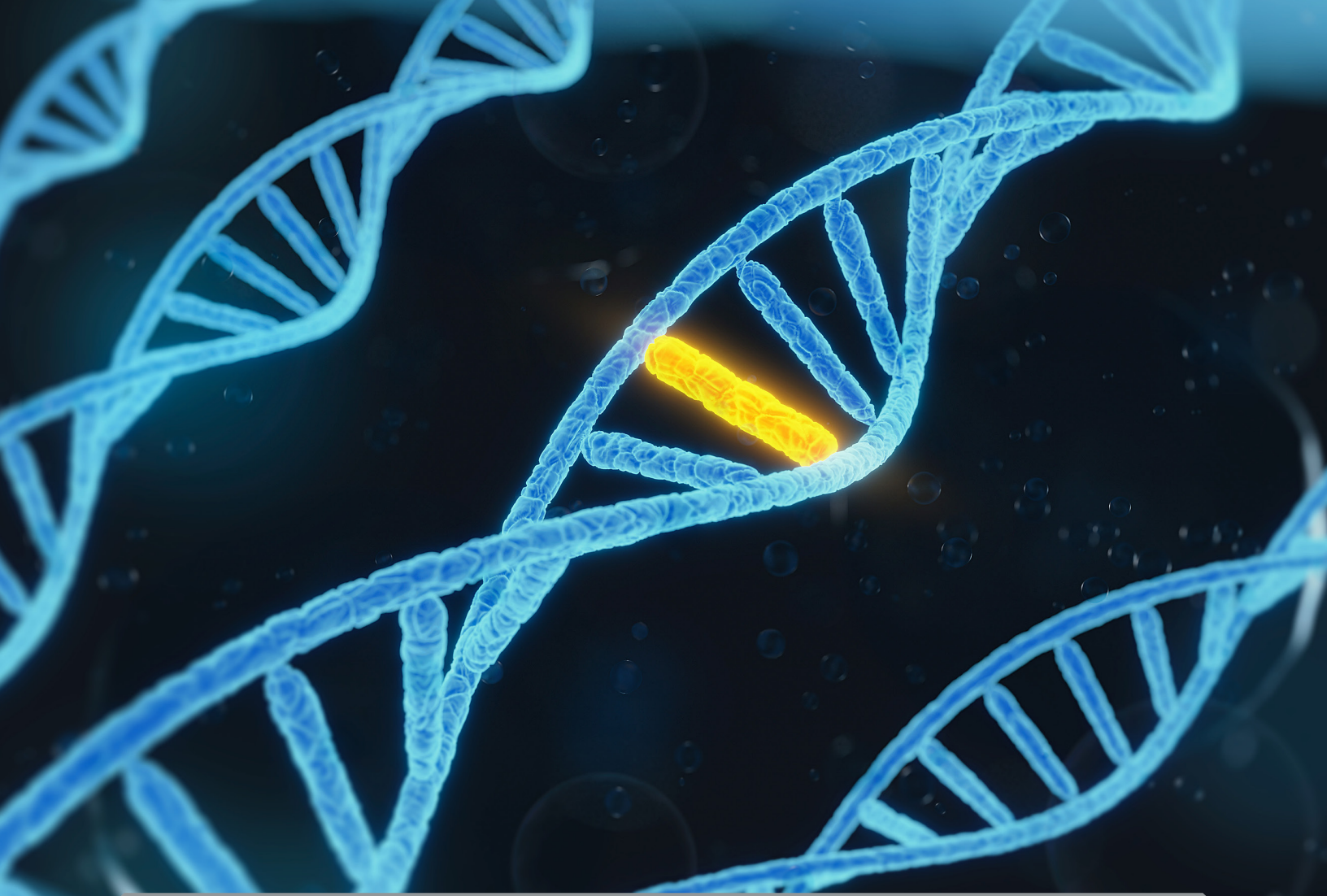


TIER ONE PROGRAM "SCIENCE & POLICY" CLASS WHITE PAPER • 2020

FINDING A BALANCE BETWEEN **SCIENTIFIC ADVANCEMENT AND NATIONAL SECURITY**

The Bush School OF GOVERNMENT & PUBLIC SERVICE TEXAS A&M UNIVERSITY

SCOWCROFT INSTITUTE OF INTERNATIONAL AFFAIRS
THE BUSH SCHOOL OF GOVERNMENT AND PUBLIC SERVICE
TEXAS A&M UNIVERSITY

TEXAS A&M UNIVERSITY

The views expressed and opinions presented in this paper are those of the Scowcroft Institute of International Affairs and do not necessarily reflect the positions of The Bush School of Government & Public Service or Texas A&M University.

SCOWCROFT INSTITUTE OF INTERNATIONAL AFFAIRS

THE BUSH SCHOOL OF GOVERNMENT AND PUBLIC SERVICE
TEXAS A&M UNIVERSITY

The Bush School OF GOVERNMENT & PUBLIC SERVICE TEXAS A&M UNIVERSITY

TEXAS A&M UNIVERSITY

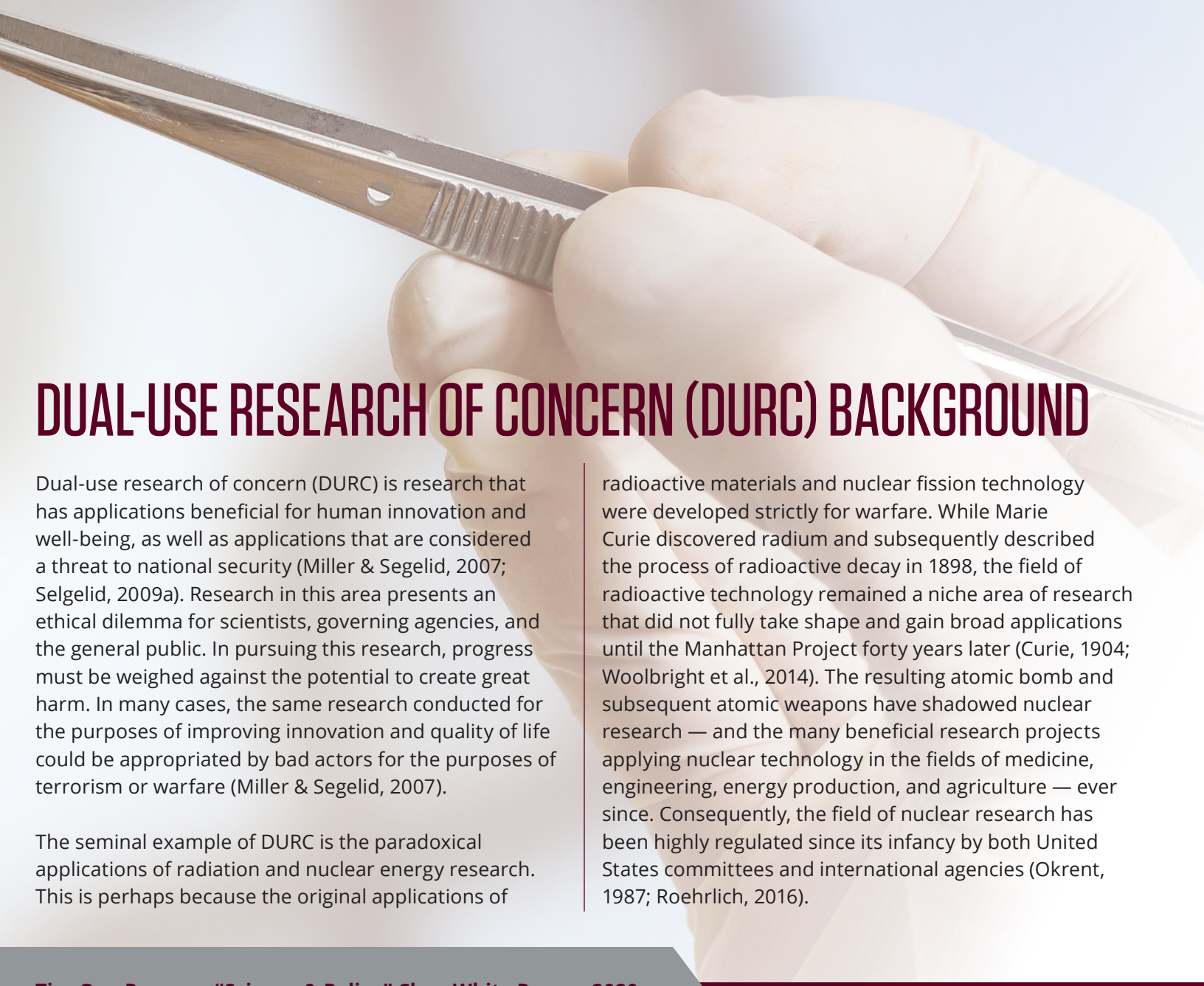
Designed and printed by CVM Communications | College of Veterinary Medicine & Biomedical Sciences
Texas A&M University | College Station, Texas, USA | *cvmcommunications@cvm.tamu.edu* | *vetmed.tamu.edu/communications*

FINDING A BALANCE BETWEEN **SCIENTIFIC ADVANCEMENT AND NATIONAL SECURITY**

Tier One Program "Science & Policy" Class White Paper • 2020

SUMMARY

Emerging technologies for gene editing have facilitated rapid advances in medicine, agriculture, industrial and biopharmaceutical manufacturing, and environmental sciences. However, the misuse or negligent use of these technologies poses significant national security risks, including the accidental or intentional pandemic emergence of engineered pathogens. The federal government requires a centralized effort to manage the risks of gene editing technologies while fostering innovation and scientific freedom. This white paper addresses challenges that present themselves to national and local governments, the scientific community, and the private sector, and provides recommendations to the federal government which aim to foster innovation and scientific freedom while maintaining national security.



DUAL-USE RESEARCH OF CONCERN (DURC) BACKGROUND

Dual-use research of concern (DURC) is research that has applications beneficial for human innovation and well-being, as well as applications that are considered a threat to national security (Miller & Segelid, 2007; Selgelid, 2009a). Research in this area presents an ethical dilemma for scientists, governing agencies, and the general public. In pursuing this research, progress must be weighed against the potential to create great harm. In many cases, the same research conducted for the purposes of improving innovation and quality of life could be appropriated by bad actors for the purposes of terrorism or warfare (Miller & Segelid, 2007).

The seminal example of DURC is the paradoxical applications of radiation and nuclear energy research. This is perhaps because the original applications of radioactive materials and nuclear fission technology were developed strictly for warfare. While Marie Curie discovered radium and subsequently described the process of radioactive decay in 1898, the field of radioactive technology remained a niche area of research that did not fully take shape and gain broad applications until the Manhattan Project forty years later (Curie, 1904; Woolbright et al., 2014). The resulting atomic bomb and subsequent atomic weapons have shadowed nuclear research — and the many beneficial research projects applying nuclear technology in the fields of medicine, engineering, energy production, and agriculture — ever since. Consequently, the field of nuclear research has been highly regulated since its infancy by both United States committees and international agencies (Okrent, 1987; Roehrlich, 2016).

In contrast, the dual-use applications of life science research did not become apparent until relatively recently (Kant & Mourya, 2010). While the fields of engineering, and particularly nuclear engineering, have had the breadth of their lifespans to address the potential harm of their research, the culture of life science research has primarily regarded ethical issues related to experimental procedures rather than applications of finished research. As innovations in the field of synthetic biology progress, the life sciences will have to contend with similar DURC ethical dilemmas that have become a cornerstone of debates and policies surrounding fields like nuclear research (Miller & Segelid, 2007).

Gene Editing and CRISPR/Cas: A DURC Example

The development and use of clustered regularly interspaced short palindromic repeats (CRISPR)-based techniques for genetic engineering has exploded since its first published use in mammalian cells in 2013 (Cong et al. 2013). CRISPR-based strategies have taken scientific research, medicine, agriculture, and manufacturing by storm because they offer a highly effective, scalable, easy-to-use, and affordable means of making precise genetic changes. This is a stark contrast to previously used techniques for genetic engineering, which were much more expensive, difficult to develop, and difficult to access. CRISPR has been quickly commercialized and adopted in labs and clinical settings all over the world.

However, the concept of 'genetic engineering' predates CRISPR, and has become more achievable with increased innovation in biochemistry and improved understanding of how genes work. Every organism contains genetic information, which is inherited from its parents and passed on to the next generation. The sum total of the genetic information of a particular organism is referred to as its genome, which contains a blueprint of all the components and processes necessary to make and maintain the organism. The genome is often compared to computer code, but one could also think of it as a recipe book—albeit a long and complicated one. The genome is made up of genes, which are like a single recipe within the recipe book or a single function in the code. Each gene provides the instructions to make a certain protein, which are the functional and structural molecules that make up the cell.

