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Research Article

Biology's Misuse Potential

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Abstract: The international community has laid down clear red lines about the use of biology to enhance national armaments. Advances in bioscience and biomedicine are, however, significantly eroding technological barriers to acquiring and using biological weapons. This article describes recent scientific trends and analyses their security implications. Three emerging fields of research that have particularly high potential for misuse are considered in more detail: potentially pandemic pathogens, synthetic biology and neurobiology. It is argued that continued efforts are required in multilateral, national and scientific spheres to strengthen the red lines and to foster responsible science.

Keywords: Biological weapons, potentially pandemic pathogens, synthetic biology, neurobiology, disarmament, non-proliferation, biosecurity, responsible science.

The Misuse of Biology

The international community has laid down clear red lines about the misuse of biology. The two biological cornerstones of the rules of war are the Biological Weapons Convention (BWC) and the Geneva Protocol. Together, they prohibit the development, production, stockpiling and use of biological weapons. Signed in 1972 and 1925 respectively, the two treaties have incorporated a mix of legal, diplomatic and political elements into the structure of international norms that are increasingly difficult to dismantle, ignore or override.

Scientific advances in biology and biomedicine are, however, significantly eroding technological barriers to acquiring and using biological weapons. This article describes recent trends in bioscience and analyses their security implications. Three emerging fields of research that have particularly high potential for misuse are then considered in more detail. Continued efforts are required in multilateral, national and scientific spheres to strengthen the red lines. Crucial areas to strengthen are (1) the international legal framework regulating biological weapons, (2) the BWC science and technology review procedure and (3) norms of transparency and public accountability.

Trends in Bioscience

There are four frequently cited security-related trends in the biological sciences:[1]

1. The *increasing pace of advances* in bioscience. Rapid advances on multiple fronts within the life sciences pose challenges for tracking and assessing that progress in terms of what it means for biological weapons development. It is difficult to establish which areas to monitor, to anticipate what new combinations of advances will result from progress in multiple fields and to expand the types of expertise required to assess new developments.
2. The *increasing convergence* of biology and biomedicine with chemistry, engineering, mathematics, computer science and information theory. These developments are, for instance, enabling both the chemical synthesis of biological molecules and the biological synthesis of chemicals. Where components are significantly different from existing biological systems, or where inorganic materials mimic biological function and thereby have biological effect, the mechanisms of action of weapons might not be clearly "biological" or "chemical" – blurring the domains of the Biological and Chemical Weapons Conventions.
3. The *increasing diffusion of capacity* in biology and biomedicine around the world, particularly in emerging economies such as China and India. There are also increasing international collaborations, not only among researchers in scientifically developed countries and between researchers in developed and developing countries, but among regional networks and increasingly among scientists within developing countries.

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[1] "The Biological and Toxin Weapon Trends Symposium," IAP Global Network of Science Academies conference, 13–15 September 2015; and "Assessing the Implications of Advances in Science and Technology for the BTW 2016," IAP Global Security Working Group Meeting, 16 September 2015, Polish Academy of Sciences, Warsaw, Poland (a summary is available at iapbwg.pan.pl); Organisation for the Prohibition of Chemical Weapons, *Convergence of Chemistry and Biology: Report of the Scientific Advisory Board's Temporary Working Group* (The Hague: OPCW, 2014); National Research Council, *Life Sciences and Related Fields: Trends Relevant to the Biological Weapons Convention* (Washington, DC: National Academies Press, 2011); "The Biological Weapon Convention Seventh Review Conference," 5–22 December 2011, Geneva, "New Scientific and Technological Developments Relevant to the Convention" (BWC/CONF.VII/INF.3).

4. The *increasing opening up of science* with new tools like wikis, blogs and microblogs altering how information is gathered, handled, disseminated and accessed; and amateur communities, scientific outreach and educational toys increasing access to hardware for wet work in the life sciences. A large number of multinational suppliers now produce kits containing reagents, enzymes and step-by-step instructions to conduct many of the basic lab techniques life scientists use, including nucleic acid and protein expression, purification, detection and analysis. Commercial services are also available for tasks like sequencing, DNA and protein synthesis, microarray construction, mass spectrometry analysis and others. The availability of smaller, more automated and easier to use bioinstrumentation also facilitates the performance of lab research.

