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Engineered Pathogens and Unnatural Biological Weapons: The Future Threat of Synthetic Biology

John K. Wickiser

Kevin O'Donovan

Michael Washington

Stephen Hummel

Fred J Burpo
john.burpo@westpoint.edu

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FEATURE ARTICLE

The Future Threat of Synthetic Biology

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Gilles de Kerchove

EU Counter-Terrorism Coordinator

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FROM THE EDITOR

The COVID-19 pandemic has renewed concerns over bioterror threats, with Microsoft founder Bill Gates recently warning that a bioterror attack involving a pathogen with a high death rate "is kind of the nightmare scenario" facing the planet. In this month's feature article, J. Kenneth Wickiser, Kevin J. O'Donovan, Lieutenant Colonel Michael Washington, Major Stephen Hummel, and Colonel F. John Burpo assess the potential future threat posed by the malevolent use of synthetic biology. They write that synthetic biology "is a rapidly developing and diffusing technology. The wide availability of the protocols, procedures, and techniques necessary to produce and modify living organisms combined with an exponential increase in the availability of genetic data is leading to a revolution in science affecting the threat landscape that can be rivaled only by the development of the atomic bomb."

The authors, who all serve at, or are affiliated with, the Department of Chemistry and Life Science at the United States Military Academy, note that synthetic biology has "placed the ability to recreate some of the deadliest infectious diseases known well within the grasp of the state-sponsored terrorist and the talented non-state actor" and that "the techniques used to propagate bacteria and viruses and to cut and paste genetic sequences from one organism to another are approaching the level of skill required to use a cookbook or a home computer." They argue that "an effective response to the threats posed by those using synthetic biology for nefarious purpose will require vigilance on the part of military planners, the development of effective medical countermeasures by the research community, and the development of diagnostic and characterization technologies capable of discriminating between natural and engineered pathogens."

In our interview, Gilles de Kerchove, the European Union's longtime Counter-Terrorism Coordinator, speaks to Raffaello Pantucci. Nuno Pinto presents a detailed case study of an alleged Portuguese Islamic State network with strong connections to the United Kingdom that sheds significant light on the foreign fighter recruitment pipeline between Europe and Syria in the last decade. Tomasz Rolbiecki, Pieter Van Ostaeyen, and Charlie Winter examine the threat posed by the Islamic State across Africa based on a study of its attack claims. They write: "As the second half of 2020 unfolds, it is critical that military and counterterrorism policymakers recognize what is at stake in Africa. The Islamic State is not just fighting a low-grade insurgency on the continent; in at least two countries, it has been able to seize and hold territory and subsequently engage in pseudo-state activities."

Paul Cruickshank, *Editor in Chief*

CTC SENTINEL

Editor in Chief
Paul Cruickshank

Managing Editor
Kristina Hummel

CONTACT

Combating Terrorism Center
U.S. Military Academy
607 Cullum Road, Lincoln Hall
West Point, NY 10996
Phone: (845) 938-8495
Email: sentinel@westpoint.edu
Web: www.ctc.usma.edu/sentinel/

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Cover: A picture taken in a laboratory shows a biohazard sticker on the entrance of a room. (Thomas Samson/AFP via Getty Images)

Engineered Pathogens and Unnatural Biological Weapons: The Future Threat of Synthetic Biology

By J. Kenneth Wickiser, Kevin J. O'Donovan, Michael Washington, Stephen Hummel, and F. John Burpo

Recent developments in biochemistry, genetics, and molecular biology have made it possible to engineer living organisms. Although these developments offer effective and efficient means with which to cure disease, increase food production, and improve quality of life for many people, they can also be used by state and non-state actors to develop engineered biological weapons. The virtuous circle of bioinformatics, engineering principles, and fundamental biological science also serves as a vicious cycle by lowering the skill-level necessary to produce weapons. The threat of bioengineered agents is all the more clear as the COVID-19 pandemic has demonstrated the enormous impact that a single biological agent, even a naturally occurring one, can have on society. It is likely that terrorist organizations are monitoring these developments closely and that the probability of a biological attack with an engineered agent is steadily increasing.

