corporate developers, or amateur hobbyists. Under this policy, the monitoring agency creates a secured synthetic DNA registry to collect metadata regarding genes, regulators, vectors, hosts, and target species. In accordance with the Imperiale Framework, its immediate emphasis would be to verify that existing pathogens are not being synthesized or modified improperly. Entities involved in sequencing or synthesizing genes for third parties would compare customer requests against that registry to screen for known malicious or suspicious sequences (at an offsite location to protect proprietary sequences), as well as to verify provenance and provide attribution during a bio-incident. Any company, university, or individual conducting independent genetic work would make declarations and submit sequence information. Sensitive equipment, such as DNA synthesizers, would be stored in secured access rooms.[70]

This kind of formal oversight would be a drastic departure from the current system, and it creates an immediate conflict with the DIY/biohacking movement. Scientific self-regulation has done an admirable job of reining in the worst abuses of biotechnology. Yet self-regulation is by

definition unenforceable, and the rapid democratization of biological tools has eroded the social power of professional ethics and norms.[71] The Centers for Disease Control and Prevention (CDC) and the NIH should examine genetic editing technology and propose a set of technical guidelines to restrict gene editing to certified laboratories. Such rules could take the form of the current regime in Germany, where the law prevents unsanctioned work on genes through fines upward of €50,000 and jail terms up to three years. Alternatively, treating key genetic editing materials such as the Cas 9 plasmid as controlled materials may be sufficient. The experts at the CDC and NIH should evaluate the likely effectiveness of such regimes and propose legislation. The moral and legal issues associated with gene editing and gene splicing of mammals and humans should also be evaluated and legislation proposed.

Control exports and investment. Increased regulation will change the business models for many globalized synthetic biology companies, with the risk that they move overseas. While the United States must remain open for biotechnology-related research, we cannot allow this technology to simply move offshore. The CFIUS must, therefore, develop the export control restrictions for synthetic biology technology related to national security that were envisioned by FIRMMA. These export control restrictions would be based on the national roadmap and defense industrial base issues surrounding synthetic biology.

Beyond the requirements of FIRMMA, the United States must examine existing business relationships to ensure they do not result in the loss of important intellectual property. In addition to reviewing new deals, the CFIUS should examine previous and existing deals by foreign companies, especially those like the BGI that have already acquired key American firms or Chinese investment firms like Ever Alpha.[72] It owns a 14.9 percent stake in Twist Bioscience, which is the Defense Advanced Research Project Agency's (DARPA) Living Foundries initiative's leading DNA synthesizer.[73] Finally, the CFIUS should include a wider range of synthetic biology experts. This will improve the committee's effectiveness in policing foreign investment while guarding against overrepresentation in the agricultural and medical sectors.

International cooperation. The United States should work to establish and standardize international rules and norms for synthetic biology research and production. The current international regulatory structure for biotechnology consists of scientific self-regulation based on professional ethics, national-level policies, various arms control treaties, and

some UN-level health initiatives.[74] There are simply too many cracks and gaps in this system.

The absence of an international control regime presents unique national security challenges because of "ethical asymmetry" in places like China, where a loose regulatory regime and strong government-led incentives to spur innovation created a climate where seemingly anything goes.[75] While it is illegal in the United States to create genetically modified babies, and has been since 2015, genetically altered children are living in China.[76] Similarly, Ukraine produced babies using mitochondrial DNA from three biological parents in an effort to avoid inherited genetic diseases for patients from Sweden, Britain, Brazil, and Israel.[77]

Once the United States has developed a sound approach to domestic regulation, the United States should propose to the World Health Organization and signatory states of the UN a set of rules and norms for international adoption. Among these rules, ensuring nation-states retain control over genetic experiments within their borders will reduce the likelihood of errant science experiments being introduced into the environment.

Horizon scanning. Horizons scanning is a frequent recommendation of studies on securing the bio-economy, and the sheer amount of data collected in a centralized gene registry will necessitate a horizon scanning capability based on machine learning.[78] Led by the CDC, this horizon scanning capability should incorporate artificial intelligence to cross-reference foreign investment and business activity derived from CFIUS filings, as well as monitoring ongoing academic research through grant proposals and research papers. Initially, this horizon scanning capability will focus on detecting potentially dangerous or malicious work on existing pathogens and organisms that could create biological toxins per the Imperiale Framework.

Machine learning shows huge potential to improve our ability to detect dangerous or malicious work in synthetic biology. However, some trends will only make sense when placed in the context of things such as unusual military activity or a simultaneous attack on the "health intelligence network" of disease surveillance and electronic medical records associated with a bizarre disease progression.[79] In the longer run, therefore, the United States should expand the Public Health Emergency Medical Countermeasures Enterprise, chaired by the Department of Health and Human Services, into an even broader interagency fusion center to combine domestic genetic horizon scanning with all other available sources.[80] Ultimately, an effective horizon scanning effort might necessitate international cooperation, such as the recent discovery by a CDC team of sev-

eral genetically distinct strains of the hemorrhagic-fever-inducing Marburg virus in Sierra Leone before any humans became sick as part of the PREDICT international partnership system.[81]

Promoting American Strength

Synthetic biology presents an opportunity for scientific and economic gains that can enhance American strength in the international arena. While the United States and China are starting at near parity in this new technological field, China continues to target the American biotechnology industry to make strides toward achieving its ambition to be the world leader in the life sciences. The NSSB will promote American strength by investing in the future. Five key lines of effort include creating a roadmap for defense-applicable synthetic biology investments, establishing an industrial base for defense-related synthetic biology based on that roadmap, investing accordingly in key technologies, creating policy for legally and ethically challenging policy areas, and winning the war for talent.

Create a defense roadmap for synthetic biology. With competing military and economic priorities, the United States needs a synthetic biology roadmap to prioritize technology investments. To develop this roadmap, the Department of Defense must integrate synthetic biology into its strategic, operational, and tactical planning processes to determine how best to apply these technologies in future wars. The roadmap will streamline the research and development processes across the federal government and act as a focusing function for technologies with operational impact (e.g., synthetic biology manufacturing processes that can create structures and runways). Finally, with a vision for future investment, the DOD can develop an industrial base that ensures the security of suppliers and supply chains alike.