Impact on Bioweapons Potential

The trends in bioscience are making it easier to develop biological weapons. The most recent assessment by the global network of science academies concludes that technological barriers to acquiring and using bioweapons have been significantly eroded over the last five years.[2]

It is now easier to acquire both natural and synthetic pathogens and to enhance and optimize them for specific purposes, including for use in biological weapons. It is also easier to produce biological agents. Critical lab equipment such as reaction vessels (including those currently covered by control lists) can now be fabricated using 3D printing technology. The increased use of biosynthesis and bio-based production, scaffolds and "biopharming" has accelerated the speed and yield of biological agent production. In addition, the space and resources required for biologics production has decreased and the physical size of production equipment has been drastically reduced. Less space and time are now required for scale up, and it is easier to conceal nefarious activities. Advances in nanotechnology and aerobiology, along with the use of chemical cofactors to increase uptake and formulations to improve absorption from the gastrointestinal tract, are making the dispersal and delivery of biological agents easier, and increasing antimicrobial resistance is complicating the administration of prophylactics. In short, the global network of science academies argues that scientific advances "could facilitate almost every step of a biological weapons programme."[3]

While the risks of small-scale bioterrorism attacks are real and present, the likelihood that scientific advances will be used to "enhance" these attacks is relatively low – many of the cutting-edge developments are expensive and

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2 "The Biological and Toxin Weapon Trends Symposium."

3 Ibid.

complicated to acquire and deploy successfully.[4] Instead, the most significant security threat from the misuse of advances in the biological sciences comes from sophisticated biological attacks from professional and well-resourced institutions like national militaries.[5] This is backed by the historical record of both biological weapons development and bioterrorism incidents.[6]

The international community has committed itself—through the BWC and the Geneva Protocol—to take precautions that scientific developments are not misused. Over the life span of the BWC, there has been no state party use of biological weapons, and most experts agree that the potential for state use is very low.[7] There are various reasons cited for this: biological weapons are not considered "good" weapons; it is difficult to produce sophisticated and reliable biological weapons and it is not politically viable to use them because the norm against biological warfare—encoded in law through the BWC—is exceptionally strong.

Yet, while the norm against biological weapons is strong, and the potential for state use is very low, a blanket rejection of the bioweapons threat from states is dangerous. It cannot be assumed that biological weapons will not be used in the future, and the likelihood that they will be used is not zero. Although twentieth-century military use of biological weapons was envisioned primarily as strategic and came to rest on delivery by bomb, missile or large area spray, there were also scientists and military planners who seriously entertained other ideas, such as tactical use and sabotage. One must not necessarily think of biological weapons today as in the twentieth century. Biological warfare can, for instance, be compared with cyber warfare in that the victim may know it has been attacked, but not by whom, or it may not know or be able to prove that it has been attacked at all – the question of who is to blame might not even be asked. The silent and invisible nature of biological weapons could, for instance, make them highly potent means for weakening the legitimacy of enemy regimes within their own populations, or for just keeping them busy. In the "best case" scenario it may be possible to actually get rid of enemy regimes without anyone recognizing foul play.

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4 Filippa Lentzos, "The Risk of Bioweapons Use: Considering the Evidence Base," *BioSocieties* 9:1 (2014): 84–93; Catherine Jefferson, Filippa Lentzos, and Claire Marris, "Synthetic Biology and Biosecurity: Challenging the 'Myths','' *Frontiers in Public Health* 2:115, http://dx.doi.org/10.3389/fpubh.2014.00115; "The Biological and Toxin Weapon Trends Symposium."

5 Iris Hunger, *et al.*, "The Future of Biothreat Governance," in *Biological Threats in the 21st Century*, ed. Filippa Lentzos (London: Imperial College Press, forthcoming); Gigi Kwik Gronvall, "The Threat of Misuse," in *Biological Threats in the 21st Century*; Lentzos, "The Risk of Bioweapons Use"; Jefferson, "Synthetic Biology and Biosecurity."

6 Lentzos, *Biological Threats in the 21st Century*.

7 Hunger, "The Future of Biothreat Governance"; Kwik Gronvall, "The Threat of Misuse"; Lentzos, "The Risk of Bioweapons Use."