The COVID-19 pandemic has demonstrated that significant biological threats can and will emerge from nature without warning, demonstrating that a single viral strain can have a profound impact on modern society. It has also demonstrated that infectious diseases can rapidly spread throughout a population without human engineering making them the ideal substrates from which to develop engineered weapons. Viruses and bacteria have been used as weapons for millennia.[1] Historically, biological weapons were derived from natural sources, such as anthrax from herbivores and domesticated animals, and smallpox from rodents. Those pathogenic organisms that were found to be suitable for weaponization were cultured directly from the environment; they were then isolated, purified, stored, propagated,[a] and used to fill biological munitions.[2] The most recent of example of this was the production and stockpiling of numerous agents by the biological weapons program of the former Soviet Union. In this program pathogens were selected for specific characteristics directly from the natural environment, propagated, and stored for later use.[3] While these pathogens have evolved in nature for the purpose of persisting, they are not optimized for maintenance, storage, and deployment in a military setting. Consequently, while biological agents have not been widely employed as strategic or tactical weapons by state or non-state actors, there are some examples of their use in conflicts. The most significant of these is the well-documented use of crude bacteriological agents by the Japanese army against China during the Second World War.[4]

Recently, the convergence of advances in computer science, engineering, biological science, and chemistry have made it pos-

Dr. J. Kenneth Wickiser is a Professor of Biochemistry and the Associate Dean for Research at the United States Military Academy (USMA) and has extensive experience working on engineered and natural genetic switches in bacteria and biomarkers in human clinical studies. He earned his PhD in Molecular Biophysics and Biochemistry from Yale University and completed his postdoctoral research training at Rockefeller University in the Laboratory of Molecular Neuro-oncology.

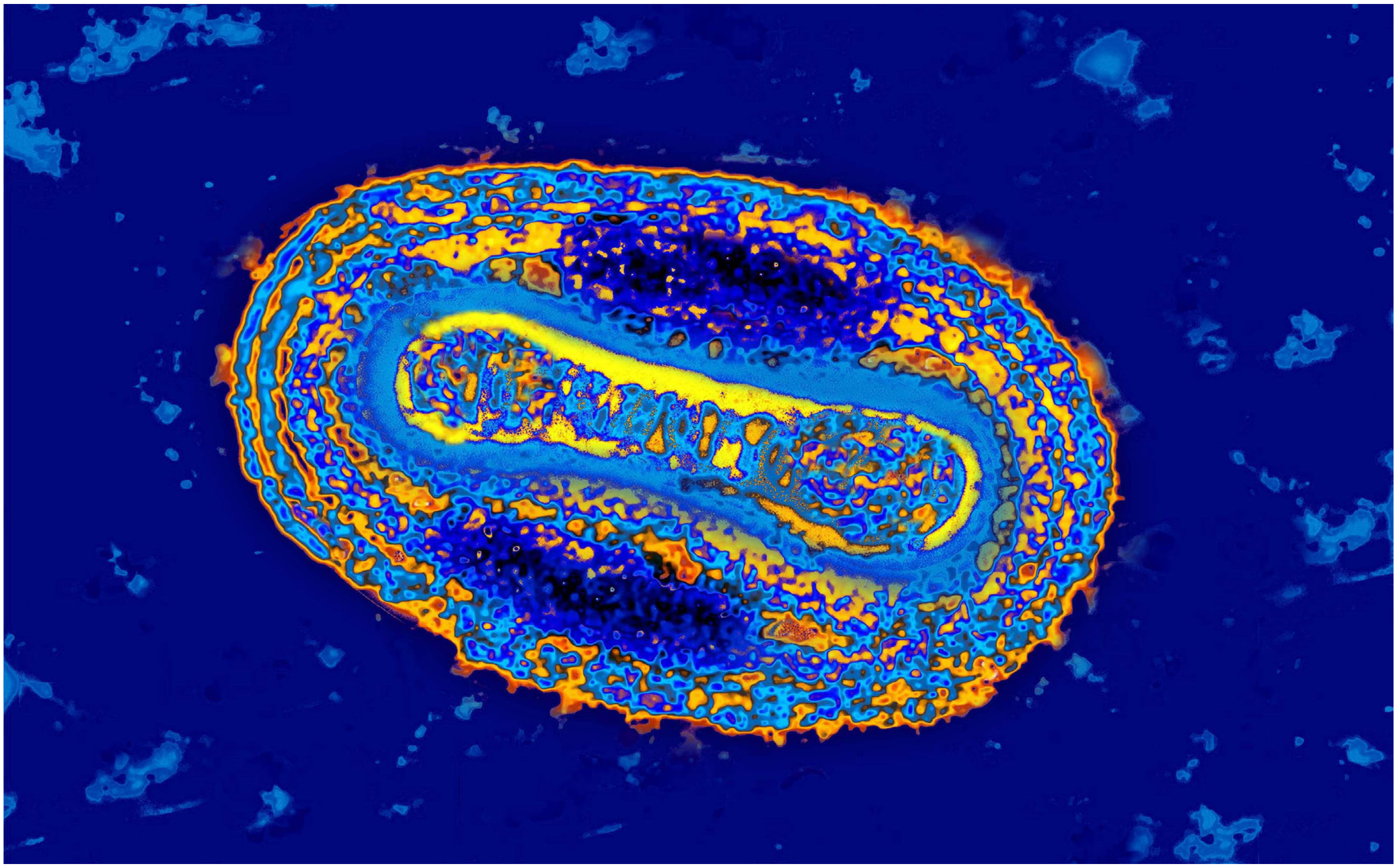
Dr. Kevin J. O'Donovan is an Associate Professor in the Department of Chemistry and Life Science at USMA with expertise in neural development and axon regeneration. He earned his PhD in Neuroscience from the Johns Hopkins University, did his postdoctoral work at Rockefeller University, and was faculty at the Burke Neurological Institute before moving to USMA.