Establish a defense industrial base for synthetic biology. There is no defense industrial base for synthetic biology. As synthetic biology has little overlap with traditional major weapon systems, the DOD and its interagency partners largely ignore it as a critical emerging defense technology.[82] This, in turn, leads to a lack of economic clout with synthetic biology manufacturers.

As the Government Accountability Office points out, an improperly secured industrial base could cause supply disruptions from things like interrupted supply chains or failed suppliers, or even contaminated or compromised products.[83] Such consequences could adversely affect military operations as well as domestic synthetic biology research, development, and manufacturing. Therefore, the DOD should acknowledge synthetic

biology as an important defense-related industry, further integrate biotech considerations into its larger strategic and acquisition efforts, and expand on recent progress made by the assistant director for biotechnology under the recently reorganized Office of the Under Secretary of Defense for Research and Engineering.[84]

The federal government should immediately lay the groundwork for a system of "trusted foundries" for both synthetic biology equipment and chemicals, using as its model the existing Defense Department Trusted Foundry program for microelectronics. These trusted foundries will vet people working in the industry, thus ensuring their ability to conduct classified work when appropriate and thereby guaranteeing uninterrupted supply chains, preventing tampering during production, and protecting products from exploitation.[85] Businesses seeking certification as trusted foundries will need to meet certain cyberbiosecurity standards, and these standards will apply to all biotech contracts—including biomanufacturing techniques, genetic sequences for defense-related products, and genetic data storage. Each federal agency that uses the trusted foundry system will need to ensure these trusted foundries remain in business through guaranteed contracts or preferential acquisition plans.

Invest in key technologies. Several key technologies within synthetic biology will enhance economic growth as well as military might. Proper investment in advanced materials, logistics, adaptive materials, living sensors, biochips, and anti-pathogens will create new industries while making our military forces more agile. Investment here collectively will promote American strength.

Advanced Materials. By using gene editing and gene synthesis to create organisms that produce rare substances—especially at the micro and nano levels—synthetic biology provides an avenue to create advanced material on demand and at scale. One of DARPA's signature programs in its $296 million Biological Technologies Office is its long-running Living Foundries initiative to manufacture "critical, high-value molecules that are often prohibitively expensive, unable to be domestically sourced, and/or impossible to manufacture using traditional synthetic approaches."[86] Initiated in 2015, the "1000 Molecules" iteration of this program created its 1,000th biologically produced molecule in 2019.[87] These exquisite materials may fill specific military niches, like radar-absorbing paint for stealth or endothermic fuel for hypersonic weapons. This could be especially game changing with nanomaterials because bacteria already operate at the micro scale and are easy to reproduce naturally. From a health perspective, biological pathways could be similarly repurposed to create "pharmacies on demand";

giving field hospitals the ability to produce medicine as needed would reduce medical logistics.[88]

Logistics. The advantages of biomanufacturing go beyond creating valuable substances: biomanufacturing has the potential to make forces leaner and more lethal. One company, bioMASON, currently sells bacteriologically produced bricks—eliminating the need to transport specialty clay and drastically shortening the normal two- to five-day kiln firing process. This process uses local materials, drastically saving on transportation costs while simultaneously saving fuel and carbon emissions.[89] In 2019, Blue Horizons' Project Medusa used bioMASON materials to create austere runways to show how biomanufacturing could provide a truly innovative approach to the strategic problem of adaptive basing in a contested environment.[90] In fact, biomanufacturing potentially magnifies the tactical and logistical value of additive manufacturing by using local biomass to manufacture the additive polymers on site, rather than relying on transportation systems.[91] Another completely different technology has already been commercialized by companies such as Ecovative, whose prototype bio-buildings are constructed from cardboard origami forms infused with a mushroom-based substance. When sprayed with water, the forms grow into buildings within a few days.[92]

Adaptive Materials. More than decreasing manufacturing and transportation costs, biomanufacturing promises to create materials capable of doing things that inert products cannot. Biologically based self-healing concrete already exists, which works when pellets containing dormant bacteria and calcium-based "fuel" are exposed to water. When cracks allow moisture into the concrete, the bacteria come to life and use the calcium to produce limestone that automatically seals the crack.[93] While this approach has limitations, DARPA has funded several additional efforts, such as the Engineering Living Materials program, that seek to create bioproducts that are not only self-healing but also can grow themselves in place or adapt to their environment. Examples of useful adaptations include adaptive camouflage or pathogenic resistance. One outgrowth of that effort is the successful development by the University of Colorado of using cyanobacteria to create green concrete, both in color and in its ability to trap carbon through photosynthesis.[94] Investment in adaptive materials will improve military adaptive basing and likely produce dividends for the construction and transportation industries.

Living Sensors. Synthetic biology takes advantage of the myriad ways that evolution has equipped organisms to monitor their environment, even beyond the electromagnetic spectrum. Additional investment may

produce bacteria able to act as a trip wire detector for submarines.[95] In one ongoing $45M tri-service program, scientists are engineering bacteria to exhibit photoluminescence in the presence of signature molecules such as lubricants, diesel fuel, or metals.[96] Similar programs are trying to engineer everyday plants to detect explosives or nuclear, chemical, and biological materials in humanitarian relief operations.[97]

Biochips. While living organisms can act as sensors, building actual sensors with synthetic biology involves biochips. A class of medical devices, biochips were initially developed by the Human Genome Project as a search function for DNA sequences, proteins, chemicals, and toxins. Biochips are especially useful for detecting novel or engineered pathogens with previously unknown DNA sequences; they can combine a search for commonly occurring viral DNA sequences with broadly focused protein searches to recognize altered viruses.

One application of biochips is micro-organs—miniaturized models of organs such as hearts, lungs, pancreases, and tumors that work like the real thing.[98] Also known as bio-microarray devices, micro-organs look like large-circuit microchips but are built out of living cells performing biological functions. Like microchips that perform millions of computations per second, these bio-microarray devices perform thousands of biological tests simultaneously as each array is a miniature test site. When integrated in a single device (known as a lab-on-a-chip), they can perform low-cost, high-speed, and high-throughput analysis despite being small.[99] Importantly, by grouping lots of miniature assays together, a lab-on-a-chip can both search for multiple things and run redundant tests to eliminate false results. The ultimate goal would be universal detectors that can sense almost anything, from germs to bombs. Due to their promise as sensors, DARPA and the National Institutes of Health have invested $100M in this technology over the past five years.