While the use of biology will not have military utility in all contemporary conflicts, the possibility that it might have military utility in a small subset of conflicts, along with the erosion of technological barriers to acquire and use bioweapons, makes it imperative that the bioweapons threat from states is dedicated a greater part of the collective vigil and that effective preventive measures are developed.

Emerging Research Areas with High Misuse Potential

Various efforts have been made, particularly in the United States, to characterize biological research with high misuse potential.[8] Examples identified of such "dual use research of concern" include experiments that increase capacity: to manipulate the pathogenicity, virulence, host-specificity, transmissibility, resistance to drugs, or ability to overcome host immunity to pathogens; to synthesize pathogens and toxins without cultivation of microorganisms or using other natural sources; to identify new mechanisms to disrupt the healthy functioning of humans, animals and plants; and to develop novel means of delivering biological agents and toxins. Early high-profile experiments that raised concern aimed to make mousepox more deadly, synthesize poliovirus from scratch and reconstruct the extinct 1918 flu virus.[9] More recently, entire fields of biological research have raised concern. These include potentially pandemic pathogens, synthetic biology and neurobiology.

Potentially Pandemic Pathogens

The security community's attention was drawn to virology in 2011 when it transpired that two leading influenza laboratories, under the leadership of Ron Fouchier and Yoshihiro Kawaoka, had conducted experiments to determine whether H5N1 avian influenza, or "bird flu," could become readily transmissible between mammals and still remain highly virulent. H5N1 does not spread easily from human to human, but it kills more than 50 percent of people infected.

[8] For example: National Research Council, *Biotechnology Research in an Age of Terrorism* (Washington, DC: National Academies Press, 2004); National Science Advisory Board for Biosecurity, *Proposed Framework for the Oversight of Dual-Use Life Sciences Research* (Washington: NSABB, 2007); *US Government Policy for Oversight of Life Sciences Dual Use Research of Concern* (March 2012); and *US Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* (September 2014), available at http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-concern.

[9] Ronald J. Jackson, *et al.*, "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology* 75 (2001): 1205–1210; Eckard Wimmer, "The Test-tube Synthesis of a Chemical Called Poliovirus. The Simple Synthesis of a Virus Has Far-reaching Societal Implications," *The European Molecular Biology Organization Reports – Special Issue* 7 (2006): S3–S9; Terrence M. Tumpey, *et al.*, "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus," *Science* 310 (2005): 77–80.

Fouchier and Kawaoka were concerned that H5N1 could become readily transmissible between mammals and still remain highly virulent, and the virologists were worried that governments were not taking the threat seriously enough. In the summer of 2011, both groups passed H5N1 among ferrets as an animal model and discovered that a mutated H5N1 virus that was air transmissible could indeed emerge. In other words, what they had developed in their labs was a novel, more contagious strain of the bird flu virus that could spread to humans and other mammals.

Kathleen Vogel describes the unfolding story in some detail.[10] In essence, Fouchier submitted his paper to the prestigious journal *Science*; Kawaoka favored *Nature.* In September 2011, Fouchier revealed his findings at a scientific meeting in Malta: his mutated virus was airborne and as efficiently transmitted as the seasonal flu virus. In public, he commented that "[t]his is a very dangerous virus."[11] His funder, the National Institutes of Health (NIH), grew concerned about the security implications if the results were published: could bioterrorists (or indeed national militaries) adopt similar "gain-of-function" techniques to increase the pathogenicity and transmissibility of viruses? The NIH asked the US National Science Advisory Board on Biosecurity (NSABB), the government advisory body on dual use life science research oversight, to review both papers. By the end of November 2011, NSABB recommended that the papers' general conclusions highlighting the novel outcome be published, but that the manuscripts not include a methods section with details of how to carry out the experiments.[12] This was the first time NSABB had recommended restrictions on scientific publications in the life sciences.

The safety and security implications of the experiment garnered a great deal of media coverage. *The New York Times* ran an editorial with the unambiguous headline, "An Engineered Doomsday," arguing that the modified flu virus could kill tens or hundreds of millions of people if it escaped the lab or was stolen. Proponents of gain-of-function research, on the other hand, argued that such studies help understand influenza transmission and can assist public health researchers in detecting an impending flu pandemic and preparing vaccines.