LTC Michael Washington currently serves as an Assistant Professor in the Department of Chemistry and Life Science at USMA. He has a PhD in Emerging Infectious Disease with an emphasis in Immunology from the Uniformed Services University of the Health Sciences.

MAJ Stephen Hummel is currently a PhD student in the Biology Department at Boston College. Previously, he served in both Iraq and Afghanistan and as a USAREUR CBRN Plans Officer, an Assistant Professor in the Department of Chemistry and Life Science at USMA, a Nuclear Operations Officer on a Nuclear Disablement Team, and most recently as the Deputy, Commander's Initiatives Group at 20th CBRNE Command.

COL F. John Burpo currently serves as the Head of the Department of Chemistry and Life Science at USMA. As an artillery officer, he served in airborne, armor, and Stryker units with humanitarian, peacekeeping, and combat operational deployments. He also served as the Deputy Commander-Transformation for the 20th CBRNE Command. He has a Sc.D. in Bioengineering from the Massachusetts Institute of Technology.

a Propagation of bacteria means to provide nutrients so that the bacteria can reproduce and be maintained as a viable entity.



Electronic Microscope X150000, Variola (Smallpox) virus (BSIP/UIG via Getty Images)

sible to engineer living systems to optimize growth and increase pathogenicity (the propensity to cause disease). This interdisciplinary approach to providing novel biological functionality has had a positive impact on the biotechnological and biopharmaceutical industries. At the same time, these engineered bacteria and viruses can be co-opted for belligerent purposes. Indeed, the use of designer biological weapons could theoretically give a state or non-state actor an asymmetric advantage over an adversary that favors conventional weapons.