Anti-pathogens. Because pathogens can evolve or be engineered to resist vaccines, multiple stakeholders—including the DOD, CDC, and NIH—should explore methods using genetic technology to fight pathogens. Scientists still do not completely understand viral phenomena—a team of virologists in Brazil recently discovered an amoebic virus with no known genetic sequences.[100] Funding cuts to the CDC and Public Health Service have done significant damage to the nation's ability to defend itself, especially in light of a drumbeat of zoonotic outbreaks (SARS, Ebola, and Covid-19).[101] Funding preventative steps makes eminent sense when the cost of responding to an outbreak such as Covid-19 is in the trillions of dollars.[102]

Recent outbreaks have shown that vaccine development is slow, expensive, and limited to the target virus. The global response to Covid-19 further demonstrates how disruptive a potential pandemic can be to an interconnected world. The response also shows the benefit of using cutting-edge tools like biochips and machine learning to speed up the genetic profiling of antibodies to mass-produce antibody serums to provide non-vaccine treatment options.[103] Research on innovative approaches, such as enlisting predatory bacteria to fight other bacterial infections, should continue.[104]

Establish policies for genetic information and human augmentation. The most controversial areas of synthetic biology are those that deal with humans: genetic information and human performance augmentation. Both genetic screening and human augmentation raise a host of ethical and legal concerns, such as whether modified humans are weapons under the Geneva Convention.[105]

Genetic information. The United States should follow the lead of China and Russia to prohibit the export or sale of citizens' genetic information to foreign entities with additional steps taken to ensure the privacy of those who serve in security-related positions. The DOD and CIA should, for instance, prohibit members from taking commercially available genetic tests while increasing the availability of prescribed medical genetic testing. Similarly, local and state governments should be precluded from storing DNA profiles of those employed in national security positions in local (sometimes called "shadow") databases. Most importantly, the DOD should clarify its policies to further restrict access to security for the 50 million DNA samples it has as part of its DOD Serum Repository.

It must also establish policies that will enable it to use genetic information to improve military performance and decrease military and veterans' health care costs. While genetic discrimination has been illegal in the United States since the 2008 Genetic Information Nondiscrimination Act (GINA) for things like issuing health insurance, the act does not apply to military recruitment.[106] Improved genetic testing provides an opportunity to test for certain genetic diseases or proclivities, and it is becoming feasible to test for positive adaptations to high-altitude/low-oxygen conditions, extremely hot/cold environments, or sleep deprivation.[107]

Human augmentation. With gene editing already in use to cure diseases, the United States must have a mechanism to determine how it will approach human augmentation, particularly in defense. In the short term, the DOD should convene a working group that includes private and public sector representatives to recommend to the president and Congress how the military should incorporate human augmentation into operations.

The time available to parse this issue is diminishing due to the pace of innovation in what Army Futures Command dubs the "Era of Accelerated Human Progress."[108] Scientists are already conducting experiments using CRISPR to tweak the immune system of people with genetic disorders such as cancer.[109] US scientists began clinical trials in 2019 to use CRISPR to treat sickle cell disease by editing a woman's blood marrow to produce fetal hemoglobin protein to compensate for the protein that creates sickle cells.[110] Early results suggest the treatment is working, providing hope to millions of people with that condition.[111] This makes possible a treatment that could just as easily give someone with normal hemoglobin the ability to process oxygen like a world-class marathon runner, which has obvious implications for military performance.

Military necessity is creating increasing pressure to pursue "bio-convergence" in military operations.[112] If the United States does not take the lead on ethically using biotechnology in both of these areas, it seems inevitable that some other country will. China has expressed interest in using synthetic biology to improve its soldiers' performance. By moving early to codify how it intends to balance military advantage with ethical restraint, the United States will be able to influence worldwide norms and expectations for what is and is not acceptable.

If using biotechnology is deemed acceptable, research could make humans less prone to disease. Defense researchers are already working on projects to modify the bacteria that make up the human microbiome that will result in increased caloric uptake and less fatigue. A similar approach may change skin bacteria to repel mosquitos that carry malaria or dengue fever or change the microbiome into a secondary immune system capable of reacting to pathogens or environmental contaminants.[113] Other efforts seek to make human beings hardier by identifying and triggering genes present in all people in a manner to give some people enhanced disease resistance when activated. Potential benefits go beyond disease protection to intrinsic resistance to infections, drug overdoses, radiation, and toxins.[114]

Win the war for talent. The United States must take seriously the "competition" part of great power competition and try to beat China in the emerging war for talent.[115] China targets academia and corporations for information largely by funding research. In many cases, including the recent arrest of Harvard's preeminent professor of chemistry, people caught transferring technology to China did so to be better researchers or entrepreneurs, not spies.[116] To compete with China's "Thousand Talents" program, the United States needs to subsidize research fellowships through the CDC, NIH, DARPA, and/or the National Laboratories, where top

researchers can get research grants, access to laboratories, and permissions to commercialize major research findings.[117] Current efforts to tighten vetting of foreign students and strengthen laws requiring the disclosure of foreign investment in American universities or research should be augmented by programs to increase American participation in graduate STEM programs, such as scholarships, internships, and targeted hiring practices. The loss of revenues for American STEM programs due to visa restrictions needs to be counterbalanced with investment lest those programs fail and disappear. Cuts to the budgets for the CDC and NIH only exacerbate this problem and should be reversed.[118]

Conclusion

Synthetic biology is going to remake the world. The tools available to scientists today create the vast potential to do great good or great harm. As innovation in biotechnology accelerates, the United States must take immediate steps to safeguard against catastrophe and capitalize on those innovations. Reducing the threat of engineered pathogens and preventing the loss of intellectual property to our strategic competitors requires a strategic approach that heavily involves regulating academia and industry. It must look beyond traditional defense and national security stakeholders to address systematic weakness and deep root causes. Policy makers will need to think differently about what national security means if they want to solve problems like an educational system that produces too few American students in STEM programs but relies on foreign students to keep those programs solvent, or a highly permissive and globalized business environment that prioritizes profits over security. Consequently, successfully implementing this strategy will require the creation of a broad-based steering committee that includes public and private stakeholders. It will also require carefully balancing security with freedom. Every regulation, restriction, or limitation incurs a cost to innovation and expansion. Many of those costs are offset by investments, research, and the creation of guaranteed supply chains and contracts, but each compromise must be carefully considered. Finally, the American approach must be exportable to the world at large. This strategy cannot be successful if America imposes unilateral restrictions on its own activities that the rest of the world ignores or exploits. As America is faced with increasing global competition and domestic partisanship, the collaborative approach demanded by this moment may seem unrealistic. The alternatives, however, demand that we try. SSQ

Lt Col Marcus A. Cunningham, USAF

Colonel Cunningham has extensive experience in command and control and air mobility operations. He holds a master of public policy from the Harvard Kennedy School, a master of military science from the Marine Corps Command and Staff College, and a master of strategic studies from the Air War College.