Like recipes are written and stored as the printed word on pages of a book, genes are written and stored as long molecules of deoxyribonucleic acid, or DNA. Each gene can be thought of like a word spelled with four different letters: A for adenine, T for thymine, C for cytosine, and G for guanine. Each is a chemically distinct molecular piece, called a base, that can be strung together to form the strand of DNA that makes up the gene, like letters are strung together to form words. A set of specialized proteins in the cell 'reads' the strands of DNA and uses the sequence of the bases as instructions to form the encoded protein from its constituent molecular parts, amino acids. Genetic engineering is the directed change and use of the gene's information, encoded in DNA, to create a desired outcome; this could be improving the health of an organism, teaching an organism how to make a new protein or chemical product, or any other myriad functions that make use of the biological machinery of a cell. Modifying the genome of an organism for directed use using gene editing techniques is referred to as 'synthetic biology'.

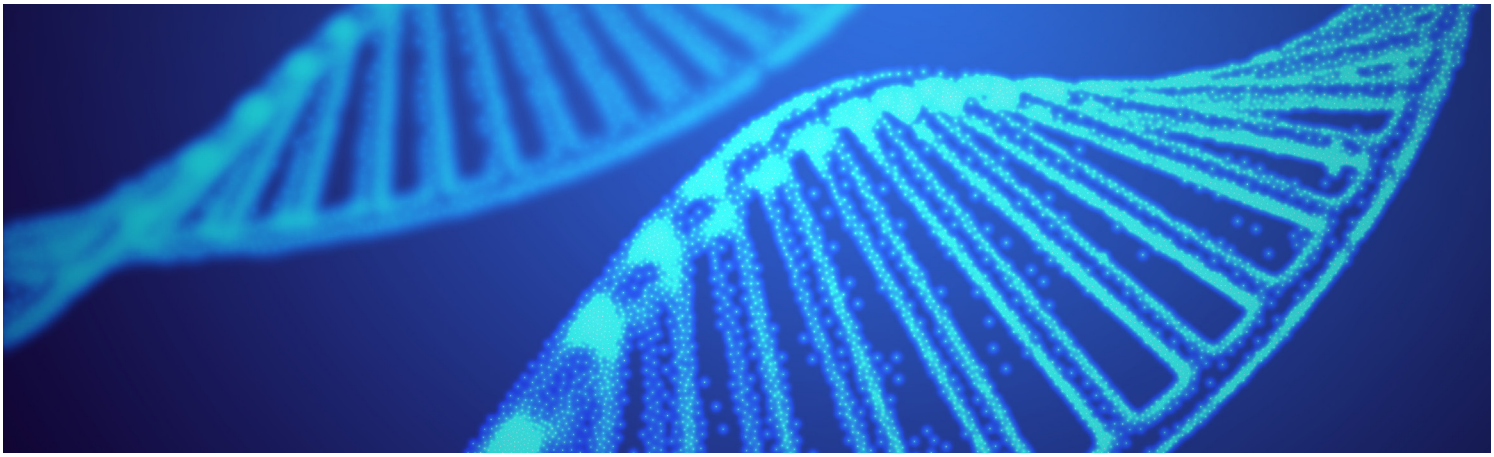
Until the introduction of CRISPR, the major limitation of the development and use of genetic engineering was the lack of effective and accessible means of making changes to the DNA. In bacterial and yeast cells, it is relatively straightforward to add new DNA. This enabled the first development of recombinant yeast and bacteria, which include DNA derived from a different organism, in the 1970s (Cohen et al., 1973). Recombinant organisms have enabled the industrial production of protein drugs, often called biologics, following the development of recombinant human insulin by Genentech and Eli Lilly in the 1980s (Quianzon & Cheikh, 2012). However, these methods could not remove genes or modify any gene that was already in the cell. Additionally, these methods could not be used effectively for animal or plant cells.

Two additional methods of editing DNA were developed later: zinc finger nucleases, or ZFNs (Carroll, 2011), and transcription activator-like effector nucleases, or TALENs (Joung & Sander, 2013). Both of these are methods that rely on engineered synthetic proteins to perform a 'cut

and paste' kind of editing to DNA. Both ZFNs and TALENs are designed to have a region which selectively binds to certain sequences of DNA and a region which then cuts the DNA in that spot. After the DNA is cut (a double stranded break, or DSB), the cell's natural DNA repair mechanisms will either paste the cut ends back together, or paste in new DNA which has been introduced to the cell. This enables the removal of defective or undesired genes from the organism and their potential repair, with some degree of control over where the new or modified gene is added. However, ZFNs and TALENs have technical and practical limitations. First, both have limitations on the length of the DNA sequence they can target, which increases the likelihood of non-specific binding and editing (Carroll, 2011; Boettcher & McManus, 2015). The larger practical limitation of both methods, however, is that they are extremely expensive and difficult to develop and produce. Every new desired genetic edit requires the production of a new custom-engineered protein, which must be extensively tested before it can be used. This made the process of genetic engineering slow and costly.

Seemingly overnight, CRISPR and its associated proteins, Cas, changed that. CRISPR/Cas uses a 'cut and paste' method similar to ZFNs and TALENs. However, instead of the engineered proteins, it uses a guide RNA (ribonucleic acid, chemically similar but not identical to DNA) and one standard Cas protein (Cas9 is most popular). The guide RNA contains one region which binds to the DNA sequence of the target gene and one region to which the Cas protein can attach, after which it cuts the DNA (Doudna & Charpentier, 2014). This was revolutionary, because producing custom RNA sequences is orders of magnitude cheaper than producing custom proteins and they can be purchased commercially. Additionally, the Cas proteins, particularly Cas9, are available commercially as well and they are affordable. As of the time of writing, the smallest quantities of Cas9 are available from the suppliers Millipore-Sigma and Thermo Fisher for less than $100.

Because of the accessibility of RNA and the standardized nature of the Cas9 protein, CRISPR/Cas is quickly adaptable to a variety of gene modifications in a variety of organisms. By 2014, approximately one year after the first publication of its use for genome engineering, CRISPR/Cas9 had demonstrated use for gene editing in human cells, mouse cells, mice, rats, fruit flies, nematodes, salamanders, frogs, rice, wheat, sorghum, and tobacco, among others (Doudna & Charpentier, 2014). Additionally, the originally published CRISPR/Cas system continues to be improved and adapted to new uses. For example, a new Cas protein, Cas13, has demonstrated use in editing RNA, which makes up the genome of many viruses (Abudayyeh et al., 2017). In addition, protein engineering has created CRISPR/Cas13 systems which can modify individual bases of RNA without cutting the RNA molecule (Cox et al., 2017). Protein engineering techniques have also been used to design versions of Cas9 with higher specificity lower rates of off-target gene editing (Slaymaker et al., 2016). Additionally, researchers have used CRISPR to cut, paste, and rearrange long sections of DNA containing many genes, instead of just one (Wang et al., 2019).



ADVANTAGES OF GENE EDITING AND SYNTHETIC BIOLOGY

Biotechnology and Medicine

Because of its ease of use and low cost, CRISPR/Cas has been rapidly adopted by research labs, the pharmaceutical industry, and the medical field. Selective editing and removal of genes and portions of DNA provide an incredibly useful tool for the study of genetics by enabling the rapid study of the biological function of genes of interest. However, the most pressing and most valuable applications of CRISPR/Cas are in medicine and the biopharmaceutical industry.

CRISPR/Cas itself has striking potential to improve human health through genomic repair, cell-based therapies, and systems for manufacturing and testing drugs and vaccines. For example, in February 2020 CRISPR/Cas was applied in a human patient for the first time by editing a rare mutation that leads to Leber's congenital amaurosis 10, the leading cause of blindness in childhood, which currently has no cure (Ledford, 2020). The trial hopes to restore vision by editing the DNA in cells in the patient's eyes. While this study is still underway, other therapies have been tested which take cells from the patient's body, edit their genes via CRISPR, and then return the cells to the body as a therapeutic agent.

For instance, CAR-T cell therapies work by removing immune cells (T-cells) from the patient's body and

then modifying them in the lab with chimeric antigen receptors (CAR) so that they specifically attack the patient's tumor cells. CRISPR/Cas streamlines this process and allows scientists to engineer the combination of molecules on the outside of the cells which enable them to attack (Eyquem et al., 2017; Jung & Lee, 2018; Hu et al., 2019). CRISPR/Cas CAR-T cell therapy has been attempted in a phase I clinical trial in three patients with advanced cancer and preliminary results demonstrated it to be safe and feasible (Stadtmauer et al. 2020). Additionally, in November 2019 the first results from a clinical trial by CRISPR Therapeutics and Vertex Pharmaceuticals to treat two rare blood disorders were reported (Al Idrus, 2019). The two patients suffered from beta thalassemia and sickle cell disease, conditions in which the red blood cells do not produce normal levels of hemoglobin, the protein that carries oxygen in the blood, and need regular transfusions. Nine months after receiving the experimental therapy, neither patient needed blood transfusions and, in both patients, over 90% of red blood cells produced fetal hemoglobin. In addition to these applications in hereditary eye diseases, cancer, and blood diseases, gene therapy with CRISPR/Cas has the potential to treat cardiovascular disease, metabolic diseases, neurodegenerative diseases, viral diseases, and other hereditary diseases such as Duchenne Muscular Dystrophy (Li et al., 2020).

Lastly, CRISPR/Cas has great potential as a means to manufacture and test new pharmaceutical drugs. Many therapeutics, including vaccines, rely on biological molecules like proteins. Often called biologics, these drugs are difficult and expensive to produce because they are large, complex molecules which, like a key to a lock, need to have just the right shape to fulfill their function. While small molecule drugs, like aspirin, can be produced readily in a lab using standard chemical synthesis techniques, biologics, like insulin or therapeutic antibodies, have almost always been impossible to manufacture without using cells—either from humans or animals—or without harvesting them from animals. However, genetic engineering has enabled the manufacture of biologics by simpler, easier-to-grow cells like yeasts and bacteria. The first example of this was in the 1980s, when Eli Lilly and Genentech added the gene for human insulin to yeast to produce an insulin analog which is still used today (Quianzon & Cheikh, 2012). CRISPR allows for more refined editing of cells to synthesize biologics, and could even edit the genes for the drugs to improve their efficacy or their retention time in the body.

Agriculture

Nearly 400 million acres of agricultural land in the United States are used for crops, and every one of them is put to good use. In 2017, agriculture constituted 1% of the United States' GDP, which equates to roughly $140 billion in revenue (U.S. Department of Agriculture, 2020). Pathogens and pests are a major threat to that revenue and can decrease crop yields anywhere from 17-23% (Savary et al., 2019). Synthetic biology has already been applied in myriad ways to help combat vectors and the harmful diseases they bring. In Hawaii, the development of a transgenic strain of papaya kept the industry from collapsing due to Papaya-ringspot virus (Gonsalves, 2002). A transgenic strain of the common bean was developed against the Golden mosaic bean virus, which had decimated entire bean yields in Latin America (Bonfim, Faria, Nogueira, Mendes, & Aragao, 2007). Additionally, plants' pest resistance has been improved using gene editing and synthetic biology. For example, the addition of the Mi gene in tomatoes provides resistance against aphids that destroy potatoes (Rossi et al., 1998). This yields multiple benefits; not only is the crop itself protected against the aphid, but it may also decrease the need for and use of pesticides. Decreasing pesticide use could help ease their potentially harmful effects on human health and reduce the burden on the public health system (Jaga & Dharmani, 2003).

Likewise, synthetic biology and gene editing can be used to increase the total biomass that crops can yield to buffer crop loss and increase revenue. Photosynthesis is the driver that dictates the yield of any crop, and increasing its efficiency can lead to much higher yields. Currently, that is what researchers at top institutions such as Cornell are trying to achieve (Lin, Occhialini, Andralojc, Parry, & Hanson, 2014). However, bioengineering has agricultural uses beyond food crops. Transgenic modification of eucalyptus, one of the most multi-use trees in the world, has yielded plants that are 1.5 times taller than their unmodified strains

while also enhancing the quality of wood (Girijashankar, 2011). Tobacco has also been genetically modified for perhaps unexpected uses beyond consumer products. Tobacco oil is a byproduct of the plant that has very useful applications in biofuel manufacturing (Andrianov et al., 2010). The tobacco plant has been modified to allow a build-up of oil within its leaves thus creating more biomass available for use in biofuel, a potential alternative energy source.

Finally, synthetic biology and gene editing have proven useful in improving plants' response to stress. In this case, stress would be any abiotic factor, such as soil or water quality, that affects how the plant grows. The main stressor for plants is availability of water, so the development of "drought-resistant plants" has been an important mainstay in plant biology. Major food crops such as maize, corn, and wheat all have modified "drought-resistant" strains that have been approved for commercial use (Khan et al., 2019). This is especially useful in arid regions of the world where limited water supplies threaten to decimate entire fields' worth of crops. In regions where water is more abundant, the diminished requirement for water reduces the cost of farming.