Synthetic biology (SynBio) is the scientific discipline that encompasses all aspects of the engineering of biological systems.[5] Beginning with the discovery of the chemical structure of DNA[b] in the 1950s, SynBio tools such as recombinant DNA technology[c] and genome editing tools[d] have developed at a fast pace as the fundamental molecular mechanisms underlying biology are discovered. These SynBio tools are lowering the education, training, cost, time, and equipment threshold required to modify and employ pathogenic organisms as biological weapons. The asymmetric threat posed by biological weapons will continue to increase as new tools and techniques are developed and as terrorist organizations become aware of and inspired by the society-wide economic, emotional, and government-destabilizing impacts caused by the COVID-19 pandemic.[e] Indeed, it can be argued that the total cost of this pandemic—including the loss of life and the stress to the economy—could be rivaled only by the deployment of an atomic bomb. Therefore, developments in SynBio should be continually monitored and reassessed within the context of technological change and its capacity to shift the geopolitical paradigm. In this article, the authors describe how biological systems' modular nature makes them amenable to engineering, the recent advances in synthetic biology, the impact of synthetic biology on the threat landscape, and the potential policy responses to the maturation of biotechnology in general, and synthetic biology in particular. This article has been developed using both primary and secondary literature sources recently published in peer-reviewed scientific papers.

b Deoxyribonucleic acid (DNA) is the genetic material in all living organisms whereas RNA can serve as the genetic material for some viruses.

c Recombinant DNA technology refers to widely employed techniques to manipulate DNA segments and, in the process, modify genes and organisms.

d Genome editing tools refers to several now widely utilized enzyme toolkits—e.g., TALEN (transcription activator-like effector nuclease) and CRISPR (clustered regularly interspaced short palindromic repeats)—to precisely modify viral, bacterial, and eukaryotic genomes to achieve a desired outcome.

e Juan Zarate, who served as Deputy National Security Advisor for Combating Terrorism from 2005 to 2009, recently noted in this publication that "the severity and extreme disruption of a novel coronavirus will likely spur the imagination of the most creative and dangerous groups and individuals to reconsider bioterrorist attacks." Paul Cruickshank and Don Rassler, "A View from the CT Foxhole: A Virtual Roundtable on COVID-19 and Counterterrorism with Audrey Kurth Cronin, Lieutenant General (Ret) Michael Nagata, Magnus Ranstorp, Ali Soufan, and Juan Zarate," *CTC Sentinel* 13:6 (2020).

The Inherent Modularity of Biological Systems

Modularity is essential to the purposeful engineering of biological systems to create weapons. In general terms, modularity refers to the ability to replace or update a piece of equipment. For example, a set of interchangeable parts is what allows an individual to modify or optimize a complex piece of equipment, such as a home computer or an automobile. The genetic material (DNA or RNA) of any organism contains all of the information required for its proper functioning and is comprised of many modular components. Specific genes can be removed from one pathogen and inserted into another as a means of altering the activity of the recipient.[6] This modularity enables a measure of predictability of the effects on the complex network of genes when employing molecular engineering methods to insert a foreign gene into a host genome. For example, the modular nature of the non-pathogenic vaccine-strain of the poliovirus genome is what enables it to acquire pathogenicity genes from other viruses and revert to a pathogenic state (horizontal gene transfer).[7] It has been postulated that molecular modularity evolved as a natural genomic tool, allowing biological systems to rapidly adapt to changing environmental conditions.[8] While the process of a virus acquiring pathogenicity has been occurring naturally through horizontal gene transfer for as long as these biological agents have existed, the use of SynBio molecular engineering tools provides a pathway to purposeful and precise changes in genomes on fast timescales not found in nature. Modular genes can be mixed and matched to increase the speed with which organisms can evolve and adapt, producing the type of functionality required of a given environment and providing the organism with a selective advantage compared to its competitors. There is currently an effort underway to identify the minimal genome necessary for the survival of the simplest strain of bacteria.[9] Once it is determined what genes are necessary for survival and reproducibility in bacteria, it may be possible to swap-out non-essential genes for genes conferring any number of desired characteristics. An increased understanding of the modularity of biological systems will impact the fields of biosecurity and military medicine by providing a "molecular toolkit" which can be used for peaceful purposes or by adversaries to design and manufacture biological agents.