John P. Geis II

Dr. Geis is the former director of the Center for Strategy and Technology. Currently, he serves on the leadership and strategy faculty at the Air War College. Dr. Geis is a retired US Air Force colonel and earned a PhD in political science from the University of Wisconsin.

Notes

1. Adapted from claims made in "The Engineering of Living Organisms Could Soon Start Changing Everything," *The Economist*, 4 April 2019, https://www.economist.com/.

2. Klaus Schwab, "The Fourth Industrial Revolution: What It Means and How to Respond," *Foreign Affairs*, 12 December 2015, https://www.foreignaffairs.com/.

3. Bill Gertz, "Australian Researchers See Virus Design Manipulation," *Washington Times*, 21 May 2020, https://www.washingtontimes.com/.

4. Department of Defense, *Summary of the 2018 National Defense Strategy of the United States of America: Sharpening the American Military's Competitive Edge* (Washington, DC: Department of Defense, 2018), https://dod.defense.gov/; and Department of State and United States Agency for International Development, *Joint Strategic Plan FY 2018–2022* (Washington, DC: US Government, 2018), https://www.state.gov/.

5. The White House, *National Biodefense Strategy* (Washington, DC: The White House), 2018, https://www.whitehouse.gov/; and Department of Health and Human Services, *National Health Security Strategy 2019–2022* (Washington, DC: Department of Health and Human Services, 2019), https://www.phe.gov/.

6. Kim Wall, "Biohackers Push Life to the Limits with DIY Biology," *The Guardian*, 18 November 2015, https://www.theguardian.com/.

7. Maren Estrada, "23andMe's DNA Test Was a Best-Seller on Black Friday, and It's Discounted Again for Cyber Monday," *BGR News*, 27 November 2017, https://www.yahoo.com/; Antonio Regalado, "2017 Was the Year Consumer DNA Testing Blew Up," *MIT Technology Review*, 12 February 2018, https://www.technologyreview.com/; and Daniel Roberts, "Once-Hot DNA Testing Unicorn 23andMe Is in Serious Trouble," *Yahoo! Finance*, 29 January 2020, https://finance.yahoo.com/.

8. "DNA Test Kits Market to Witness Highest Growth by 2027 with Leading Players," press release, Transparency Market Research, openPR, 10 February 2020, https://www.openpr.com/.

9. Most notably, in 2018 investigators caught the infamous Golden State Killer using a website called GEDmatch where amateur genealogists voluntarily post test results. Clark Bentson, "Dog DNA Used to Track Down Owners Who Don't Clean Up after Their Pets," *ABC News,* 9 August 2018, https://abcnews.go.com/; and Heather Murphy, "How an Unlikely Family History Website Transformed Cold Case Investigations," *New York Times*, 15 October 2018, sec. Science, https://www.nytimes.com/.

10. "Genome Editing: The Age of the Red Pen," *The Economist*, 22 August 2015, https://www.economist.com/. Humans have been able to modify DNA directly since 1973, when Boyer and Stanley created the first genetically engineered bacteria. The Su-

preme Court in the US ruled in favor of patenting genetically modified organisms in 1980, and the first genetically modified crops were approved by the FDA in 1990. Gabriel Rangel, "From Corgis to Corn: A Brief Look at the Long History of GMO Technology," *Science in the News* (blog), Harvard University Graduate School of Arts and Sciences, 9 August 2015, http://sitn.hms.harvard.edu/.

11. Carl Zimmer, "Breakthrough DNA Editor Born of Bacteria," *Quanta Magazine,* 6 February 2015, https://www.quantamagazine.org/. Also, a second variant uses Cas13 to edit RNA. See Brad Plumer et al., "A Simple Guide to CRISPR, One of the Biggest Science Stories of the Decade," *Vox*, 23 July 2018 (updated 27 December 2018), https://www.vox.com/.

12. Tamar Haspel, "The Public Doesn't Trust GMOs. Will It Trust CRISPR?," *Vox*, 18 July 2018 (updated 26 July 2018), https://www.vox.com/.

13. Plumer et al., "Simple Guide to CRISPR."

14. Examples of gene editing tools are NgAgo and Lambda Red. See Heidi Ledford, "Beyond CRISPR: A Guide to the Many Other Ways to Edit a Genome," *Nature News*, 9 August 2016, https://doi.org/10.1038/536136b.

15. Ben Guarino, "Nobel Prize in Chemistry Goes to Three Scientists Who Harnessed 'The Power of Evolution,' " *Washington Post*, 3 October 2018, https://www.washingtonpost.com/.

16. Randall A. Hughes and Andrew D. Ellington, "Synthetic DNA Synthesis and Assembly: Putting the Synthetic in Synthetic Biology," *Cold Spring Harbor Perspectives in Biology* 9, no. 1 (January 2017): 2, https://doi.org/10.1101/cshperspect.a023812.

17. The term "gene synthesis" technically applies to the part of the process where the smaller bits are built from these strands. Its impact on the global health market is difficult to even guess at—it has already produced several groundbreaking cancer treatments. See Claudia Vickers and Ian Small, "The Synthetic Biology Revolution Is Now—Here's What That Means," *The Conversation*, accessed 21 January 2019, http://theconversation.com/.