The beneficial applications of synthetic biology in agriculture also extend to livestock management. Recent debates on the overuse of antibiotics in livestock have brought attention to antibiotic resistant microbes, which many professionals consider to be a ticking bomb (Kirchelle, 2018). There is concern that drug-resistant superbugs could spill over into human populations and spread rapidly - with immunity to existing medications. The obvious solution would seem to be reducing the use of antibiotics in livestock animals, but that would require scaling down production and increasing labor cost, making production more costly and less efficient. Gene-editing with synthetic biology offers exciting promise in the development of new antimicrobial drugs and treatments. Genetically engineered antimicrobials could attack specific targets and lower the chance of increasing the antibiotic resistance of non-target pathogens (Goold et al., 2018). Further, advances in genome editing made possible by CRISPR will likely improve the production of livestock breeding programs as well as the quality of products derived from livestock (Li et al., 2017; Yum et al., 2018; Bishop & Van Eenennaam, 2020).

Environmental Sciences & Disease Vectors

Synthetic biology also has promising applications in the field of environmental science, especially for methods of disease vector control. Malaria kills hundreds of thousands of people a year, and is just one example of the many diseases transmitted by mosquitoes (Tolle, 2009). Conventional wisdom dictates that the fewer mosquitos there are in an environment shared with humans, the lower the risk of transmitting mosquito-borne diseases. However, previous and current attempts to control mosquito populations have proven to be difficult. In order for insecticides to be effective, they must be applied frequently and broadly in treated areas, and evolving mosquito resistance to insecticides must be monitored closely (Hemingway & Ranson, 2000; World Health Organization, 2016).

Novel research addressing mosquito population control has found a way to employ CRISPR technology with

great success. Gene editing with CRISPR has been used to modify genes which induce sterility in female mosquitos in both the lab and in the field (Hammond et al., 2016). Essentially, male mosquitoes can be genetically engineered in a lab to produce no viable offspring. They are then released into a natural environment where mosquito control is needed. Here, they mate with wild female mosquitoes resulting in inviable offspring and reducing the mosquito population in the area.

This experiment utilizes the gene drive editing abilities of CRISPR technology. Gene drive editing is a way of changing the genome of an organism in a way that allows the change to be passed down to new generations. Essentially, while topical applications of CRISPR change the genetic make-up of one organism, and die with that organism, gene drive changes the organism's germline, so changes made can be passed down to offspring and radiate out through the population. CRISPR-enabled gene drive editing can also be applied as a method of population control in invasive species. The house mouse is a hugely problematic ecosystem pest. In areas where it is introduced, it outcompetes other small mammals and breeds tremendously quickly, overrunning resources and threatening the balance of fragile ecosystems. Methods employed to combat invasive mice such as poison and trapping campaigns often have deleterious effects on the ecosystems they are meant to protect. New research conducted using CRISPR gene drive technology aims to address the issue of invasive mice with similar methods as the sterile mosquito project. Laboratory mice have successfully been modified to create offspring that develop physically as males, even when they are genetically coded to develop as females (Manser et al., 2019). This method is then able to eradicate mouse populations by removing females from entire generations.

NATIONAL SECURITY CONCERNS: DUAL-USE IN BIOTECHNOLOGIES

Duplication and Gain-of-Function

The use of synthetic biology and gene editing have clear implications for national security, especially when considering their potential role in duplication and gain-of-function research on pathogens with pandemic potential. Dual-use gain-of-function research involves giving a pathogen new capabilities to increase its infectivity or change its method of transmission (Selgelid, 2016). For example, in 2011, Dutch scientists altered the avian flu virus H5N1 to enable its transmission through the air among ferrets (Herfst et al., 2012). According to the World Health Organization (WHO), there have been only 577 confirmed cases of H5N1, but with its mortality rate of 60% the prospect of increased transmissibility is worrisome. Additionally, there were concerns that the virus could be transmitted from the lab ferrets to humans. The gene-edited strain from the lab could have the potential to cause a pandemic with a combination of high rates of transmission and significantly higher mortality than COVID-19. While there was no viral release, the publication of the methods for creating the more transmissible H5N1 strain created a significant security risk.

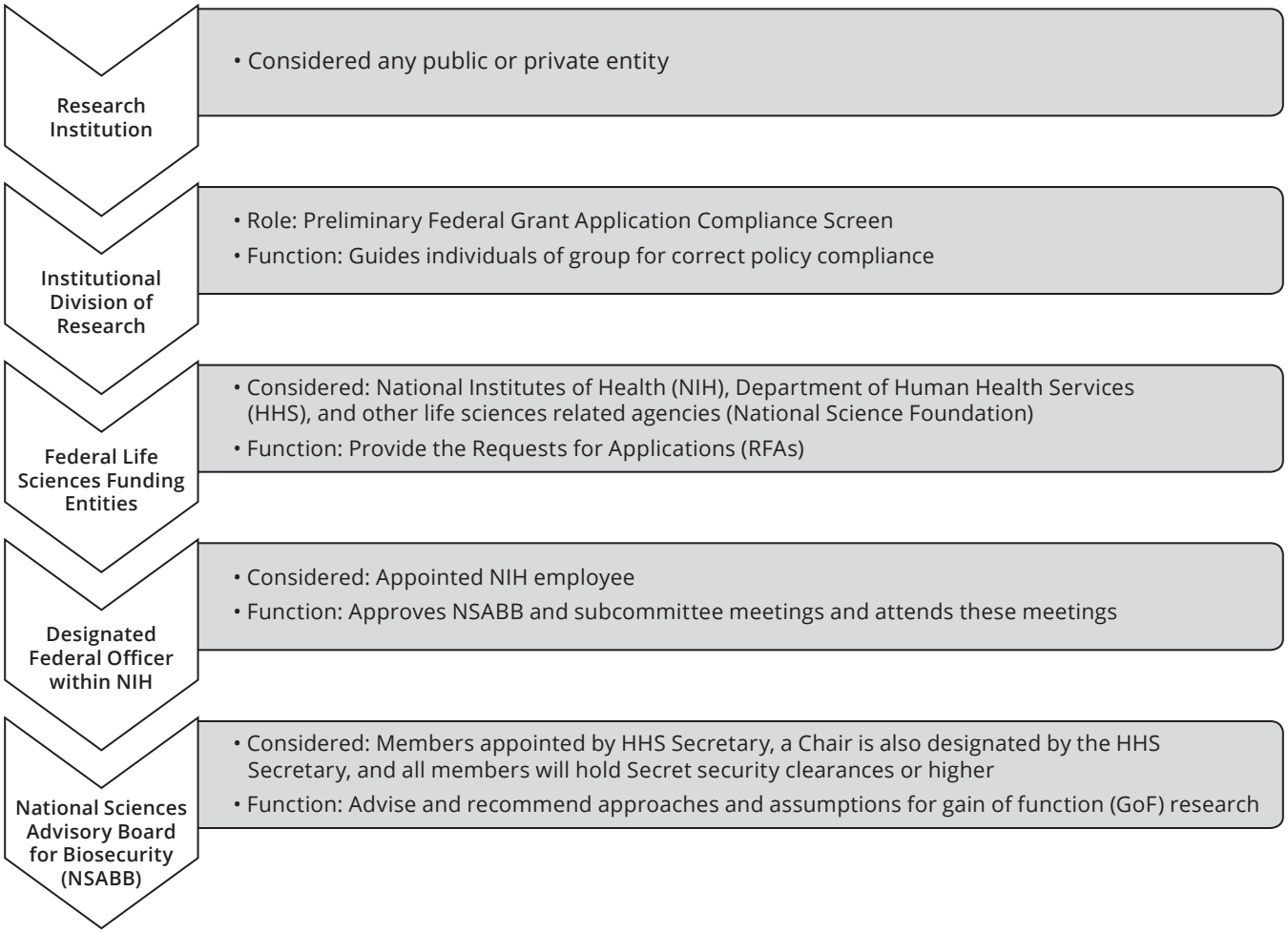
While controversial, this type of research continues under updated federal guidelines, which typically follow

the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. These guidelines provide general biosafety and biocontainment practices for research institutions. However, should the research have potential gain-of-function, the National Science Advisory Board for Biosecurity (NSABB) becomes involved. The schematic depicted in Figure 1 provides an overview of how a gain-of-function research proposal may be processed.

In another use of synthetic biology, Canadian scientists synthesized Horsepox virus in 2017. (Noyce et al., 2018). The Horsepox virus is similar to the Smallpox virus, which claimed an estimated 300 million lives in the twentieth century and was only eradicated in 1977 due to an aggressive vaccination campaign (Henderson, 2011). Though Horsepox does not cause disease in humans, the scientific and political communities were concerned that if viruses like Horsepox could be synthesized from scratch then so could similar and more dangerous viruses like Smallpox. Scenarios like these motivate the stockpiling of Smallpox vaccines in countries like the United States. However, in places that lack resources to generate vaccines or the infrastructure for vaccine distribution, the consequences of Smallpox-like viruses reemerging could be catastrophic.

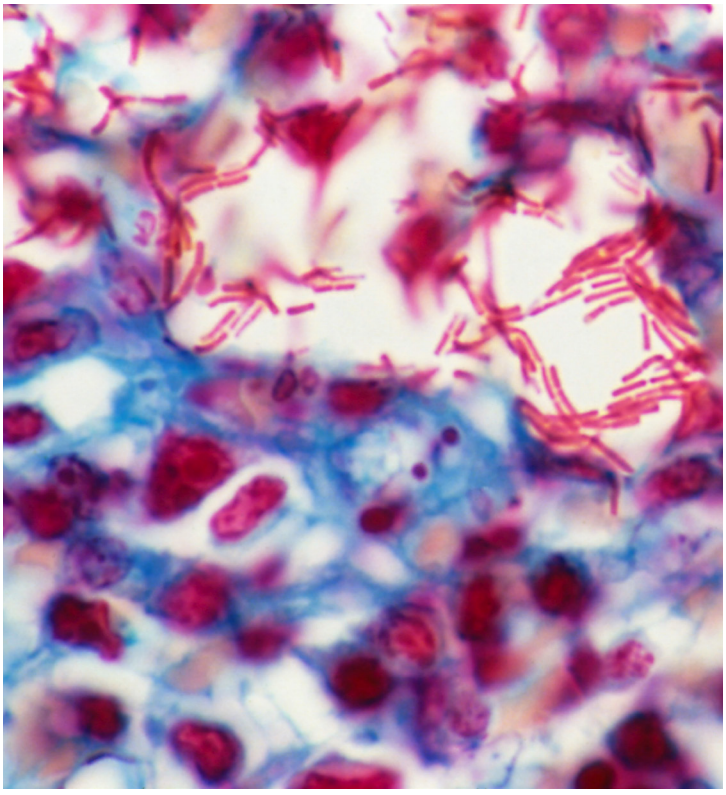
Research involving high consequence pathogens, those that are exceptionally dangerous, is usually subject to strict guidelines and must occur under the supervision of a governing body. Laboratories in the United States must adhere to strict guidelines, such as the previously mentioned NIH biosafety guidelines. These guidelines codify the biosafety and biocontainment measures

Figure 1



required to handle high consequence pathogens. For example, non-pathogenic E. coli can safely be handled in a biosafety level 1 laboratory with standard lab safety gear like gloves and eye protection, while something much more dangerous, such as Nipah virus, must be handled in a biosafety level 4 laboratory with strict security requirements. Security requirements for level 4 laboratories demand particular attentions to biosafety, such as heavy protective gear and detailed decontamination protocols. Most of the research labs in Western countries have similar stringent protocols and procedures in place, but not every lab is created equal. Research conducted in labs that do not maintain the same biosecurity standards risks creating and releasing unintended products (Gronvall, 2019).

Lastly, the 1979 anthrax outbreak in Sverdlovsk, Russia demonstrates the devastating effects of unintended release of a pathogen used for research. Anthrax was accidently released from a military laboratory nestled within the city. 77 people were infected, of which 66 died (Meselson et al., 1994). Although research with select agents is typically conducted in academic and state run laboratories, there are also independently-



operated domestic labs which have garnered increased attention from scholars and politicians alike. Non-academic scientific communities such as DIY Bio have come under increased scrutiny for their use of synthetic biology despite their members' inexperience (Gronvall, 2018). Gene editing technology becomes cheaper and more accessible as it advances. In addition, publicly accessible DIY Bio lab space enables anyone who is interested to do synthetic biology experiments. To set biosafety standards, DIY Bio labs have codes of conduct, but their members do not receive any formal ethics or lab training (Kolodziejczyk, 2017). To further complicate the issue, gene editing technologies have a high rate of off-target effects, mutations or changes to the genome made in an area other than the intended target. For example, CRISPR/Cas9 can have a high percentage of off target mutations (Zhang et al., 2019). The easy access to laboratory space, cheap materials, inexperienced parties and variable facility status of the DIY Bio communities create potentially disastrous security vulnerabilities. However, the laboratories in compliance with local guidelines still face the issue of balancing the risks and benefits of gain-of-function research.