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10 Kathleen M. Vogel, "Expert Knowledge in Intelligence Assessments: Bird Flu and Bioterrorism," *International Security* 38 (Winter 2013–2014): 39–71.

11 Quoted in Katherine Harmon, "What Really Happened in Malta This September When Contagious Bird Flu Was First Announced," *Scientific American* (blog), 30 September 2011, http://blogs.scientificamerican.com/observations/what-really-happened-in-malta-this-september-when-contagious-bird-flu-was-first-announced/. In late September, an article in *New Scientist*, a weekly science and technology news magazine, first reported that Fouchier's modified H5N1 virus was lethal to the ferrets in the experiments – see Debora MacKenzie, "Five Easy Mutations to Make Bird Flu a Lethal Pandemic," *New Scientist*, 26 September 2011, www.newscientist.com/article/mg21128314-600-five-easy-mutations-to-make-bird-flu-a-lethal-pandemic/.

12 U.S. Department of Health and Human Services, "Press Statement on the NSABB Review of H5N1 Research," *NIH News*, 20 December 2011, http://www.nih.gov/news/health/dec2011/od-20.htm.

In January 2012, a prominent group of virologists wrote to NSABB to reconsider. NSABB published an explanation and defense in both *Nature* and *Science*. The primary reason for the unprecedented redaction was that "publishing these experiments in detail would provide information to some person, organization, or government that would help them develop similar mammal-adapted influenza A/H5N1 viruses for harmful purposes." By mid-February 2012, the World Health Organization (WHO) convened a technical consultation on the Fouchier and Kawaoka experiments.[13] Both scientists attended and presented new data related to the manuscripts. The WHO meeting agreed a temporary moratorium was needed to address public concerns. Fouchier and Kawaoka were to revise their manuscripts with new details and submit them to NSABB for a second security review.

Fouchier backtracked. He then stated that his group's mutated virus was not lethal when inhaled by ferrets and would not spread "like wildfire" through the air; rather, transmission would not be easy. He also said that most of the ferrets that had contracted the virus via aerosol transmission had hardly become sick, and none had died. He clarified, however, that the mutated virus did cause disease when injected in very high concentrations into the lower respiratory tract of ferrets.

In the end, NSABB recommended publication of Kawaoka's revised paper in full, but some board members continued to have concerns about Fouchier's paper. They felt it was "immediately and directly enabling" for terrorism (and biological warfare) and a "pretty complete cookbook" for causing harm. By May 2012 Kawaoka's paper was published in *Nature*. Fouchier's paper followed suit and was published in *Science* in June 2012.

Following the voluntary moratorium, work resumed on potentially pandemic pathogens in 2013, with scientists in multiple labs adding new properties to biological agents and creating modified variants of viruses that do not currently exist in nature. Within a short space of time, however, new papers on human-made H5N1 and other dangerous flu strains rekindled concerns about potentially pandemic pathogens created in the lab – in part because a series of lab accidents and breaches at the NIH and Centers for Disease Control and Prevention (CDC) raised questions about safety at high-containment labs. On 17 October 2014, the US government stepped in, imposing a federal funding pause on potentially pandemic pathogen experiments and announcing an extended deliberative process, which is still on-going.[14]

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[13] World Health Organization, "Technical Consultation on H5N1 Research Issues – Consensus Points," 16–17 February 2012, http://www.who.int/influenza/human_animal_interface/consensus_points/en/index.html; and World Health Organization, "Public Health, Influenza Experts Agree H5N1 Research Critical but Extend Delay," 17 February 2012, www.who.int/mediacentre/news/releases/2012/h5n1_research_20120217/en/index.html.

[14] "U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS

Synthetic Biology

Many have viewed the controversy around potentially pandemic pathogens as a test case of what is to come when the still-emerging field of "synthetic biology" begins to mature. Synthetic biology aims to engineer biology, or "to design and engineer biologically based parts, novel devices and systems, as well as redesigning existing, natural biological systems."[15] The aspirations and pace of advance in synthetic biology have raised a number of security concerns. Some of these are legitimate, others less so.[16]

One of the main trepidations raised in the political and security discourse is that synthetic biology is making it easier to create dangerous pathogens from scratch. The claim is that well-characterized biological parts can be easily obtained from open-source online registries and then assembled, by people with no specialist training outside professional scientific institutions, into genetic circuits, devices and systems that will reliably perform desired functions in live organisms. This narrative rests on misleading assumptions about synthetic biology.