18. Coincidentally, the engineered virus was a coronavirus, and the event was intended to help the Trump administration prepare for a pandemic outbreak. See Johns Hopkins School for Public Health, "About Clade X," accessed 5 April 2019, http://www.centerforhealthsecurity.org/.

19. Kevin Loria, "A Leading Medical Institution Created a Simulation That Shows How a New Disease Could Kill 900 Million People—and It Reveals How Unprepared We Are," *Business Insider,* 29 July 2018, https://www.businessinsider.com/.

20. Mark Perry, "America's Pandemic War Games Don't End Well," *Foreign Policy*, 1 April 2020, https://foreignpolicy.com/.

21. Hughes and Ellington, "Synthetic DNA," 3.

22. John Geis and Theodore C. Hailes, "Deterring Emergent Technologies," *Strategic Studies Quarterly* 10, no. 3 (2016): 51, https://www.airuniversity.af.edu/; and Tanya Basu, "This Eradicated Disease Could Come Back as a Terrifying Biological Weapon," *Daily Beast*, 1 April 2018, https://www.thedailybeast.com/.

23. Jennifer Kahn, "The Gene Drive Dilemma: We Can Alter Entire Species, but Should We?," *New York Times Magazine*, 8 January 2020, https://www.nytimes.com/.

24. Kahn, "Gene Drive Dilemma."

25. National Academies of Sciences, Engineering, and Medicine (NASEM), *Biodefense in the Age of Synthetic Biology* (Washington, DC: The National Academies Press, 2018), 1, https://doi.org/10.17226/24890. In 2016, the director of national intelligence highlighted

gene drives as a national security threat. See Ewen Callaway, "U.S. Defense Agencies Grapple with Gene Drives," *Scientific American*, 24 July 2017, https://www.scientificamerican.com/.

26. National Research Council (US) Committee on a New Government-University Partnership for Science and Security, "Biosecurity and Dual-Use Research in the Life Sciences," in *Science and Security in a Post 9/11 World: A Report Based on Regional Discussions between the Science and Security Communities* (Washington, DC: National Academies Press, 2007), 57–68, https://www.ncbi.nlm.nih.gov/.

27. Ryan S. Noyce, Seth Lederman, and David H. Evans, "Construction of an Infectious Horsepox Virus Vaccine from Chemically Synthesized DNA Fragments," *PLOS ONE* 13, no. 1 (19 January 2018), https://doi.org/10.1371/journal.pone.0188453.

28. Cassidy Nelson. "Engineered Pathogens: The Opportunities, Risks and Challenges," *Biochemist*, June 2019, https://www.researchgate.net/.

29. Kasey Panetta, "5 Trends Emerge in the Gartner Hype Cycle for Emerging Technologies, 2018," Gartner, 16 August 2018, https://www.gartner.com/. One biohacker in Montgomery, Alabama, became widely known for injecting a personally engineered herpes vaccine. This individual later died in a sensory deprivation tank with evidence of ketamine in his blood. This example is emblematic of the "edgy" reputation of some in the biohacking community. See Kristen V. Brown, "What Does an Infamous Biohacker's Death Mean for the Future of DIY Science?," *The Atlantic*, 5 May 2018, https://www.theatlantic.com/.

30. And for $1,849, you can get a "Genetic Engineering Home Lab Kit" that includes a "Genotyping Kit" and a "DIY CRISPR Kit." See The ODIN's website, accessed 16 June 2020, http://www.the-odin.com/.

31. Printeria, 2018, http://2018.igem.org/.

32. Sheryl Gay Stolberg, "The Biotech Death of Jesse Gelsinger," *New York Times Magazine*, 28 November 1999, https://www.nytimes.com/.

33. "Mouse Pox or Bioweapon?," *BBC World Service*, 17 January 2001, http://www.bbc.co.uk/.

34. William J. Broad, "Australians Create a Deadly Mouse Virus," *New York Times*, 23 January 2001, A6, https://www.nytimes.com/

35. Rick Weiss, "Engineered Virus Related to Smallpox Evades Vaccine," *Washington Post*, 1 November 2003, https://www.washingtonpost.com/.

36. US Department of Health and Human Services, "Dual Use Research of Concern – S3," accessed 9 December 2018, https://www.phe.gov/.

37. Andrea Howard, "The Pandemic and America's Response to Future Bioweapons," *War on the Rocks*, 1 May 2020, https://warontherocks.com/.

38. Sarah L. Frazar et al., "Defining the Synthetic Biology Supply Chain," *Health Security* 15, no. 4 (2017): 399, https://doi.org/10.1089/hs.2016.0083.

39. John Geis et al., *Blue Horizons IV: Deterrence in the Age of Surprise* (Maxwell AFB, AL: Air University Press, 2014), 14, https://media.defense.gov/.

40. Elsa B. Kania and Wilson Vorndick, "Weaponizing Biotech: How China's Military Is Preparing for a 'New Domain of Warfare,'" *Defense One*, 14 August 2019, https://www.defenseone.com/.

41. Christian Brose, "The New Revolution in Military Affairs: War's Sci-Fi Future," *Foreign Affairs* 98, no. 3 (May/June 2019), https://www.foreignaffairs.com/.

42. Douglas Main, "Chinese Researchers Use Genetic Modification to Make Buff Beagles," *Newsweek*, 20 October 2015, https://www.newsweek.com/.

43. White House Office of Trade and Manufacturing Policy, *How China's Economic Aggression Threatens the Technologies and Intellectual Property of the United States and the World* (Washington, DC: White House, June 2018), 1, https://www.whitehouse.gov/.

44. Adolfo Arranz, "Betting Big on Biotech," Made in China 2025 series, pt. 5, *South China Morning Post*, 9 October 2018, https://multimedia.scmp.com/.

45. Tang Shubiao, "China's New Vision for the Next Five Years," *China Today*, 11 March 2016, http://www.china.org.cn/. See also Cong Cao, Richard P. Suttmeier, and Denis Fred Simon, "China's 15-Year Science and Technology Plan," *Physics Today* 59, no. 12 (December 2006): 38–43, https://doi.org/10.1063/1.2435680; and Yoko Kubota, "China's New $21 Billion High-Tech Manufacturing Fund Likely to Rankle U.S," *Wall Street Journal*, 20 November 2019, https://www.wsj.com/.