Bioeconomy

The US government defines the bioeconomy as "economic activity that is driven by research and innovation in the life sciences and biotechnology" (National Academies of Sciences, 2020). China has made investment in their biotechnology sector a priority, making it an increasingly larger competitor with the US. China plans to continue expansion in their biotechnology sector, its current expectation is to be at $405 million in revenue by 2022 (Oanh Ha & Bloomberg, 2019). The security implications extend beyond the bioeconomy to the broader US economy. Without immediate efforts to secure the US bioeconomy, the security threats will continue into the future.

One current security threat is the dependence of the US pharmaceuticals industry on China for both materials and production. The US imports about 80% of its active pharmaceutical ingredients (API) from countries like China and India (Exploring the Growing US Reliance on China's Biotech and Pharmaceutical Products, 2019). In 2018, 13.4% of prescription drug imports came from

China, according to the FDA (Exploring the Growing US Reliance on China's Biotech and Pharmaceutical Products, 2019). The US is at risk of drug shortages if that supply chain is disrupted. Additionally, the FDA is unable to adequately regulate the quality of the API that is imported (Gibson & Singh, 2018). Another security vulnerability is a loss of domestic production capability of penicillin and generic antibiotics. Chinese companies in the biotechnology sector have targeted production of these drugs to drive US production out of the market (Exploring the Growing US Reliance on China's Biotech and Pharmaceutical Products, 2019). Chinese companies control 97% of the US market for antibiotics (Exploring the Growing US Reliance on China's Biotech and Pharmaceutical Products, 2019). The reliance on China for pharmaceuticals is only one of the risks facing the US biotechnology sector.

In the future, as gene editing technologies like CRISPR advance, China's investment in genetic sequencing and research is of concern for safeguarding the US biotechnology sector. In 2015 China already maintained roughly 30% of the world's genetic sequencing machines (Sun, 2017). One of China's largest genetic testing companies, 23Mofang, is projected to have 1.4 million customers by the end of 2020 (Oanh Ha & Bloomberg, 2019). China's investment in genomics extends beyond its own borders into the US. In the last 16 years, China has invested about 3.6 billion USD in the US biotechnology sector (Mui, 2016). This investment has focused on companies that develop and process genetic tests, like 23andMe (Mui, 2016). For example, in 2015 Chinese investment firm WuXi Healthcare Ventures contributed to a 115 million USD financing of 23andMe (BioSpace, 2015). In that same year, WuXi acquired the US-based genomics company NextCODE (WuXi PharmaTech, 2015), and has subsequently formed WuXi NextCODE which sells sequencing, analysis, and storage of genetic data in the US and Europe.

Importantly, there is concern that Chinese companies are collecting the data generated by their sequencing

services. The genetic data that is gathered from companies like 23andMe, WuXi NextCODE and others is placed into large databases. These databases have raised major concerns. First, the security and privacy of this data are likely inadequate (Mui, 2016). Neither the US nor China has strong regulations or laws protecting the privacy of genetic data maintained within these databases, which leaves the collected data available for potentially objectionable uses. China has already made use of this data to enhance their surveillance efforts of the Uyghur minority group (Oanh Ha & Bloomberg, 2019).

Perhaps most concerning, Chinese investments in US based companies have granted Chinese access to genetic data from US consumers. Recent scrutiny by the US government has halted some of the foreign investment in the US biotechnology sector (Pagliarulo, 2018). However, the halting of foreign investment has diminished the capital available to the US biotechnology sector. Allowing the US biotechnology sector to enter the same massive deficit as US pharmaceuticals would be in a reactionary position for all future developments of biotechnology more broadly. In a reactionary position, the US will have little authority to determine the best practices for ethics and technological development.

Many of these developments in biotechnology, especially synthetic biology, will have a significant global impact on human populations, agriculture, and livestock populations. As beneficial developments occur in the field, without policy action the US will become reliant on other countries for the research, development, and manufacturing of these beneficial technologies, as it already is for pharmaceutical products.

Bioterrorism & Accidental Release

From a bioweapon and bioterrorism perspective, DURC and dual-use technologies already pose a threat to national security. Numerous non-state actors and state actors including Russia, China, North Korea, Cuba, and Iran are suspected of pursuing biological weapons (Arms Control Association, 2020). However, more concerning is the threat from non-state actors who are entirely unconstrained by treaties or agreements. For instance, in the 1980s and 1990s the Rajneeshees cult and Aum Shinrikyo, both non-state actors, pursued biological weapons (Danzig et al., 2012). More recently, terrorist

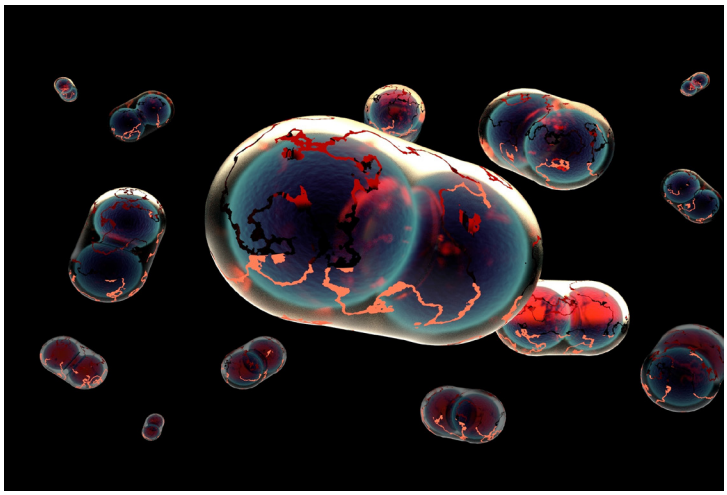
organizations like Al-Qaeda have made attempts to pursue biological weapons (Mowatt-Larssen, 2010).

Bioterrorism and biocrimes related to DURC and synthetic biology require ease of material acquisition, alteration of pathogens, and feasible program cost. The essential step for the creation of a bioweapon is the acquisition of a pathogen. Previously, acquisition required either collection of a pathogen from the environment or purchase from a laboratory source. Current efforts to limit the acquisition of pathogens by those with harmful motives use a list approach. In this approach, the CDC and USDA maintain a list of pathogens that are extremely harmful to humans and agriculture, and access to those agents is heavily regulated (Federal Select Agent Program, n.d.).

Synthetic biology technologies enable researchers to build pathogens from their sequenced genetic information without following the list approach (Couzin-Frankel, 2002). Concerningly, many pathogen genomes are publically available on the Internet, including the 1918 Influenza virus, the Poliovirus, and the Smallpox virus. Therefore, the wide accessibility of gene editing technologies and information for pathogen manufacturing creates serious challenges to methodological control of potential acts of bioterrorism or biowarfare by non-state and state actors.

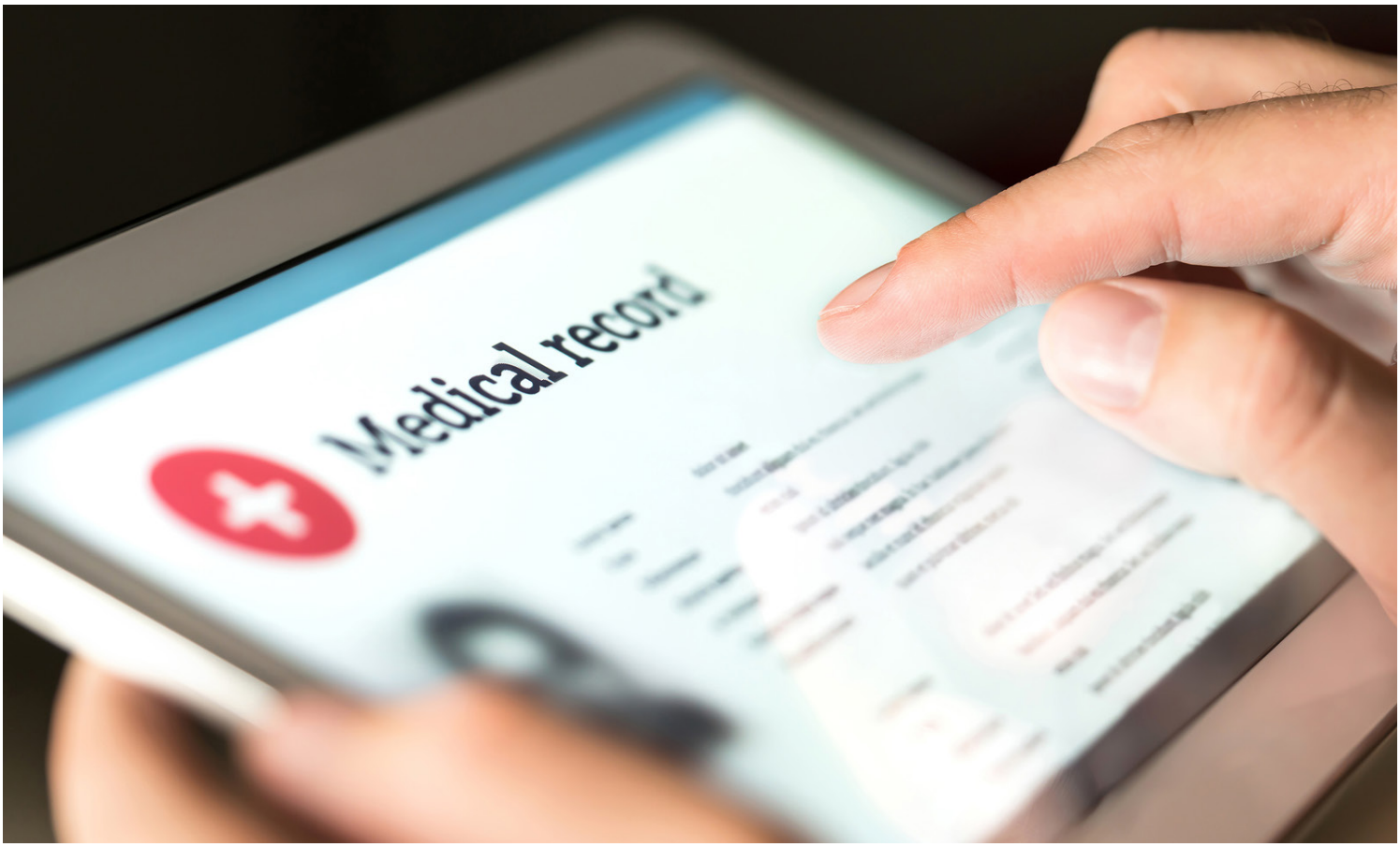
Historically, examples of non-state actor acquisition of pathogens include the doomsday cult Aum Shinrikyo. The self-sufficient cult collected strains of Clostridium botulinum and Bacillus anthracis (Danzig et al., 2012). Fortunately the strains they collected were harmless (Danzig et al., 2012), but it is likely their biological weapons program would have had greater success with modern synthetic biology technology. Additionally, domestic terror organizations, such as white supremacisits, have demonstrated during the COVID-19 pandemic that when given easy access to a pathogen, or the ability to exploit a pathogen, they will utilize the pathogen for terror attacks (Margolin, 2020).

Though gain of function research can alter pathogens for beneficial reasons, it can also be used to intentionally alter pathogens for a violent attack against a given



target. One could potentially modify the agent's virulence, its potency to cause disease, or the pathogen's pathogenesis, its ability to spread (Herfst et al., 2012; Jackson et al., 2001). Consider Smallpox, one of the few diseases which have been eliminated from the population through vaccination. Should it become vaccine resistant, it could be used as a devastating bioweapon with no existing barriers to counter its spread. One present limitation of bioweapon pathogens is their dispersal method. Once deployed, the pathogen may not infect enough of the intended population or the pathogen may infect the local population or troops instead of the intended target population. With gene editing technology like CRISPR, a state or non-actor could engineer their pathogen to:1) effectively spread with a restricted release duration or 2) only require a limited quantity for infection which reduces the risk to their people.

Possibly the most pressing concern for synthetic biology's application to bioterrorism is its radically low cost compared to other weapons technologies. Research and development that previously cost tens of thousands of dollars is now only a fraction of the cost (Charlet, 2018). This consequently lowers the hurdle for state actors looking to expand their bioweapons programs, such as the Russian Federation (Zilinskas, 2012), and also for non-state actors that seek to develop any bioweapons capabilities. If the trend of cost depreciation continues, it will lower the cost of entry to the level where even individuals could experiment with bioweapons to commit 'lone wolf' type attacks.



POTENTIAL NEW STRATEGIES TO MITIGATE RISKS

Duplication and Gain-of-Function

While it is impossible to predict all risks and benefits associated with dual-use research, the National Science Advisory Board for Biosecurity (NSABB) provides guidance and recommendations for such risk-benefit analysis. In general the NSABB framework requests submissions with clear problem statement or statements, a comprehensive consideration of the pathogen to be used for the gain-of-function research, and a separate risk assessment and benefit assessment (National Science Advisory Board for Biosecurty, 2007). Additionally, the NSABB emphasizes the importance of researchers' consideration of the role of public trust and how the research may hinder this trust. Some other key areas in this risk-benefit analysis may include how the proposed experiments promote public wellbeing and how the likelihood of unintentional or intentional consequences could threaten public safety (Presidential Commission for the Study of Bioethical Issues, 2010). Once the risk-benefit analysis has been considered in addition to all alternative methods, the next step is for the appropriate agencies to determine whether the research will be approved.