The narrative does not reflect the situation facing people with no specialist training who work outside professional scientific institutions, nor does it even reflect current realities in academic or commercial science laboratories: academic and commercial researchers are still struggling with every stage of the standardization and mechanization process. More than a decade in, the translation of proof-of-concept designs into real-world applications is still a major challenge. As recently noted in the scientific literature surveying progress in synthetic biology, "The synthetic part is easy, it's the biology part that's confounding."[17] However, even if the engineering approaches offered by synthetic biology make processes more systematic and more reproducible, skills do not become irrelevant, and all aspects of the work do not become easier. Further, importantly, "easier" does not mean "easy." Aeronautical engineering provides a useful analogy: planes are built from a large number of well-characterized parts in a systematic way, but this does not mean that any member of the general public can build a plane, make it fly and use it for commercial transportation. Thus, advances in synthetic biology do not make it easier for just anybody to engineer biological systems, including dangerous ones.

Viruses," 17 October 2014, http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf (accessed 20 January 2016).

[15] The Royal Academy of Engineering, *Synthetic Biology: Scope, Applications and Implications* (London: The Royal Academy of Engineering, 2009).

[16] Filippa Lentzos, Catherine Jefferson, and Claire Marris, "The Myths (and Realities) of Synthetic Bioweapons," *The Bulletin of Atomic Scientists*, 18 September 2014, http://thebulletin.org/myths-and-realities-synthetic-bioweapons7626; Jefferson, *et al.*, "Synthetic Biology and Biosecurity."

[17] Timothy S. Gardner, *et al.*, "Synthetic Biology: From Hype to Impact," *Trends in Biotechnology* 31:3 (2013): 123–125, quoted in *Nature Reviews Microbiology* 12:5 (2014): 309.

This leads to a second concern raised in the political and security discourse: that synthetic biology is breaking down the expert and non-expert boundary. In other words, the growth of a do-it-yourself biology (DIY bio) community, along with DNA synthesis becoming cheaper and easily outsourced, could make it easier for terrorists to obtain the basic materials to create biological threat agents. However, the link between synthetic biology and DIY bio, and the level of sophistication of the experiments typically being performed, is grossly overstated. DIY biologists typically comprise a wide range of participants of varying levels of expertise, ranging from complete novices with no prior background in biology to trained scientists who conduct experiments in their own time. Some DIY biologists work in home laboratories assembled from everyday household tools and second-hand laboratory equipment purchased online; the majority conduct their experiments in community labs or "hackerspaces." Studies of scientific practice in community labs demonstrate the challenges that amateur biologists face while trying to successfully conduct even rudimentary biological experiments. These amateurs particularly lack access to the shared knowledge available to institutional researchers, highlighting the importance of local, specialized knowledge and enculturation in laboratory practices.

DNA synthesis is one of the key enabling technologies of synthetic biology. There are now a number of commercial companies that provide DNA synthesis services, so the process can be outsourced: a client can order a DNA sequence online and receive the synthesized DNA material by post within days or weeks. The price charged by these companies has greatly reduced over the last 20 years and the service is now within reach of a broad range of actors. This has led to routine statements suggesting that it is now cheap and easy to obtain a synthesized version of any desired DNA sequence.

There are, however, several challenges that need to be taken into account when assessing the potential for misuse that inexpensive DNA sequencing might enable. First, simply ordering online the full-length genome sequence of a small virus (or those of larger bacteria) is not currently possible. The alternative, ordering short DNA sequences and assembling them into a genome, requires specialist expertise, experience and equipment available in academic laboratories, but not easily accessible to an amateur working from home. As noted by NSABB, while the "technology for synthesizing DNA is readily accessible, straightforward and a fundamental tool used in current biological research … the science of constructing and expressing viruses in the laboratory is more complex and somewhat of an art. It is the laboratory procedures downstream from the actual synthesis of DNA that are the limiting steps in recovering viruses from genetic material."[18] Again, it is the biology and not the synthetic part that is complicated, and DNA synthesis requires extensive training in basic molecular-biology techniques, such as ligation and cloning, including