46. William Carter, Statement Before the House Armed Services Committee Subcommittee on Emerging Threats and Capabilities, "Chinese Advances in Emerging Technologies and their Implications for U.S. National Security," 9 January 2018, https://docs.house.gov/.

47. Bryan Thompson, "Spies in the Field: As Farming Goes High-Tech, Espionage Threat Grows," NPR, 8 June 2018, https://www.npr.org/.

48. Thompson; and Ellen Barry, "Stolen Research: Chinese Scientist Is Accused of Smuggling Lab Samples," *New York Times*, 31 December 2019, https://www.nytimes.com/.

49. Megan Molteni, "A Chinese Genome Giant Sets Its Sights on the Ultimate Sequencer," *Wired*, 18 May 2017, https://www.wired.com/.

50. *Biosecurity* is defined as "securing valuable biological material from misuse or harm" while *cybersecurity* is defined as "the protection of computer systems from theft and damage to their hardware, software, or information, as well as from disruption or misdirection." Lauren C. Richardson et al., "Cyberbiosecurity: A Call for Cooperation in a New Threat Landscape," Frontiers in Bioengineering and Biotechnology, 6 June 2019, https://www.frontiersin.org/.

51. Andy Greenberg, "Biohackers Encoded Malware in a Strand of DNA," *Wired*, 10 August 2017, https://www.wired.com/.

52. Yanqing Ye, a recently indicted former student at Boston College, lied on her visa application to conceal that she was a lieutenant in the PLA and conducted research into military-related projects and scientists. See Ryan Lucas, "Harvard Chemistry Professor Arrested and Accused of Lying about Ties to China," NPR, 28 January 2020, https://www.npr.org/. Also, universities in general have done an incredibly poor job of enforcing laws designed to prevent spying, and they are now being called to account. See Scott Neuman and Cory Turner, "Harvard, Yale Accused of Failing to Report Hundreds of Millions in Foreign Donations," NPR, 13 February 2020, https://www.npr.org/.

53. C. K. Hickey, "New Data Shows Slowdown in Growth of International Students in the U.S," *Foreign Policy*, 20 November 2019, https://foreignpolicy.com/; and Stephanie Saul, "As Flow of Foreign Students Wanes, U.S. Universities Feel the Sting," *New York Times*, 2 January 2018, https://www.nytimes.com/. As of 2019, roughly 360,000 Chinese students were enrolled in the US with an estimated economic impact of $13 billion. Study International Staff, "How Are Chinese Students Being Affected by the US-China Trade War," *SI News*, 28 May 2019, https://www.studyinternational.com/.

54. Josh Lederman and Ted Bridis, "AP Sources: US to Impose Limits on Some Chinese Visas," *AP News*, 29 May 2018, https://apnews.com/.

55. Lloyd's of London will sell insurance worth $60 million in coverage for a $424,000 per year premium. See Brook Larmer, "One of America's Most Vital Exports, Education, Never Goes Abroad, but It Still Faces Threats," *New York Times Magazine*, 3 January 2019, https://www.nytimes.com/; and Janet Lorin, "Trump's Trade War with China Could Squeeze U.S. Colleges Next," *Bloomberg,* 18 June 2019, https://www.bloomberg.com/.

56. Samuel Rubenfeld, "The Morning Risk Report: CFIUS Reform Becomes Law," *Wall Street Journal* (blog), 15 August 2018, https://blogs.wsj.com/.

57. "Provisions Pertaining to Certain Investments in the United States by Foreign Persons," 31 C.F.R. part 800, *Federal Register* 85, no. 12 (17 January 2020): 3112, https://home.treasury.gov/.

58. Under North American Industry Classification System (NAICS), Class 541714. See also John Beahn and Robert LaRussa, "United States: Final CFIUS Regulations Implement Significant Changes by Broadening Jurisdiction and Updating Scope of Reviews," Mondaq, 16 January 2020, http://www.mondaq.com/; Foley Hoag LLP, "Expanded CFIUS Regulations in Effect February 13, 2020," 31 January 2020, https://www.jdsupra.com/; and Michael E. Leiter et al., "CFIUS Pilot Program Expands Jurisdiction to Certain Noncontrolling Investments, Requires Mandatory Declarations for Some Critical Technology Investments," Skadden, Arps, Slate, Meagher & Flom LLP, 11 October 2018, https://www.skadden.com/.

59. Compare the final rules with the solicitation for comments, which specifically requests public input on cutting-edge biotechnologies. See Bureau of Industry and Security, Department of Commerce, "Implementation of Certain New Controls on Emerging Technologies Agreed at Wassenaar Arrangement 2018 Plenary," *Federal Register*, 23 May 2019, https://www.federalregister.gov/; "Review of Controls for Certain Emerging Technologies," Bureau of Industry and Security, Department of Commerce, *Federal Register*, 19 November 2018, https://www.federalregister.gov/; and Peter Lichtenbaum, Victor Ban, and Lisa Ann Johnson, "Defining 'Emerging Technologies': Industry Weighs In on Potential New Export Controls," *China Business Review*, 17 April 2019, https://www.chinabusinessreview.com/.

60. Alexander Davis, "Investors Get a Win as US Rules on National Security Reviews are Unveiled," PitchBook, 17 January 2020, https://pitchbook.com/.

61. Such methods could include agents collecting DNA from one's garbage and facilities in/on military posts or obtaining DNA from databases maintained by commercial entities.

62. Jenna McLaughlin and Zach Dorfman, "Exclusive: Pentagon Warns Military Members DNA Kits Pose 'Personal and Operational Risks,'" *Yahoo! News*, 23 December 2019, https://www.yahoo.com/news/.

63. Max Boot, "Covid-19 Is Killing Off Our Traditional Notions of National Defense," *Washington Post*, 31 March 2020, https://www.washingtonpost.com/.

64. NASEM, *Biodefense in the Age of Synthetic Biology*; and National Academies for Sciences, Engineering, and Medicine, *Safeguarding the Bioeconomy* (Washington, DC: The National Academies Press, 2020), https://doi.org/10.17226/25525.

65. Imperiale Framework in NASEM, *Biodefense in the Age of Synthetic Biology,* 3.

66. The framework was updated in 2017 to clarify the roles of the Food and Drug Administration, Department of Agriculture, and the Environmental Protection Agency. See Obama White House, "Modernizing the Regulatory System for Biotechnology

Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology," January 2017, https://obamawhitehouse.archives.gov/.