However, in addition to developing extensive risk-benefit analysis, DURC researchers face additional hurdles should their research involve stem cells. To provide context, the United States Department of Health, Education, and Welfare banned human embryonic stem cell research in the United States in 1973. This ban was upheld until 1993 when it was lifted by the Clinton Administration. But in 1996, the Dickey-Wicker Amendment was passed which granted the Department of Health and Human Services (HHS) the authority to prohibit the creation and destruction of human embryos for research purposes (National Academies of Sciences,

Engineering, and Medicine, Policy and Global Affairs et al., 2017; Tomlinson, 2018).

As a result, the 'Coordinated Framework' was established to help address this emerging field of science as well as provide an adaptive framework should other fields of science also emerge in time (Tomlinson, 2018). However, by 2017 very few changes had been made to the framework. Embryonic stem cell research was still limited in part to the 1996 Dickey-Wicker Amendment, but also due to the 2016 bill rider that ensured the Food and Drug Administration (FDA) would ignore any applications that involved human embryonic stem cell research (National Academies of Sciences, Engineering, and Medicine, Policy and Global Affairs et al., 2017; Tomlinson, 2018). Thus, despite the Executive Order 13505 "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," the National Institutes of Health - in conjunction with HHS - faces challenges in developing policies to address rapidly developing technologies involving stem cells and emerging biotechnology (Obama, 2009, NIH Office of Science Policy, 2016).

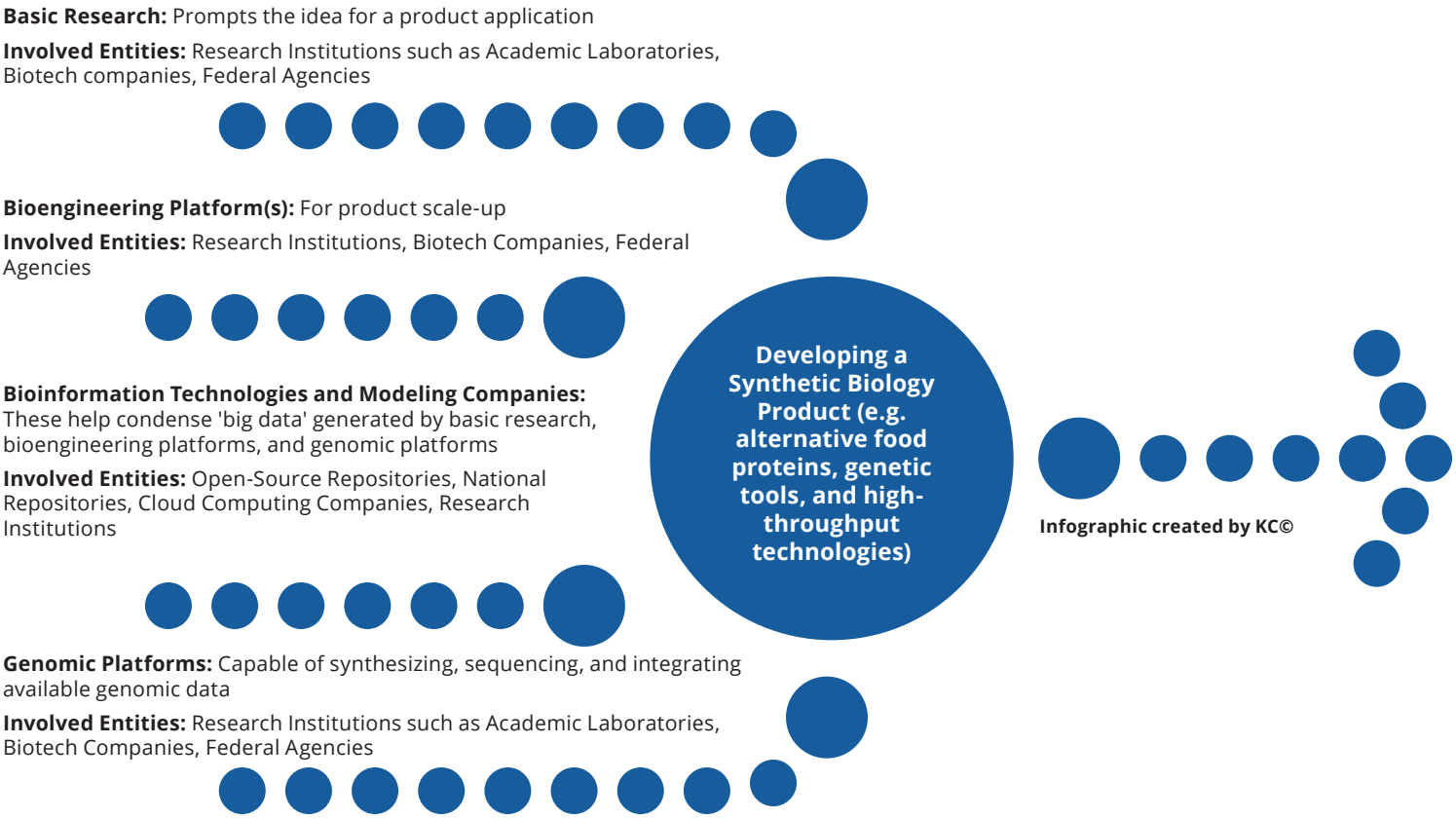
When researchers are ready to publish their findings in scientific publications they have the ethical duty to once again consider risk-benefit analysis. If the security risks of publicly publishing the data outweigh the benefits offered by the research, proper safeguards should be enacted to reduce these risks. Such safeguards may include extensive peer-review and limited publication of their methods and materials sections. Additionally, while reproducibility remains a fundamental pillar of the scientific method, private publishing companies and open source journals need to be aware of the risk associated with releasing information and data that could allow the replication, revival, or synthetic creation of pathogens with pandemic potential. For instance, one open access journal, PloS One, maintains the public availability of the genomic structure of H1N1 (Pan et al., 2010).

It is not suggested, however, that detailed method sections and genomic sequencing of pathogens be made entirely unavailable to all parties. Several journals have avenues in place for colleagues to request complete data sets from lead authors. This method allows the scientific

community to conduct internal checks to monitor the distribution of potentially harmful information. Another check may be achieved through licensing bodies that possess the ability to grant access to data deemed 'at-risk' for individuals requesting it within the scientific community. Thus, collaboration between the federal government, scientists, and publishing companies will be essential to ensuring the flow of scientific communication and progress continues, but at a rate that minimizes the potential of information misuse.

Bioeconomy

In order to prepare for emerging threats from synthetic biology (e.g. potential public health crises), the United States should form a Bioeconomy Security Act. Through this act, the US would be investing in the preservation and development of the US biotechnology sector, which would be capable of enhancing domestic manufacturing abilities for biotechnology and synthetic biology products. Figure 2 below illustrates this investment and expands upon the ideology presented in Figure 5-2 (p. 216) of the 2020 National Academies Report on "Safeguarding the Bioeconomy." It aims to highlight: 1) the associated levels contributing to a synthetic product, 2) how each level eventually converges and is dependent upon the other levels for their supportive technologies and analytic capabilities, and 3) involved entities are not limited to research labs but can include biotech companies that are either located in the US or internationally.



It is also necessary to note the National Academies discussion regarding the 'gap in manufacturing innovation;' an area that is typically assessed using comparative Technology Readiness Levels (TRL) (Medicine 2020). From Figure 2, we can visually note the complexity of synthetic product manufacturing. In addition, the manufacturing gap, the gap in technological readiness between the private sector and basic research institutions is substantial and has been considered the "valley of death" (National Academies of Science, Engineering, and Medicine, 2020, p. 224). While Figure 2 considers the private and public sector roles equally, the National Academy committee recommended further expansion of the TRL tool to help continue assessing and addressing likely technology readiness gaps (National Academies of Science, Engineering, and Medicine, 2020).

In order to address the "valley of death," support the US biotechnology sector's development, and ensure domestic preparedness for novel threats that could emerge from synthetic biology, we propose the following: 1) incentivize research in life sciences, in particular synthetic biology, and 2) adapt the Maritime Security Act (MSA) for the development of a similar program that is specific to and supportive of the biotechnology sector. Specifically, the suggested forms of incentives to be considered under this act are: first, tax incentives for both pharmaceutical companies and small biotech companies, and second, provisions for additional federal grant funding opportunities for research institutions. Then, once the MSA has been adapted to suit the biotechnology sector, the aim of this program is to incentivise strategic manufacturing capabilities within the US thereby bolstering the US's ability to produce active pharmaceutical ingredients (APIs) for our pharmaceutical industry, vaccine seeds for vaccine development, relevant personal protective equipment (PPE), and medical supply parts for equipment like BARD

ventilators and bedside physiologic monitors. As a result of this increased domestic production, the Strategic National Stockpile (SNS) increases as would production costs; therefore, the Bioeconomy Security Act would have select provisions to help offset these costs.

These legislative preparations through the Bioeconomy Security Act would encourage domestic preparedness by first, scaling current private sector production to match required needs, and second, equipping the US with materials capable of aiding in potential disaster and public health crises. The Bioeconomy Security Act would also help grow the domestic health sector by bringing job opportunities back to the US via domestic production facilities. Therefore, engaging the private sector in assisting to revamp the SNS would establish a national buy-in and position the United States to save resources. This avoids the need to federalize production facilities that would otherwise lay dormant during interim health or disaster crises. Consequently, a Bioeconomy Security Act will assist in improving US preparedness efforts as well as supporting the development of the US biotechnology sector.

Bioterrorism & Accidental Release

To dissuade potential bad actors, public-private partnerships with companies which provide the components used for synthetic biology and gene editing can improve monitoring of potential security threats and limit access. This can be done by leveraging current industry consortiums and formalizing security requirements for biotechnology companies. For instance, the International Gene Synthesis Consortium (IGSC) is an international industry consortium which represents 80% of the global market for gene synthesis. All members of IGSC voluntarily screen orders for RNA and DNA for genes from select agents. Though the Department of Health and Human Services (HHS) has published guidance for providers of synthetic double-stranded DNA (U.S. Department of Health and Human Services, 2014) there are no formal or legal requirements for gene synthesis companies to screen orders. In addition, the plummeting costs of DNA and RNA synthesis relative to the increasing cost of screening methods may discourage companies from continuing screening efforts (DiEuliis et al., 2017).

Private-public partnerships were successfully employed in the 2009 H1N1 pandemic, when HHS's Biomedical Advanced Research and Development Authority (BARDA) supported the proof of concept experiments for synthetic vaccine seed development (Dormitzer et al., 2013). This synthetic biology partnership involved Novartis Vaccine and Diagnostics (NV&D), J. Craig Venter Institute (JCVI), and Synthetic Genomics Vaccines Inc. (SGVI) (Dormitzer et al., 2013). Based on the study's results, there was a call for regulating bodies to support the development and manufacturing of synthetic products by supporting open sequence and antigen data (e.g. bioinformatic software and platforms, cloud computing abilities) as well as revising biosafety standards for this particular area of research (Dormitzer et al., 2013; National Academies of Science, Engineering, and Medicine, 2020).

To improve threat monitoring capabilities, federal sequence and antigen databases should be created and maintained to help offset screening cost while increasing compliance by gene synthesizing companies (DiEuliis et al., 2017). Also, federal grant recipients and federal contractors could be required to purchase DNA and RNA from companies which comply with screening (Carter and Friedman, 2015). While synthetic DNA and RNA screening is highly important because synthetic DNA and RNA is affordable and easy to misuse, there are other biotechnology resources that should be monitored for potential misuse. For instance, benchtop DNA synthesis setups can make synthetic DNA which might be screened out as dangerous by commercial providers. Registration of benchtop DNA synthesis setups in private labs and licensing of users would enable active monitoring of those who have access and could create potentially dangerous synthetic DNA (Garfunkel et al., 2007).

Furthermore, to reduce the risk of accidental release, US scientific training supported by federal funding should include 1) curricula covering potential adverse consequences misuse of DURC research, 2) awareness of available resources to help reduce or mitigate these risks, and 3) development of institutional best-practices for biosafety in labs engaging in biotechnologies like CRISPR and synthetic biology (Giordano & Evers, 2018; Presidential Commission for the Study of Bioethical

Issues, 2010). The scientific community should also consider upholding a set of standard stewardship practices to encourage responsible and ethical considerations of their DURC research. In turn this stewardship helps establish a culture of accountability, while also promoting responsible intellectual freedom practices (Douglas & Savulescu, 2010; Presidential Commission for the Study of Bioethical Issues, 2010).