[18] National Science Advisory Board for Biosecurity (NSABB), *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* (Bethesda, MD: National Institutes of Health, 2006), 4.

hands-on experience that is not "reducible to recipes, equipment, and infrastructure."[19]

A third frequently voiced concern is that synthetic biology may enable radically new pathogens to be designed and synthetic biology could be used to enhance the virulence or increase the transmissibility of known pathogens, creating novel threat agents. Again, it is not that simple. The mousepox and bird flu (H5N1) experiments are frequently cited to demonstrate how dangerous new pathogens could be created. However, assessments of this threat tend to overlook a salient fact: in both these experiments, the researchers did not actually design the pathogens. With respect to H5N1, researchers had indeed been trying to design an air-transmissible virus variant for some time, without success. The ferret experiment was set up as an alternative approach, to see whether natural mutations could generate an air-transmissible variant. The researchers had no influence on the specific mutations induced. In the mousepox experiment, researchers inserted the gene for interleukin-4 into the mousepox virus to induce infertility in mice and serve as an infectious contraceptive for pest control. The result—that the altered virus was lethal to mice—was unanticipated by the researchers; namely, it was not designed.

Moreover, some of the lessons that came out of the extensive Soviet program to weaponize biological agents involve the trade-offs between improving characteristics that are desired in the context of a bioweapons program, such as virulence, and diminishing other equally desired characteristics, such as transmissibility or stability. Pleiotropic effects—that is, when a single gene affects more than one characteristic and genetic instability—are common in microorganisms. While it is too simple to say that increased transmissibility will always be associated with reduced virulence, this is often the case for strains produced in laboratories. As other commentators have noted,

> To create … an artificial pathogen, a capable synthetic biologist would need to assemble complexes of genes that, working in union, enable a microbe to infect a human host and cause illness and death. Designing the organism to be contagious, or capable of spreading from person to person, would be even more difficult. A synthetic pathogen would also have to be equipped with mechanisms to block the immunological defenses of the host, characteristics that natural pathogens have acquired over eons of evolution. Given these daunting technical obstacles, the threat of a synthetic 'super-pathogen' appears exaggerated, at least for the foreseeable future.[20]

In sum, it is likely, in the near future, that synthetic biology will make it possible to create dangerous viruses from scratch. However, while synthetic biology is "deskilling" the science, it is not doing this to the extent that people with

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19 Kathleen Vogel, "Bioweapons Proliferation: Where Science Studies and Public Policy Collide," *Social Studies of Science* 36:5 (2006): 676.

20 Jonathan B. Tucker and Raymond A. Zilinskas, "The Promise and Perils of Synthetic Biology," *The New Atlantis* 25 (2006): 38.

no specialist training operating outside professional scientific institutions can assemble biological parts into circuits, devices and systems that will reliably perform desired functions in live organisms, and even professionals will have a hard time creating radically new pathogens or synthetic "super-pathogens." The most significant misuse risks from synthetic biology do not, therefore, arise from bioterrorists, but from professional and well-resourced institutions like national militaries.[21]

The most recent figures available on US trends in synthetic biology research funding indicate that two thirds of the $200 million invested in 2014 came from the Department of Defense (DoD) or its research agency DARPA.[22] From an international security perspective, the extensive influx of military funding can be perceived as threatening to analysts in other countries following these developments. The DoD declared just over $655 million on national biodefense research in 2014; synthetic biology research would appear, then, to make up about a fifth of the biodefense budget.[23]

Funding in other countries is also increasing rapidly. In 2014, the UK and European Commission investment in synthetic biology made up nearly 30 percent of total Euro-American synthetic biology funding.[24] Some of this European funding is also defense-related. In the UK, for instance, which spends twice as much as the European Commission on synthetic biology, the field is one of five emerging technologies identified by the Ministry of Defence as having the most potential for national security. It is crucial that military research in this field remain as transparent as possible to ensure there is confidence that the fine line between permitted defense work and non-permitted offensive work does not become muddled.

Neurobiology

Neurobiology is another emerging area with high misuse potential.[25] Military interest in neurobiology mainly relates to enhancement, involving efforts to

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21 Jefferson, *et al.*, "Synthetic Biology and Biosecurity."

22 "US Trends in Synthetic Biology Research Funding" (Washington DC: Wilson Center, 2015), available at http://www.synbioproject.org/site/assets/files/1386/final_web_print_sept2015.pdf (accessed 20 January 2016).