Synthetic Biology Enables the Design and Development of Biological Weapons

In 1997, a team of accomplished scientists within a group known as the JASON[f] group met to discuss the future of biological warfare.[10] They identified six emerging biological threats that needed to be monitored by military planners and strategists: (1) the development of binary weapons,[g] (2) the construction of designer genes, (3) the use of gene therapy as a weapon, (4) the development of viruses that evade the immune response of the host, (5) the use of viruses that can move between insects, animals, and humans, and (6) the development of designer diseases. These threats were once considered to be futuristic and speculative. Advances in SynBio techniques, however, have moved many of these predicted contingencies from the realm of speculation into the realm of reality. As the molecular engineering techniques of the synthetic biologist become more robust and widespread, the probability of encountering one or more of these threats is approaching certainty.

"As the molecular engineering techniques of the synthetic biologist become more robust and widespread, the probability of encountering one or more of these threats is approaching certainty."

The extent and impact of SynBio on future state-on-state conflicts and terrorist violence will increase as the tools and techniques of this discipline continue to mature and diffuse throughout the scientific community, as well as among the novice citizen-scientists in the do-it-yourself biology labs that have emerged around the world in recent years.[11] The ability to produce custom-designed bacterial and viral pathogens will enhance the ability of hostile state and non-state actors to develop and deploy relatively inexpensive and efficient biological weapons. Additionally, some of these weapons will likely be engineered with increased pathogenicity, environmental stability,[h] and the ability to withstand the shock of the rapid changes in temperature and pressure that may accompany delivery by explosive warhead. Below are several notable 21st century examples where scientists employed emergent SynBio techniques to rediscover or recreate pathogenic microorganisms.

In 2002, scientists from the State University of New York at Stony Brook chemically synthesized the complete poliovirus genome, highlighting the transformative potential of SynBio.[12] While this effort was accomplished by experienced professional scientists over the course of years in well-equipped laboratories, the playbook is now freely available and the tremendous advances in molecular engineering techniques since then have only reduced the complexity of this once-monumental effort. This achievement was followed by the first chemical synthesis of a much larger bacterial genome in 2008 and the development of an entirely synthetic cell in 2010.[13] The use of SynBio tools has endowed scientists with the ability to purposefully dissect the inherently complex series of coupled chemical reactions that compose fundamental cellular metabolism. These networks of reactions can be engineered using modular genes and molecular tools to enhance synthetically produced organisms with desired biochemical properties.[14] Significantly, by combining standard molecular and cellular laboratory techniques with cellular selection (or evolution) strategies, which are accomplished daily by high school and college students in biology classes and research competitions across the world, detailed knowledge of the nature of

f Founded in 1960, JASON is a group of American scientists dedicated to producing reports of value to the U.S. federal government. The organization's relationship with the Department of Defense changed in 2019 when the Assistant Secretary of Defense (Research & Engineering) (ASD (R&E)) cut ties with it. "Update: Legislator asks Pentagon to restore contract for storied Jason science advisory group," *Science Magazine*, April 11, 2019.

g Binary biological weapons are organisms or biological products that are non-lethal when separated and only become lethal upon mixing the separate components together.

h Environmental stability refers to the ability of a pathogen to survive outside of a host where it is exposed to UV light, reactive oxygen species, and other elements that could degrade or destroy the pathogen.

each chemical reaction is not required to achieve the desired outcome for the engineered biological agent.[15]