Lastly, when responding to biosecurity threats and potential events related to synthetic biological threats, the US utilizes the National Response Framework (NRF) and National Incident Management System (NIMS) to support and initiate response efforts--first at the local level and then as far as the federal levels. However, public health preparedness efforts at the local level must be improved and expanded upon to help prepare for threats related to synthetic biology. Any measures taken in this sphere will serve the dual purpose of improving overall public health infrastructure. These efforts will require community buy-in from state and local governments, as well as participation from members of the medical community. Therefore, under a biosecurity preparedness task force, HHS, the CDC, and DHS would be guided to develop frameworks and processes for handling requests for assistance during pandemic and biosecurity events. In turn, such a task force would be able to partner with public and private institutions to establish compliance standards for their research materials and verify there are training available within these institutions engaging in DURC and synthetic biology research.

RECOMMENDATIONS TO SAFEGUARD DURC - BIOTECHNOLOGIES

1. Establish a Bioeconomy Security Act

The government should legislate to encourage synthetic biology research in the United States to ensure American competitiveness in emerging biotechnology. Additionally, ensuring competitiveness on the world stage requires improving American synthetic biology translational infrastructure, including biomanufacturing and the bioeconomy.

2. Establish a Bipartisan Biosecurity Preparedness Task Force

The government should establish a biosecurity preparedness task force in the Office of the Vice President to formulate and coordinate potential frameworks for response to both intentional and unintentional synthetic biology security threats, encourage a scientific culture of accountability, and increase involvement of the private sector, researchers, and local government in threat surveillance.

CONCLUSIONS

CRISPR and synthetic biology technology have the potential to revolutionize modern medicine and biopharmaceuticals, and can be utilized in agricultural industries and environmental initiatives. There exist, however, several national security concerns that need to be considered when advancing synthetic biology and gene editing technology. Both domestic and international laboratories may be vulnerable to accidental release of agents with pandemic potential. International groups and nations may use this technology for advanced biological warfare, or non-state actors may utilize synthetic biology and gene editing technology to engage in bioterrorism. Other nations, particularly China, already have a significant hold of the bioeconomy and are developing gene editing technology at a faster rate than the United States. Therefore, merely restricting gene editing and synthetic biology research in the United States leaves the nation vulnerable. Current guidelines including the NSABB are currently insufficient in properly addressing this quickly evolving technology.

We therefore recommend the United States government to 1) Establish a biosecurity preparedness task force; and 2) Establish a Bioeconomy Security Act. Such recommendations develop and maintain a response to potential security threats by state and non-state actors. We encourage utilizing existing frameworks of research funding opportunities and legislature that encourage and monitor safe laboratory practices. Developing and maintaining the government's response to this technology is also necessary. The United States must be at the forefront of these efforts to set a global example on handling gene editing and synthetic biology and other dual-use technological developments. At this juncture, our country has the opportunity to lead innovation in the field of synthetic biology while protecting national security and public welfare.

REFERENCES

1. Abudayyeh, O.O., Gootenberg, J. S., Essletzbichler, P., Han, S., Joung, J., Belanto, J.J., Verdine, V., Cox, D.B.T., Kellner, M.J., Regev, A., Lander, E.S., Voytas, D.F., Ting, A.Y., & Zhang, F. (2017). RNA targeting with CRISPR–Cas13. *Nature, 550*(7675), 280–284. https://doi.org/10.1038/nature24049

2. Al Idrus, A. (2019, Nov 20). Vertex, CRISPR's gene-editing treatment for blood disorders shows promise in early data. *FierceBiotech*. https://www.fiercebiotech.com/biotech/vertex-crispr-s-gene-editing-treatment-for-blood-disorders-shows-promise-early-data

3. Andrianov, V., Borisjuk, N., Pogrebnyak, N., Brinker, A., Dixon, J., Spitsin, S., . . . Koprowski, H. (2010). Tobacco as a production platform for biofuel: overexpression of Arabidopsis DGAT and LEC2 genes increases accumulation and shifts the composition of lipids in green biomass. *Plant Biotechnol J, 8*(3), 277-287. doi:10.1111/j.1467-7652.2009.00458.x

4. Appel, J.M. (2009). Is all fair in biological warfare? The controversy over genetically engineered biological weapons. *Journal of Medical Ethics, 35*(7), 429–432. https://doi.org/10.1136/jme.2008.028944

5. Arms Control Association. (2020, April). Chemical and Biological Weapons Status at a Glance https://www.armscontrol.org/factsheets/cbwprolif

6. Benelli, G. (2016). Green synthesized nanoparticles in the fight against mosquito-borne diseases and cancer—A brief review. *Enzyme and Microbial Technology, 95*, 58–68. https://doi.org/10.1016/j.enzmictec.2016.08.022

7. BioSpace. (2015, October 21). *WuXi Healthcare Invests in US Genomics Testmaker 23andMe*. https://www.biospace.com/article/releases/-b-wuxi-healthcare-b-invests-in-us-genomics-testmaker-23andme-/

8. Bishop, T.F., & Van Eenennaam, A.L. (2020). Genome editing approaches to augment livestock breeding programs. *The Journal of Experimental Biology, 223*(Pt Suppl 1). https://doi.org/10.1242/jeb.207159

9. Boddie, C., Watson, M., & Sell, T.K. (2016). Federal Funding for Health Security in FY2017. *Health Security, 14*(5), 284–304. https://doi.org/10.1089/hs.2016.0063

10. Boettcher, M., & McManus, M.T. (2015). Choosing the Right Tool for the Job: RNAi, TALEN, or CRISPR. *Molecular Cell, 58*(4), 575–585. https://doi.org/10.1016/j.molcel.2015.04.028

11. Bonfim, K., Faria, J.C., Nogueira, E.O., Mendes, E.A., & Aragao, F.J. (2007). RNAi-mediated resistance to Bean golden mosaic virus in genetically engineered common bean (Phaseolus vulgaris). *Mol Plant Microbe Interact, 20*(6), 717-726. doi:10.1094/MPMI-20-6-0717

12. Carroll, D. (2011). Genome Engineering with Zinc-Finger Nucleases. *Genetics, 188*(4), 773–782. https://doi.org/10.1534/genetics.111.131433

13. Charlet, K. (2018). The new killer pathogens: Countering the coming bioweapons threat. *Foreign Affairs, 97*(3), 178-185.

14. Cohen, S.N., Annie C.Y. Chang, Boyer, H.W., & Helling, R.B. (1973). Construction of biologically functional bacterial plasmids in vitro. *Proceedings of the National Academy of Sciences of the United States of America, 70*(11), 3240–3244.

15. Cong, L., Ran, F.A., Cox, D., Lin, S., Barretto, R., Habib, N., Hsu, P.D., Wu, X., Jiang, W., Marraffini, L.A., & Zhang, F. (2013). Multiplex genome engineering using CRISPR/Cas systems. *Science, 339*(6121), 819–823.

16. Couzin-Frankel (2002, July 11). Poliovirus Baked From Scratch. Science | AAAS. https://www.sciencemag.org/news/2002/07/poliovirus-baked-scratch

17. Cox, D.B.T., Gootenberg, J.S., Abudayyeh, O.O., Franklin, B., Kellner, M.J., Joung, J., & Zhang, F. (2017). RNA editing with CRISPR-Cas13. *Science, 358*(6366), 1019-1027. https://doi.org/10.1126/science.aaq0180

18. Curie, M.S. (1904). *Radio-active substances* (2nd edition). Scholar's Choice.

19. Danzig, R., Sageman, M., Leighton, T., Hough, L., Yuki, H., Kotani, R., & Hosford, Z.M. (2012). Aum Shinkrikyo: Insights into how Terrorists Develop Biological and Chemical Weapons. *Center for a New American Security*. https://s3.amazonaws.com/files.cnas.org/documents/CNAS_AumShinrikyo_Danzig_1.pdf?mtime=20160906080509

20. Dormitzer, P.R., Suphaphiphat, P., Gibson, D.G., Wentworth, D.E., Stockwell, T.B., Algire, M.A., Alperovich, N., Barro, M., Brown, D.M., Craig, S., Dattilo, B.M., Denisova, E.A., De Souza, I., Eickmann, M., Dugan, V.G., Ferrari, A., Gomila, R.C., Han, L., Judge, C., … Venter, J.C. (2013). Synthetic Generation of Influenza Vaccine Viruses for Rapid Response to Pandemics. *Science Translational Medicine, 5*(185), 1–14. https://doi.org/10.1126/scitranslmed.3006368

21. Douglas, T., & Savulescu, J. (2010). Synthetic Biology and the Ethics of Knowledge. *Journal of Medical Ethics, 36*(11), 687-93. DOI: 10.1136/jme.2010.038232.

22. Federal Select Agent Program. (n.d.) *Select Agents and Toxins List*. https://www.selectagents.gov/SelectAgentsandToxinsList.html

23. Gibson, R., & Singh, J.P. (2018). China Rx: *Exposing the risks of America's dependence on China for medicine*. Prometheus Books.

24. Giordano, J., & Evers, K. (2018). Dual use in neuroscientific and neurotechnological research: A need for ethical address and guidance. In Z. Koporc (Ed.), *Ethics and integrity in health and life sciences research* (Vol. 4) (pp. 129-145). Emerald Publishing Limited.

25. Girijashankar, V. (2011). Genetic transformation of eucalyptus. *Physiol Mol Biol Plants, 17*(1), 9-23. doi:10.1007/s12298-010-0048-0

26. Goold, H.D., Wright, P., & Hailstones, D. (2018). Emerging Opportunities for Synthetic Biology in Agriculture. *Genes, 9*(7), 341. https://doi.org/10.3390/genes9070341

27. Golub, N.D.A. and S.H. (2016). The new federalism: State policies regarding embryonic stem cell research. *The Journal of Law, Medicine & Ethics, 44*(3), 419–436. https://doi.org/10.1016/j.physbeh.2017.03.040

28. Gonsalves, D. (2002). Coat protein transgenic papaya: "acquired" immunity for controlling papaya ringspot virus. *Curr Top Microbiol Immunol, 266*, 73-83. doi:10.1007/978-3-662-04700-2_6

29. Gronvall, G.K. (2015). Mitigating the risks of synthetic biology. *Council on Foreign Relations*.

30. Gronvall, G.K. (2019). Synthetic Biology: Biosecurity and Biosafety Implications. Defense Against Biological Attacks, p. 225-232.

31. Gronvall, G.K. (2018). Safety, security, and serving the public interest in synthetic biology. *Journal of Industrial Microbiology & Biotechnology, 45* (7): 463-466.

32. Hammond, A., Galizi, R., Kyrou, K., Simoni, A., Siniscalchi, C., Katsanos, D., Gribble, M., Baker, D., Marois, E., Russell, S., Burt, A., Windbichler, N., Crisanti, A., & Nolan, T. (2016). A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae. Nature Biotechnology, 34*(1), 78–83. https://doi.org/10.1038/nbt.3439

33. Hemingway, J., & Ranson, H. (2000). Insecticide Resistance in Insect Vectors of Human Disease. *Annual Review of Entomology, 45*(1), 371–391. https://doi.org/10.1146/annurev.ento.45.1.371

34. Herfst, S., Schrauwen, E.J.A., Linster, M., Chutinimitkul, S., de Wit, E., Munster, V.J., Sorrell, E.M., Bestebroer, T. M., Burke, D.F., Smith, D.J., Rimmelzwaan, G.F., Osterhaus, A.D.M.E., & Fouchier, R.A.M. (2012). Airborne Transmission of Influenza A/H5N1 Virus between Ferrets. *Science, 336*(6088), 1534. https://doi.org/10.1126/science.1213362

35. Jackson, R.J., Ramsay, A.J., Christensen, C.D., Beaton, S., Hall, D.F., & Ramshaw, I.A. (2001). Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *Journal of Virology, 75*(3), 1205–1210. https://doi.org/10.1128/JVI.75.3.1205-1210.2001

36. Jaga, K., & Dharmani, C. (2003). Sources of exposure to and public health implications of organophosphate pesticides. *Rev Panam Salud Publica, 14*(3), 171-185. doi:10.1590/s1020-49892003000800004

37. Joung, J.K., & Sander, J.D. (2013). TALENs: A widely applicable technology for targeted genome editing. *Nature Reviews Molecular Cell Biology, 14*(1), 49–55. https://doi.org/10.1038/nrm3486

38. Kant, L., & Mourya, D.T. (2010). Managing Dual Use Technology: It Takes Two to Tango. *Science and Engineering Ethics, 16*(1), 77–83. https://doi.org/10.1007/s11948-008-9062-9

39. Khan, S., Anwar, S., Yu, S., Sun, M., Yang, Z., & Gao, Z.Q. (2019). Development of Drought-Tolerant Transgenic Wheat: Achievements and Limitations. *Int J Mol Sci, 20*(13). doi:10.3390/ijms20133350