67. The White House, Executive Order 13874, Modernizing the Regulatory Framework for Agricultural Biotechnology Products, 11 June 2019, https://www.whitehouse.gov/.

68. Marc Heller, "U.S. Agencies Clash over Who Should Regulate Genetically Engineered Livestock," *Science*, 19 April 2018, https://www.sciencemag.org/; and Kristen V. Brown, "The FDA Is Cracking Down On Rogue Genetic Engineers," *Gizmodo*, 31 January 2017, https://gizmodo.com/.

69. Megan Molteni, "A Cow, a Controversy, and a Dashed Dream of More Humane Farms," *Wired*, 8 October 2019, https://www.wired.com/.

70. Sarah L. Frazar et al., "Defining the Synthetic Biology Supply Chain," *Health Security* 15, no. 4 (2017): 399.

71. NASEM, *Biodefense in the Age of Synthetic Biology,* 125.

72. Ron Leuty, "Staring Down IP Theft Lawsuit, Synthetic Biology Company Seeks $86M IPO," *San Francisco Business Times,* 4 October 2018, https://www.bizjournals.com/.

73. John Keller, "DARPA Works with Six Organizations on Biological Materials for Military Applications," *Military Aerospace Electronics*, 1 October 2015, https://www.militaryaerospace.com/.

74. Imperiale Framework in NASEM, *Biodefense in the Age of Synthetic Biology*, 125.

75. Sui-Lee Wee and Elsie Chen, "In China, Gene-Edited Babies Are the Latest in a String of Ethical Dilemmas," *New York Times*, 30 November 2018, https://www.nytimes.com/.

76. Rob Stein, "House Committee Votes to Continue Ban on Genetically Modified Babies," NPR, 4 June 2019, https://www.npr.org/.

77. Rob Stein, "Clinic Claims Success in Making Babies with 3 Parents' DNA," NPR, 6 June 2018, https://www.npr.org/.

78. Charles Schmidt, "Why the Coronavirus Slipped Past Disease Detectives," *Scientific American*, 3 April 2020, https://www.scientificamerican.com/.

79. Margaret Bourdeaux et al., "Weaponizing Digital Health Intelligence," Belfer Center, January 2020, https://www.belfercenter.org/.

80. US Department of Health and Human Services, *2017–2018 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan* (Washington, DC: Department of Health and Human Services, 2017), https://www.phe.gov/.

81. Centers for Disease Control and Prevention, "Deadly Marburg Virus Found in Sierra Leone Bats," press release, 21 December 2018, https://www.cdc.gov/.

82. Department of Defense, *Assessing and Strengthening the Manufacturing and Defense Industrial Base and Supply Chain Resiliency of the United States: Report to President Donald J. Trump by the Interagency Task Force in Fulfillment of Executive Order 13806* (Washington, DC: Office of the Secretary of Defense, 2018), https://media.defense.gov/.

83. Government Accountability Office, *Defense Industrial Base: Integrating Existing Supplier Data and Addressing Workforce Challenges Could Improve Risk Analysis*, Report to the Chairman of the Committee on Armed Services, House of Representatives, GAO 18-435 (Washington, DC: GAO, June 2018), https://www.gao.gov/.

84. John Cumbers, " 'With Great Power Comes Great Responsibility'—Meet Alexander Titus The Department of Defense's Head of Biotechnology," *Forbes*, 24 September 2019, https://www.forbes.com/.

85. Defense Microelectronics Activity, "Trusted Accreditation," accessed 3 January 2020, https://www.dmea.osd.mil/.

86. Renee Wegrzyn, "Living Foundries," DARPA, accessed 5 April 2019, https://www.darpa.mil/; and Dina Fine Maron, "DARPA's Biotech Chief Says 2017 Will 'Blow Our Minds,'" *Scientific American*, 9 January 2017, https://www.scientificamerican.com/.

87. Oliver Morton, "The Engineering of Living Organisms Could Soon Start Changing Everything," *The Economist*, 4th Quarter, 2019, https://www.economist.com/.

88. Kerri Dugan, "Battlefield Medicine," DARPA, accessed 5 April 2019, https://www.darpa.mil/.

89. Nsikan Akpan and Matt Ehrichs, "Want to Cut Carbon Emissions? Try Growing Cement Bricks with Bacteria," PBS NewsHour, 7 March 2017, https://www.pbs.org/.

90. Brian Ripple, 88th Air Base Wing Public Affairs, "Future Deployers: Don't Forget to Feed the Runway," *Air Force News*, 5 June 2019, https://www.af.mil/.

91. Amanda M. Schrand, "Additive Manufacturing: From Form to Function," *Strategic Studies Quarterly* 10, no. 3 (Fall 2016): 79, https://www.airuniversity.af.edu/.

92. Ecovative Design, "Ecovative Design Awarded $9.1 Million U.S. Department of Defense Research Contract to Develop and Scale a New Generation of Living Building Materials," press release, SynBioBeta, 28 June 2017, https://synbiobeta.com/.

93. John Wenz, "Here's a Living Concrete That Repairs Itself," *Popular Mechanics*, 15 May 2015, https://www.popularmechanics.com/.

94. Amos Zeeberg, "Bricks Alive! Scientists Create Living Concrete," *New York Times*, 15 January 2020, https://www.nytimes.com/.

95. Lori Adornato, "Persistent Aquatic Living Sensors (PALS)," DARPA, accessed 23 January 2019, https://www.darpa.mil/; and Marisa Alia-Novobilski, "Tri-Service Effort Leverages Synthetic Biology Expertise to Address Future Warfighter Needs," *Wright-Patterson AFB News*, 27 September 2017, http://www.wpafb.af.mil/.

96. Patrick Tucker, "The US Military Is Genetically Engineering New Life Forms to Detect Enemy Subs," *Defense One*, 1 December 2018, https://www.defenseone.com/.

97. Blake Bextine, "Advanced Plant Technologies," DARPA, accessed 23 January 2019, https://www.darpa.mil/.

98. Megan Molteni, "Scientists Build a Menstrual Biochip That Does Everything but Bleed," *Wired*, 28 March 2017, https://www.wired.com/.