In 2005, a group of researchers from the U.S. Centers for Disease Control (CDC), the Mount Sinai School of Medicine, the Armed Forces Institute of Pathology, and the Southeast Poultry Research Laboratory reconstructed the 1918 pandemic influenza virus. This was a particularly striking example of how the modular nature of a viral genome could be used to manufacture a pathogen.[16] The reconstruction was performed by first determining the genomic coding sequences of the virus from lung tissue specimens obtained from pandemic victims who were preserved in permafrost.[17] The relevant DNA sequences were then inserted into a set of circular DNA strands known as plasmids, which were subsequently used to infect host human kidney cells. As predicted, fully functional and replicative viral particles emerged from the kidney cells. The pathogenicity of the reconstructed virus was evaluated in mice, ferrets, and non-human primates, and it was found that the 1918 influenza strain was significantly more lethal than modern strains.[18] It produced severe damage to the lungs, it stimulated an aberrant immune response, and it led to the development of high viral titers (levels of virus) in both the upper and lower respiratory tracts.[19] The reconstruction procedure was conducted in a standard molecular biology laboratory setting, and all the materials needed for the construction of this viral particle are present in many university biology laboratories. The methods that were employed are not beyond the means of the talented amateur and therefore not beyond the means of a dedicated, well-resourced terrorist organization.[20]

More recently in 2018, a small Canadian research group was successful in constructing infectious horsepox virus directly from genetic information obtained solely from a public database for the relatively modest sum of $100,000 in U.S. currency.[21] Horsepox is a genetically distinct relative of the now extremely rare smallpox virus. Smallpox was once a highly feared pandemic disease that either permanently disfigured or ended the lives of millions of people worldwide. The same techniques used to construct horsepox can easily be adapted to construct smallpox with a minimal investment of time and money. SynBio has therefore placed the ability to recreate some of the deadliest infectious diseases known well within the grasp of the state-sponsored terrorist and the talented non-state actor.

The International Genetically Engineered Machine (iGEM) competition provides another striking example of the ease by which genetic engineering can be mastered at the undergraduate level.[22] The iGEM competition was initiated by a group of non-biologist researchers at the Massachusetts Institute of Technology (MIT) who wanted to develop and use synthetic biology tools similar to the way electrical engineers use a breadboard[i] and a set of interchangeable and scalable parts such as resistors and capacitors. These scientists and engineers wanted to develop an easy-to-use system to genetically engineer bacteria by swapping genetic parts around to create unique genes and gene sets that produce novel and useful proteins and to force the organisms to perform tasks that they normally would not accomplish. At its heart, the iGEM competition is an agreed-upon set of molecular engineering techniques and a large library of DNA parts that are accessed by the competitors in their bid to create novel cellular tools, biological circuits, and gene products. As the competition progressed over the years, the participants have taken advantage of nascent SynBio tools to improve the complexity of their designs. Today the sophistication of the high school and undergraduate student research projects has matched that of many highly trained personnel who were working in advanced laboratories less than a decade ago. While it has been claimed that the young student competitors directed by a responsible Principal Investigator are not truly independent,[23] it is important to note that the iGEM competition has a loose minimum age requirement,[24] so the high school students are inexperienced with lab procedures and have only a thin understanding of biology at the outset of the competition. Yet by the time these students defend their work at the Jamboree (international science fair held each fall), they have either attained a full understanding of the work or they are judged poorly. iGEM has helped democratize the science and engineering of biological systems for the benefit of mankind. The organization has dedicated significant resources to biosafety, bioethics, and biosecurity efforts[25] drawing from the expertise of leaders in academia and industry. Defense leaders need to take note of the spread of this information because both state and non-state actors with nefarious intent can benefit from the good work of these young scientists.

A case study in the dual-use nature of these activities can found in the 2017 winning project. A team from Lithuania created a tool to improve the rate of inheritance of genetically altered sequences throughout generations of microbes. While this tool may eventually be used by thousands of researchers for peaceful purposes, there is a possibility that it could be harnessed to develop engineered biological weapons by rapidly altering the genomes of the starting material. The Lithuanian team was just one of 295 teams competing that year. There were 125 from Asia, 84 from North America, 74 from Europe, 10 from Latin America, and two from Africa. This competition and these technologies are truly global in nature, and while they are intended for peaceful and mutually beneficial purposes, the science and tools created may be manipulated by those with bad intentions.[26]