40. Kirchhelle, C. (2018). Pharming animals: A global history of antibiotics in food production (1935–2017). *Palgrave Communications, 4*(1), 1–13. https://doi.org/10.1057/s41599-018-0152-2

41. Ledford, H. (2020, Mar 5). CRISPR treatment inserted directly into the body for first time. *Nature*. https://www.nature.com/articles/d41586-020-00655-8

42. Li, W.R., Liu, C.X., Zhang, X.M., Chen, L., Peng, X.R., He, S.G., Lin, J.P., Han, B., Wang, L.Q., Huang, J.C., & Liu, M.J. (2017). CRISPR/Cas9-mediated loss of FGF5 function increases wool staple length in sheep. *The FEBS Journal, 284*(17), 2764–2773. https://doi.org/10.1111/febs.14144

43. Lin, M.T., Occhialini, A., Andralojc, P.J., Parry, M.A., & Hanson, M.R. (2014). A faster Rubisco with potential to increase photosynthesis in crops. *Nature, 513*(7519), 547-550. doi:10.1038/nature13776

44. Manser, A., Cornell, S. J., Sutter, A., Blondel, D.V., Serr, M., Godwin, J., & Price, T.A.R. (2019). Controlling invasive rodents via synthetic gene drive and the role of polyandry. *Proceedings of the Royal Society B: Biological Sciences, 286*(1909), 20190852. https://doi.org/10.1098/rspb.2019.0852

45. Margolin, J. (2020). White supremacists encouraging their members to spread coronavirus to cops, Jews, FBI says. *ABC News*. https://abcnews.go.com/US/white-supremacists-encouraging-members-spread-coronavirus-cops-jews/story?id=69737522

46. Miller, S. & Selgelid, M.J. (2007). Ethical and philosophical consideration of the dual-use dilemma in the biological sciences. *Science and Engineering Ethics, 13*(4), 523-580. DOI: 10.1007/s11948-007-9043-4

47. Mowatt-Larssen, R. (2010). Al Qaeda's Pursuit of Weapons of Mass Destruction. *Foreign Policy*. https://foreignpolicy.com/2010/01/25/al-qaedas-pursuit-of-weapons-of-mass-destruction/

48. Mui, Y.Q. (2016). China's $9 billion effort to beat the U.S. in genetic testing. *Washington Post*. https://www.washingtonpost.com/news/wonk/wp/2016/12/30/chinas-9-billion-effort-to-beat-the-u-s-in-genetic-testing/

49. National Academies of Sciences. (2020, January 14). U.S. Bioeconomy is Strong, but Faces Challenges; Expanded Efforts in Coordination, Ralent, Security, and Fundamental Research are Needed. https://www.nationalacademies.org/news/2020/01/us-bioeconomy-is-strong-but-faces-challenges-expanded-efforts-in-coordination-talent-security-and-fundamental-research-are-needed

50. National Academies of Science, Engineering, and Medicine. (2020). Safeguarding the Bioeconomy. *The National Academies Press*. https://doi.org/10.17226/25525

51. National Academies of Sciences, Engineering, and Medicine, Policy and Global Affairs, Committee on Science, Technology, and Law, & Committee on Dual Use Research of Concern: Options for Future Management. (2017). *Dual use research of concern in the life sciences: Current issues and controversies*. National Academies Press.

52. National Research Council. (2004). *Biotechnology Research in an Age of Terrorism*. The National Academies Press. https://doi.org/10.17226/10827

53. National Science Advisory Board for Biosecurity. (2007). Proposed framework for the oversight of dual use life sciences research: Strategies for minimizing the potential misuse of research Information. *National Science Advisory Board for Biosecurity*.

54. Noyce, R.S., Lederman, S., & Evans, D.H. (2018). Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS ONE, 13*(1), e0188453. doi:10.1371/journal.pone.0188453

55. Oanh Ha, K., & Bloomberg. (2019, November 30). A reporter took DNA tests in the U.S. and China. The results left her worried. *Fortune*. https://fortune.com/2019/11/30/dna-tests-us-china-results/

56. Okrent, D. (1987). The safety goals of the U.S. Nuclear Regulatory Commission. *Science, 236*(4799), 296-300. DOI: https://doi.org/10.1126/science.3563510

57. Pagliarulo, N. (2018, October 11). US tightens scrutiny of foreign investment into biotech sector. *BioPharma Dive*. https://www.biopharmadive.com/news/us-tightens-scrutiny-of-foreign-investment-into-biotech-sector/539437/

58. Pan, C., Cheung, B., Tan, S., Li, C., Li, L., Liu, S., & Jian, S. (2010). Genomic Signature and Mutation Trend Analysis of Pandemic (H1N1) 2009 influenza A Virus. *PLoS One, 5*(3), e9549. DOI: https://doi.org/10.1371/journal.pone.0009549

59. Presidential Commission for the Study of Bioethical Issues (2010). *New directions: The Ethics of Synthetic Biology and Emerging Technologies*. https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf

60. Quianzon, C.C., & Cheikh, I. (2012). History of insulin. *Journal of Community Hospital Internal Medicine Perspectives, 2*(2). https://doi.org/10.3402/jchimp.v2i2.18701

61. Roehrlich, E. (2016). The Cold War, the developing world, and the creation of the International Atomic Energy Agency (IAEA), 1953–1957. *Cold War History, 16*(2), 195–212. https://doi.org/10.1080/14682745.2015.1129607

62. Rossi, M., Goggin, F.L., Milligan, S.B., Kaloshian, I., Ullman, D.E., & Williamson, V.M. (1998). The nematode resistance gene Mi of tomato confers resistance against the potato aphid. *Proc Natl Acad Sci U S A, 95*(17), 9750-9754. doi:10.1073/pnas.95.17.9750

63. Savary, S., Willocquet, L., Pethybridge, S.J., Esker, P., McRoberts, N., & Nelson, A. (2019). The global burden of pathogens and pests on major food crops. *Nat Ecol Evol, 3*(3), 430-439. doi:10.1038/s41559-018-0793-y

64. Selgelid, M.J. (2007). A Tale of Two Studies: Ethics, Bioterrorism, and the Censorship of Science. *Hastings Center Report, 37*(3), 35–43. https://doi.org/10.1353/hcr.2007.0046

65. Selgelid, M.J. (2009a). Dual-Use Research Codes of Conduct: Lessons from the Life Sciences. *NanoEthics, 3*(3), 175–183. https://doi.org/10.1007/s11569-009-0074-y

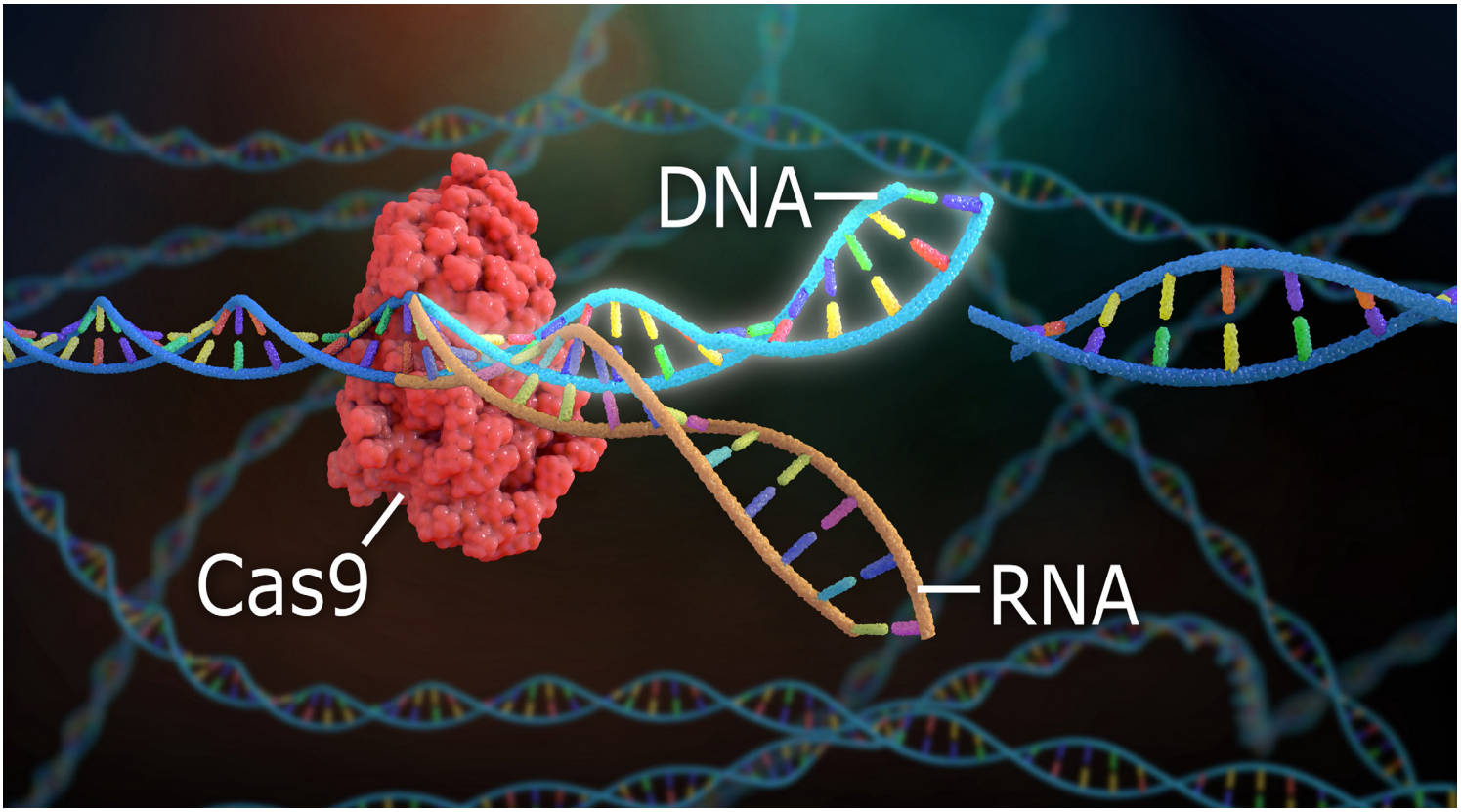
66. Selgelid, M.J. (2009b). Governance of dual-use research: An ethical dilemma. *Bulletin of the World Health Organization, 87*(9), 720–723. https://doi.org/10.2471/BLT.08.051383

67. Selgelid, M.J. (2016). Gain-of-function research: Ethical analysis. *Sci Eng Ethics, 22*(4), 923-964. doi:10.1007/s11948-016-9810-1

68. Slaymaker, I.M., Gao, L., Zetsche, B., Scott, D.A., Yan, W.X., & Zhang, F. (2016). Rationally engineered Cas9 nucleases with improved specificity. *Science, 351*(6268), 84–88. https://doi.org/10.1126/science.aad5227

69. Stadtmauer, E.A., Fraietta, J.A., Davis, M.M., Cohen, A.D., Weber, K.L., Lancaster, E., Mangan, P.A., Kulikovskaya, I., Gupta, M., Chen, F., Tian, L., Gonzalez, V.E., Xu, J., Jung, I., Melenhorst, J.J., Plesa, G., Shea, J., Matlawski, T., Cervini, A., … June, C.H. (2020). CRISPR-engineered T cells in patients with refractory cancer. *Science, 367*(6481), eaba7365. https://doi.org/10.1126/science.aba7365

70. Suk, J.E., Zmorzynska, A., Hunger, I., Biederbick, W., Sasse, J., Maidhof, H., & Semenza, J.C. (2011). Dual-Use Research and Technological Diffusion: Reconsidering the Bioterrorism Threat Spectrum. *PLoS Pathogens, 7*(1), e1001253. https://doi.org/10.1371/journal.ppat.1001253



71. Sun, Y. (2017, November 2). China Doubles Down on the Double Helix. *NEO.LIFE*. https://neo.life/2017/11/china-doubles-down-on-the-double-helix/

72. Tomlinson, T. (2018). A CRISPR future for gene-editing regulation: A proposal for an updated biotechnology regulatory system in an era of human genomic editing. *Fordham Law Review, 87*(1), 437–483.