23 US Department of State, *Confidence-Building Measure Return Covering 2014: Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*, submitted to the United Nations on 15 April 2015, available at www.unog.ch/80256EDD006B8954/(httpAssets)/4631533639F1D34AC1257E380046511B/$file/BWC_CBM_2015_USA_Public.pdf (accessed 20 January 2016).

24 *US Trends in Synthetic Biology.*

25 National Research Council, *Emerging Cognitive Neuroscience and Related Technologies* (Washington, DC: National Academies Press, 2008); The Royal Society, *Neuroscience, Conflict and Security* (London: The Royal Society, 2012), http://royalsociety.org/policy/projects/brain-waves/society-policy/ (accessed 20 January 2016); Tim Requarth, "This is Your Brain. This Is Your Brain as a Weapon," *Foreign Policy*, 14 September 2015, http://foreignpolicy.com/2015/09/14/this-is-your-brain-this-is-your-

improve the operational performance of national forces, and to degradation, involving efforts to diminish the performance of the enemy.

There are various ways neurobiology might confer performance advantages in a military context.[26] One of these is through the use of neuropharmacological agents to enhance cognitive functions like perception, attention, learning, memory, language, thinking, planning and decision-making. There has been significant military interest in cognitive enhancement. Modafinil—discovered by French scientists in the 1970s and since licensed as a common treatment for narcolepsy, but which has also been shown to enhance working memory and executive functioning in non-sleep-deprived individuals—is thought to have been used by the French army in Iraq in the early 1990s to combat fatigue and by the US Air Force in 2003 to improve alertness and concentration during long flights.[27] Military interest in sustaining and enhancing brain function and performance continues, demonstrated by the large number of DARPA projects devoted to this goal.[28] Neurobiology has also been identified by the UK Ministry of Defence as an important and rapidly developing field with potential relevance to defense and security.[29]

Degrading enemy performance through neurobiology has focused particularly on the development of incapacitating biochemical agents, or so-called non-lethal weapons. Incapacitants generally target the central nervous system to reduce alertness and, as the dose increases, produce sedation, sleep, anesthesia and death; these are distinct from riot control agents, such as tear gas, which cause local irritation to eyes, skin and the respiratory tract, and have long been used by police forces around the world.

Despite international agreement on the Chemical Weapons Convention (CWC) in 1993, there are indications of continued interest in incapacitating biochemicals among a number of states. The CWC bans the use of all toxic chemicals as weapons in war, but it does not prevent states from using toxic chemicals such as "tear gasses" for law enforcement and domestic riot control. Though the range of permitted toxic chemicals is restricted by types and quantities consistent with law enforcement purposes, some states have interpreted this law enforcement exemption to extend to incapacitating chemical agents.

Concern over state interest in incapacitants was heightened following a case of actual use by the Russian Federation in October 2002.[30] A group of armed Chechen separatists raided the Dubrovka Theater in Moscow and took approximately 800 hostages. They demanded the withdrawal of Russian troops from

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brain-as-a-weapon-darpa-dual-use-neuroscience/ (accessed 20 January 2016).

[26] Royal Society, *Neuroscience, Conflict and Security*, Chapter 4 "Performance Enhancement."

[27] Ibid.

[28] Ibid., 6 and 35–36.

[29] Ibid.

[30] Neal Davison, *"Non-Lethal" Weapons* (London: Palgrave Macmillan, 2009), 12–13.

Chechnya and threatened to kill the hostages if their demand was not met. Russian Special Forces disseminated an incapacitating chemical agent—reportedly a mixture of derivatives of the synthetic opiate fentanyl—through the ventilation system of the theater, rendering both the hostages and the hostage-takers unconscious. Shortly afterwards, the troops stormed in, killing all of the hostage-takers and bringing the siege to an end. 129 of the hostages died from use of the incapacitant and many others suffered serious and long-term injury. The refusal of the Russian Special Forces to disclose the identity of the incapacitating agent at the time of the siege prevented emergency medical personnel from responding effectively. There are also indications that the Russian Federation has continued research into incapacitating biochemical agents following this event.[31] The US, too, has had a long-standing interest in incapacitating biochemical agents.[32]