The Impact of Synthetic Biology on the Threat Landscape

The threat landscape is constantly evolving as advances are made in materials, computational power and speed, and the bioengineering of viruses and cells. While there are challenges to weaponizing a biological system, including contending with the analog nature of biology, the advantages of bioweapons compared to relying on conventional explosives or nuclear weapons include their self-generating properties and the ease in creating a binary weapon allowing for safe production and assembly.[27] Thus, it is possible for an unsophisticated adversary to design biological weapons with enhanced virulence and infectivity. As already noted, one challenge to weaponizing a biological system is the analog nature of most metabolic circuitry (compared to the digital signals governing much of the electronic world). Further challenges are the presence of significant noise in the normal operation and response of these biochemical circuits and the difficulty in optimizing synthetic pathways while retaining the viability and reproducibility of the living system.[28] However, the use of natural selection techniques in the lab preclude the need for detailed rational design so that an amateur scientist member of a terrorist organization can simply employ SynBio tech-

i A breadboard is a base platform used in custom-designing electronic circuits. Resistors, capacitors, and other electrical engineering components are plugged into the breadboard to form a circuit to perform a desired function.

"The techniques used to propagate bacteria and viruses and to cut and paste genetic sequences from one organism to another are approaching the level of skill required to use a cookbook or a home computer."

niques for a large number of cells and select those that perform to the desired effect.

Cells are the fundamental unit of life containing all the molecular architecture required to engage in metabolism (transfer energy), grow, adapt to their environment, respond to stimuli, reproduce, and evolve. Under the right conditions, cells will replenish and increase their numbers if there exists enough food and space. A scientist who has engineered a cell with novel properties can keep producing that system by simply feeding the cells, clearing out the waste products, and harvesting cells when desired. Cell-based systems have co-evolved with viruses that target very specific cell types using lock-and-key-like receptor proteins on both the virus and cell. While viruses rely on cells to reproduce, it is standard lab practice to produce significant quantities of viruses using their cognate cells [cells taken over by the viruses] as hosts. Unlike conventional weapons, biological weapon development requires all the work up front and then the system will reproduce and provide the bad actor with a supply of the weapon as long as the growth-permissive environment is maintained.

SynBio also facilitates the development of binary biological weapons. Although the design and production of binary biological weapons may have been difficult in the past, the ability to engineer and 'boot-up' entire genomes has revolutionized the process. With modern synthetic biology tools, an undergraduate student could conceivably engineer and produce two related, non-lethal viruses that are individually harmless. However, following host infection with the two viruses, mixing of the two strains allows for a full restoration and production of highly infectious, pathogenic viruses. Importantly, such genetic mixing has also been documented in nature wherein two or more non-pathogenic poliovirus vaccine strains can recombine to form pathogenic recombinants.[29] Thus, it is not difficult to imagine a non-state actor developing binary weapons consisting of components stored separately for safety in transport and then brought together in a biological munition prior to delivery.

The advances in SynBio have not occurred in isolation. The increase in the understanding of biological systems and the development of the tools of molecular biology that occurred in the late 20th and early 21st centuries were paralleled by commensurate developments in automation, engineering, computer science, and information technology. In particular, the ease of scaling-up the production of bacteria and viruses has increased exponentially in recent decades due to the availability of inexpensive instrumentation for the growth, or culture, of biological material, and the development of standardized reagents such as bacterial growth media by commercial laboratories.[30] Once the purview of scientists with doctorates in microbiology, genetic engineering is practiced every day in high schools and colleges across the world. The instructions, or protocols, for these processes are freely available on the internet and in undergraduate microbiology and cell biology textbooks. Many of the difficulties faced by early microbiologists and cell biologists in the culturing of microorganisms have lessened; indeed, many advanced placement biology programs in high schools across the United States include blocks of instruction on culturing and engineering *Escherichia coli* (*E. coli*) and other benign bacterial species.[31] Some authors have argued that the skills and abilities developed over the course of a career in the biological sciences are not available to the amateur and that this may hinder the widespread use of synthetic biology for the development of biological weapons.[32] While this argument may be true for some of the more complex techniques in biochemistry and molecular biology, the techniques used to propagate bacteria and viruses and to cut and paste genetic sequences from one organism to another are approaching the level of skill required to use a cookbook or a home computer. A vast amount of knowledge would be necessary to describe in detail the biochemistry, genetics, and physiology of baker's yeast, but anyone with a cookbook, flour, yeast, and sugar can bake bread. Similarly, understanding the algorithms necessary to manipulate images on a computer screen requires expert knowledge, but anyone can point at an icon with a mouse to open it. As technology increases and spreads, those with a simple home laboratory system may be able to manipulate bacterial and viral genes without expert training or years of experience.