73. Tolle, M.A. (2009). Mosquito-borne Diseases. *Current Problems in Pediatric and Adolescent Health Care, 39*(4), 97–140. https://doi.org/10.1016/j.cppeds.2009.01.001

74. Tucker, J.B., & Zilinskas, R.A. (2006). The promise and perils of synthetic biology. *The New Atlantis, 12*, 25-45.

75. U.S. Department of Agriculture (2020). Ag and Food Sectors and the Economy. (n.d.). https://www.ers.usda.gov/data-products/ag-and-food-statistics-charting-the-essentials/ag-and-food-sectors-and-the-economy/

76. U.S. Department of Health and Human Services. Services. (2014). *BARDA Strategic Plan 2011-2016*. https://doi.org/10.23919/acc.2004.1384612

77. Walker, S.J., & Wellock, T.R. (2010, September). A Short History of Nuclear Regulation, 1946–2009 (NUREG/BR-0175, Revision 2). *United States Nuclear Regulatory Commission*. https://www.nrc.gov/reading-rm/doc-collections/nuregs/brochures/br0175/

78. Wang, K., de la Torre, D., Robertson, W.E., & Chin, J.W. (2019). Programmed chromosome fission and fusion enable precise large-scale genome rearrangement and assembly. *Science, 365*(6456), 922-926. https://doi.org/10.1126/science.aay0737

79. Woolbright, S.J., Schumacher, J.P., & Michonova-Alexova, E.I. (2014). From the dawn of nuclear physics to the first atomic bombs. *Asian Journal of Physics, 23*(1&2), 1-20.

80. World Health Organization. (2016). *Monitoring and managing insecticide resistance in Aedes mosquito populations: interim guidance for entomologists*. World Health Organization. https://apps.who.int/iris/handle/10665/204588

81. WuXi PharmaTech. (2015, January 9). WuXi PharmaTech Acquires NextCODE Health to Create Global Leader in Genomic Medicine. *PR Newswire*. https://www.prnewswire.com/news-releases/wuxi-pharmatech-acquires-nextcode-health-to-create-global-leader-in-genomic-medicine-300018311.html

82. Yum, S.Y., Youn, K.Y., Choi, W.J., & Jang, G. (2018). Development of genome engineering technologies in cattle: From random to specific. *Journal of Animal Science and Biotechnology, 9*(1), 16. https://doi.org/10.1186/s40104-018-0232-6

83. Zhang, X., Lin, Y., Wu, Q., Wang, Y., & Chen, G.Q. (2019). Synthetic Biology and Genome-Editing Tools for Improving PHA Metabolic Engineering. *Trends in Biotechnology*. https://doi.org/10.1016/j.tibtech.2019.10.006

84. Zhang, X.H., Tee, L.Y., Wang, X.G., Huang, Q.S., & Yang, S.H. (2015). Off-target Effects in CRISPR/Cas9-mediated Genome Engineering. *Mol Ther Nucleic Acids, 4*, e264. doi:10.1038/mtna.2015.37

85. Zilinskas, R.A. (2012). Take Russia to "task" on bioweapons transparency. *Nature Medicine, 18*(6), 850–850. https://doi.org/10.1038/nm0612-850

AUTHORS*

Krisa Camargo

Ms. Camargo is a current PhD candidate at Texas A&M University (TAMU), where she is a trainee under the TAMU Superfund Center Project 1 and a Science Mathematics and Research for Transformation (SMART) scholar. Her dissertation work is characterizing complex environmental mixtures in Galveston Bay and the Houston Ship Channel (GB/HSC) soils and sediments through the development and application of analytical tools and methods. She is also currently pursuing her Certificate in Homeland Security with an emphasis on Emergency Management and Crisis Preparedness at the Bush School of Government & Public Service. Ms. Camargo received her Bachelor of Science in Neuroscience from George Mason University (Mason) in 2016. While as an undergraduate, she interned at Tuft's Cummings School of Veterinary Medicine Wildlife clinic during Summer 2015 where her mentor, Dr. Mark Pokras, introduced her to wildlife toxicology and veterinary pathology. These interests ultimately lead her to her current career path in toxicology. Ms. Camargo has three co-authored papers and has served as a volunteer for the National Center for Environmental Assessment (NCEA) Evidence Mapping Student Training Activity (USEPA, Fall 2018-Summer 2019). She is also the President of the Aggies in Science Technology Engineering Policy (Fall 2019-Present) and is a current Aggie Network Student Ambassador (2018-present).

Edward Davila

Edward Davila is a PhD student in the Veterinary Integrative Biosciences department at the Texas A&M College of Veterinary Medicine and Biomedical Sciences. His research focuses on infectious disease epidemiology, specifically, using animals as sentinels for human disease. He obtained both his MPH and BS degrees from Texas A&M University. After completion of his master's degree, Edward worked for the Houston Health Department as a Staff Epidemiologist where he focused on Zika virus surveillance before returning to Texas A&M to begin his PhD in 2018.

Victoria M. Green

Victoria M. Green is a PhD student in the Department of Philosophy at Texas A&M University and focuses on applied ethics. Specifically, she researches the moral relationship between scientists and nonhuman subjects through environmental and animal ethics. She received a BS in Evolutionary Anthropology and Philosophy from Rutgers University and an MS in Primate Behavior from Central Washington University, where she studied primatologists' ethical concerns regarding their impacts on wild primate subjects.

Konnor Heyde

Konnor Heyde is a graduate student in the Master of International Affairs program at The Bush School of Government & Public Service. His areas of concentration are conflict and development, intelligence, and biosecurity. Prior to the Bush School, he received a Bachelor of Arts in Political Science and Russian Language and Cultural from the University of Wisconsin – Madison.

Samantha Holt

Samantha Holt is a PhD candidate in Biomedical Engineering at Texas A&M University. Her research focus is developing novel hydrogel biomaterials for use in tissue engineering, with ultimate applications in regenerative medicine and modeling human diseases such as cancer.

Currently, she is involved in program development and evaluation for the DeBakey Executive Research Leadership Program, which aims to improve leadership training for early-career researchers as well as facilitate undergraduate research education. She is active in community educational outreach including Saturday Morning Biophysics, an annual outreach program to encourage middle school and high school girls to pursue STEM careers. She holds a BS in Bioengineering from the University of Illinois Urbana-Champaign, where she also worked as a marketing intern for the Office of Technology Management. Her policy interests include STEM higher education reform, consumer protections in the healthcare industry, particularly in light of emerging biomedical technologies, and biosecurity.

Hunter L. Malone

Hunter L. Malone is a masters degree candidate in the International Affairs department at The Bush School of Public Service. His focus centers around conflict and development, specifically as it pertains to vulnerable populations. Prior to the Bush School, Hunter worked overseas with a faith-based NGO in the developing world. He graduated with a bachelor's degree in youth development from Texas A&M University in 2016. Hunter plans to graduate from the Bush School in 2021.

Austin Reid

Austin Reid is a graduate student at the Bush School of Government and Public Service at Texas A&M University studying cybersecurity and security policy management. He Graduated from Texas A&M University Galveston Campus with a bachelor's of science in maritime administration in 2015. Austin has also been developing maritime sector cybersecurity case studies for use in educating future industry professionals. Before coming to the Bush School Austin Worked in the maritime industry overseeing breakbulk and automated container terminal operations. He has served as a stevedore superintendent in Mobile Alabama and in an operations monitoring role at a remote operations center in Texas for a leading automated container terminal on the west coast.

Lilianna Wolf

Lilianna Wolf is a researcher and graduate student at Texas A&M University. Her thesis research investigates the spread of disease among bats in Texas and Mexico. Aside from her research, Lilianna is a worker at the Scowcroft Institute of International Affairs at the Bush School of Government and Public Service where she contributes to projects examining issues of environmental conservation, conflict, and global health. Lilianna graduated with her bachelor's in Wildlife Biology from Texas A&M University in 2016. She has held research associate positions and positions in environmental consulting.

**All authors contributed equally to this white paper*

About "Science & Policy"

"Science & Policy" is a class funded through the Tier One Program by the Office of the President at Texas A&M University. It's an interdisciplinary graduate level course designed to bring together Masters and PhD students from the social sciences and sciences from across the university. Students are challenged to work together over the course of the semester on a research topic within the scope of the course.

President George H.W. Bush & Lt. Gen. Brent Scowcroft

"We live in an era of tremendous global change. Policy makers will confront unfamiliar challenges, new opportunities, and difficult choices in the years ahead. I look forward to the Scowcroft Institute supporting policy-relevant research that will contribute to our understanding of these changes, illuminating their implications for our national interest, and fostering lively exchanges about how the United States can help shape a world that best serves our interests and reflects our values."

— Lt. Gen. Brent Scowcroft, USAF (Ret.)

The views expressed and opinions presented in this paper are those of the Scowcroft Institute of International Affairs and do not necessarily reflect the positions of The Bush School of Government & Public Service or Texas A&M University.

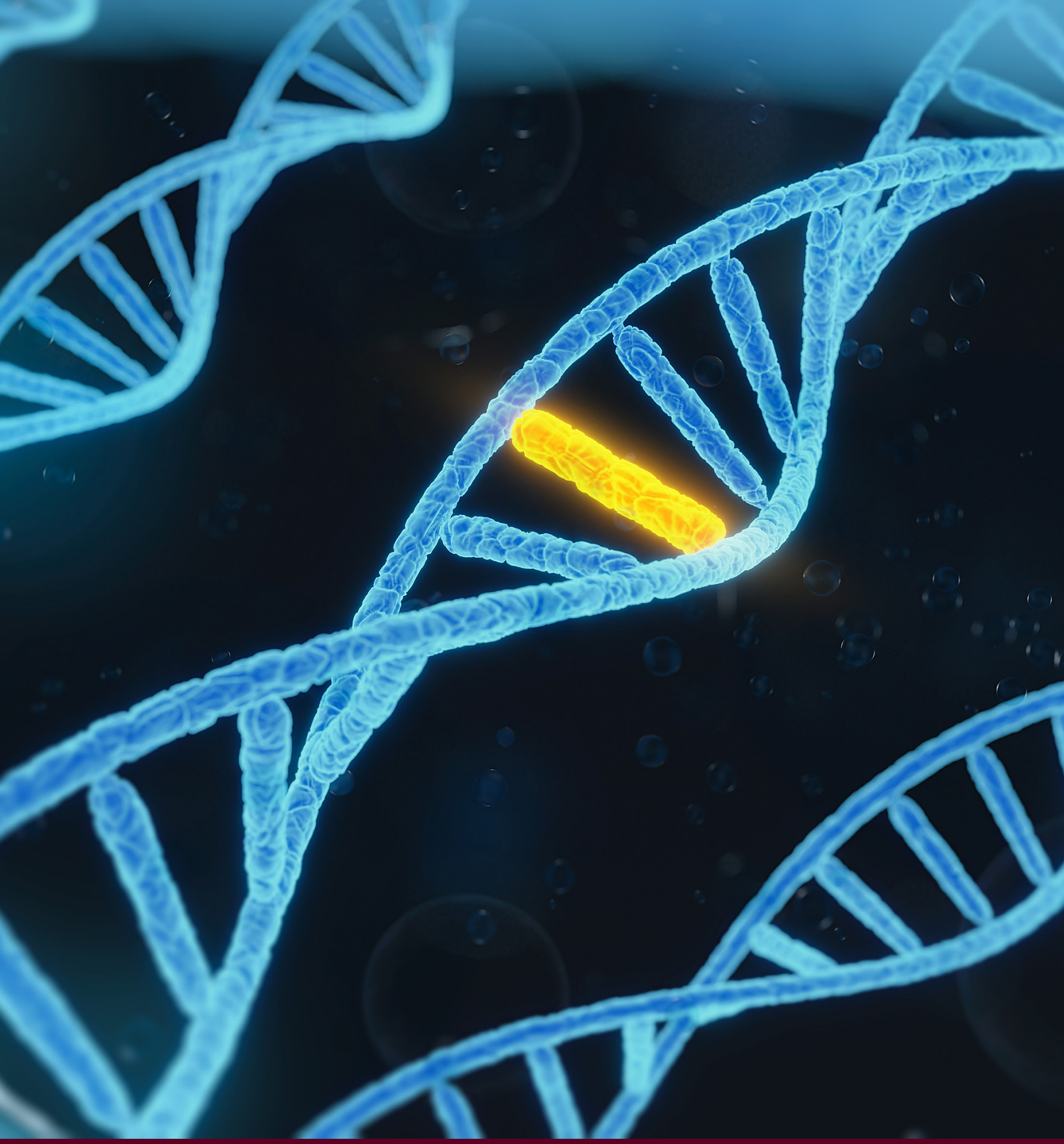
SCOWCROFT INSTITUTE OF INTERNATIONAL AFFAIRS

THE BUSH SCHOOL OF GOVERNMENT AND PUBLIC SERVICE
TEXAS A&M UNIVERSITY

The Bush School OF GOVERNMENT & PUBLIC SERVICE TEXAS A&M UNIVERSITY

TEXAS A&M UNIVERSITY

Designed and printed by CVM Communications | College of Veterinary Medicine & Biomedical Sciences
Texas A&M University | College Station, Texas, USA | *cvmcommunications@cvm.tamu.edu* | *vetmed.tamu.edu/communications*



The Bush School
OF GOVERNMENT & PUBLIC SERVICE
TEXAS A&M UNIVERSITY

SCOWCROFT INSTITUTE
OF INTERNATIONAL AFFAIRS
THE BUSH SCHOOL OF GOVERNMENT AND PUBLIC SERVICE
TEXAS A&M UNIVERSITY

TEXAS A&M
UNIVERSITY