99. Chang Ming Li et al., "Biochips – Fundamentals and Applications," chap. 11, in *Electrochemical Sensors, Biosensors and Their Biomedical Applications,* Xueji Zhang, Huangxian Ju, and Joseph Wang, eds. (Academic Press: Cambridge, 2008), https://doi.org/10.1016/B978-012373738-0.50013-1.

100. Peter Dockrill, "Scientists Discover Mysterious Virus in Brazil with No Known Genes They Can Identify," *Science Alert*, 10 February 2020, https://www.sciencealert.com/.

101. Funding for the CDC dropped by over 9 percent in the proposed FY 2021 budget, and funding for the Public Health Service was cut by over 40 percent. These cuts make the US less prepared to handle pathogenic disease outbreaks. Laurie Garrett, "Trump Has Sabotaged America's Coronavirus Response," *Foreign Policy*, 31 January 2020, https://foreignpolicy.com/; and Linda J. Bilmes, "The Trump Administration Has Made the US Less Ready for Infectious Disease Outbreaks Like Coronavirus," *The Conversation*, 3 February 2020, https://theconversation.com/.

102. For an expected budget request, see Erica Werner, Jeff Stein, and Lena H. Sun, "White House Asks Congress for $1.8 Billion to Bolster Coronavirus Response," *Washington Post,* 24 February 2020, https://www.washingtonpost.com/.

103. DARPA's Pathogen Prevention Program (P3) is one agency seeking such solutions. See Eric Niiler, "Darpa Cranks Up Antibody Research to Stall Coronavirus," *Wired*, 14 February 2020, https://www.wired.com/.

104. Following 9/11, DARPA pursued several programs to attempt to grapple with the issue of novel pathogens. One such program was its "Unconventional Pathogen Countermeasures" initiative, which sought to create countermeasures to the most dangerous known pathogens—such as smallpox and anthrax—because they attack fundamental cellular processes rather than specific pathogens. Joel Garreau, *Radical Evolution: The Promise and Peril of Enhancing our Minds, Our Bodies—and What It Means to Be Human* (New York: Doubleday, 2005), 30. For current budget issues, see Office of Management and Budget, *A Budget for America's Future*: *Budget of the U.S. Government*; *FY 2021* (Washington, DC: US Government Publishing Office, 2020), https://www.whitehouse.gov/.

105. Patrick Lin, "Could Human Enhancement Turn Soldiers into Weapons That Violate International Law? Yes," *The Atlantic*, 4 January 2013, https://www.theatlantic.com/.

106. Mauricio De Castro et al., "Genomic Medicine in the Military," *Npj Genomic Medicine* 1, 15008 (2016), https://doi.org/10.1038/npjgenmed.2015.8.

107. Bryan Helwig, "The Thin Red Line of Predictive Genetic Testing in the Military," blog post, 16 March 2015, http://blogs.kentlaw.iit.edu/; and Susannah Baruch and Kathy Hudson, "Civilian and Military Genetics: Nondiscrimination Policy in a Post-GINA World," *American Journal of Human Genetics* 83, no. 4 (2008): 435–44, https://doi.org/10.1016/j.ajhg.2008.09.003.

108. US Army Training and Doctrine Command (TRADOC), "What We Are Learning about the Operational Environment," *Mad Scientist Laboratory* (blog), 4 November 2019, https://madsciblog.tradoc.army.mil/.

109. Denise Grady, "Crispr Takes Its First Steps in Editing Genes to Fight Cancer," *New York Times*, 6 November 2019, https://www.nytimes.com/.

110. Rob Stein, "In a 1st, Doctors in the U.S. Use CRISPR Tool to Treat Patient with Genetic Disorder," 29 July 2019, NPR, https://www.npr.org/.

111. Rob Stein, "Gene-Edited 'Supercells' Make Progress in Fight against Sickle Cell Disease," NPR, 19 November 2019, https://www.npr.org/.

112. "Bio-convergence" is a concept that speculates that advances in artificial intelligence, robotics, and artificial reality will irrevocably intertwine with biological technologies as humanity seeks to stay relevant in the fast tempo and lethality of future battlefields. An example of a key bio-convergence technology is optogenetics, which would use gene therapy to make brain cells more receptive to light signals delivered by fiber optics. Optogenetic modification may be a prerequisite to creating the brain-machine interface that might be required to operate in future AI-enhanced conflicts. See TRADOC, "Bio Convergence and Soldier 2050 Conference Final Report," *Mad Scientist Laboratory* (blog), 16 July 2018, https://madsciblog.tradoc.army.mil/.

113. Rebecca Trager, "Darpa Wants to Genetically Engineer Soldiers' Skin Bacteria to Protect Them from Mosquitoes," *Chemistry World*, 17 May 2019, https://www.chemistryworld.com/.

114. Renee Wegrzyn, "PReemptive Expression of Protective Alleles and Response Elements (PREPARE)," DARPA, accessed 10 January 2019, https://www.darpa.mil/.

115. "Can China Become a Scientific Superpower?," *The Economist*, 12 January 2019, https://www.economist.com/.

116. Joe Palca, "China Expands Research Funding, Luring U.S. Scientists and Students," NPR, 27 November 2018, https://www.npr.org/.

117. The Department of Energy has provisions where researchers may patent their research and sell their findings to commercial enterprises. See Palca for more about the 1000 Talents program.

118. CDC funding is slated to be cut further in the federal 2021 budget proposed by President Trump. See Bess Levin, "Trump's New Budget Proposal Slashes Medicaid, Medicare, Pesky CDC Funding," *Vanity Fair*, accessed 10 February 2020, https://www.vanityfair.com/. Among the proposals is an $85M reduction in the Emerging and Zoonotic Infectious Diseases Program that would research epidemics like the ongoing Coronavirus outbreak. See Levin; and Department of Health and Human Services, Centers for Disease Control and Prevention, *Justification of Estimates for Appropriation Committees, Fiscal Year 2021* (Washington, DC: Department of Health and Human Services, 2021), https://www.cdc.gov/. Note that these cuts are on top of cuts in the FY 2020 budget. See "FY 2020 President's Budget Table," accessed 18 June 2020, https://www.cdc.gov/.