Policy Responses to the Potential Threats Posed by Synthetic Biology

An effective response to the threats posed by those using synthetic biology for nefarious purpose will require vigilance on the part of military planners, the development of effective medical countermeasures[j] by the research community, and the development of diagnostic and characterization technologies capable of discriminating between natural and engineered pathogens. A 2002 biological warfare counterproliferation study identified six key basic biological research areas that should be emphasized to protect against the threat: human genomics; immunology and the development of methods for the boosting the immune response; bacterial and viral genomics; bacterial and viral assay development;[k] vaccine development; and the development of novel antiviral agents and antibiotics.[33] A continued research and education effort within the Department of Defense will be required to develop and maintain expertise in each of these areas.

The rapid availability of experienced civilian and military personnel is a prerequisite for effective incident response. Therefore, training and education in SynBio, biological engineering, and related disciplines should be emphasized and funded. Many organizations already exist to meet the threat of natural, man-made, and weaponized biological material. These organizations include the Defense Threat Reduction Agency (DTRA); the Chemical and

j According to the U.S. government, "Medical countermeasures, or MCMs, are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, or a naturally occurring emerging disease." "What are Medical Countermeasures?" fda.gov, accessed August 27, 2020.

k Viral and bacterial assay development refers to generating new methods for the rapid detection and identification of viral and bacterial pathogens.

"The wide availability of the protocols, procedures, and techniques necessary to produce and modify living organisms combined with an exponential increase in the availability of genetic data is leading to a revolution in science affecting the threat landscape that can be rivaled only by the development of the atomic bomb."

Biological Center (CBC) at Edgewood, Maryland; the Defense Advanced Research Projects Agency (DARPA); the Biomedical Advanced Research and Development Authority (BARDA); the National Institutes of Health (NIH); the Centers for Disease Control (CDC); and United Stated Department of Agriculture-Agricultural Research Service (USDA-ARS) within the United States. The World Health Organization (WHO), a specialized organization within the United Nations, and several research and response organizations in other countries have historically served similar purposes. Each of these entities deal with systems rooted in the natural world, and while some organizations restrict their focus to naturally occurring threats, they all deal—in one way or another—with the extraordinary pace of technology development unique to the biomedical community. Every advancement in biomedicine is dual-use, and so it is incumbent upon those privileged to work in the scientific field to predict the ways that these technologies might be used for nefarious purpose and to develop the technologies and systems necessary to undermine the efforts of those who might use these unique biological entities as weapons.

Conclusion

SynBio is a rapidly developing and diffusing technology. The wide availability of the protocols, procedures, and techniques necessary to produce and modify living organisms combined with an exponential increase in the availability of genetic data is leading to a revolution in science affecting the threat landscape that can be rivaled only by the development of the atomic bomb. As the technology improves, the level of education and skills necessary to engineer biological agents decreases. Whereas only state actors historically had the resources to develop and employ biological weapons, SynBio is changing the threat paradigm. The economic and social impact of COVID-19 has highlighted the broad and lasting effects that can result from the spread of a novel biological agent. This collective experience has increased the chance that terrorist organizations will attempt to use biological agents to asymmetrically attack the United States and its allies. This possibility should be anticipated and planned for at all levels of government. CTC

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