As with synthetic biology, current investments in the field of neurobiology are considerable. The European Commission-funded Human Brain Project, established in 2013, has an estimated € 1 190 million price tag over ten years.[33] The US equivalent, the BRAIN Initiative, was also launched in 2013, as a public-private partnership with about $ 100 million in the President's Fiscal Year 2014 Budget.[34] Approximately half of the US funding comes from the DoD and DARPA.[35]

Developments in anesthetics and neuropharmacological drug research, coupled with developments in drug delivery, are making precise manipulation of neurological function increasingly feasible and there are concerns about the risk incapacitants pose to the international ban on chemical weapons. Particularly relevant to the BWC are bioregulators and their synthetic derivatives.[36] Bioregulators are specialized chemicals that carry messages from the brain to the rest of the body, between neurons or within cells, and modulate the function of the target cell or organ. They are naturally occurring biochemical compounds, such as hormones, neurotransmitters or signaling factors that control vital homeostatic systems like temperature, sleep, blood pressure, heart rate and immune response. However, while they occur naturally in the body at low concentrations, they can be extremely toxic at higher concentrations or if the molecular structure is changed. While many bioregulators tend to be unstable in aerosolized form and are rapidly broken down by enzymes in the body, engineered variants could be synthetized, and considerable developments have

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31 Royal Society, *Neuroscience, Conflict and Security*.

32 Ibid.

33 *The Human Brain Project: A Report to the European Commission* (Lausanne: The HBP-PS Consortium, 2012), https://www.humanbrainproject.eu/documents/10180/17648/TheHBPReport_LR.pdf (accessed 20 January 2016).

34 The White House, "Fact Sheet: BRAIN Initiative," 2 April 2013, www.whitehouse.gov/the-press-office/2013/04/02/fact-sheet-brain-initiative (accessed 20 January 2016).

35 Ibid.

36 Royal Society, *Neuroscience, Conflict and Security*, 49–50.

taken place in the *in vitro* synthesis of bioregulators for pharmaceutical purposes. Aerosol technology is also advancing rapidly and is already in use to deliver effective inhaled drug therapy for the treatment of disease.[37] Propellant metered-dose inhalers, dry powder inhalers and nebulizers are used to deliver drugs directly to the lungs, promoting rapid absorption into the blood. Advances in research into inhalation based methods of drug and vaccine delivery may also offer potential applications in the delivery of bioregulators. With advances in neurobiology, it may eventually become possible to develop modified bioregulators that can be disseminated over large crowds of people and that will cross the blood-brain barrier to induce states of sleep, confusion, placidity, fear, addiction or aggression.[38]

The European Human Brain Project has made an explicit commitment not to take funds from the military or to develop applications with military objectives.[39] It also has an "ethics and society" component that aims "to explore the project's social, ethical and philosophical implications, promote engagement with decision-makers and the general public, foster responsible research and innovation by raising social and ethical awareness among projects partners and ensure that the project complies with relevant legal and ethical norms."[40] To date, there are no such equivalent efforts underway in the American program.

Fostering Responsible Science

Pandemic pathogens, synthetic biology and neurobiology are three fields of bioscience that have particularly high potential for misuse. There are, of course, also other areas of research with misuse potential. While the BWC and Geneva Protocol provide a legal and normative frame, continued efforts are required in multilateral, national and scientific spheres to strengthen the red lines about the misuse of biology. Crucial areas to strengthen are (1) the international legal framework regulating biological weapons, (2) the BWC science and technology review procedure and (3) norms of transparency and public accountability.

1. Strengthen the international legal framework regulating biological weapons

Article IV of the BWC commits Member States to both prohibit and prevent biological weapons activities. This means they are not only obliged to respond to prohibited activities but also to stop them from happening. An important mechanism of enforcement is criminalization.

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37 Ibid., 50.

38 Ibid.

39 https://www.humanbrainproject.eu/documents/10180/538356/HBP_FPA_PRINT_29-07-14.pdf (accessed 20 January 2016).

40 https://www.humanbrainproject.eu/discover/ethics (accessed 20 January 2016).

Criminalization at the international level, as an international crime or war crime, provides the strongest and most effective measure for individual liability for violations of international law. Neither weaponization of biology nor use of biological weapons has been comprehensively criminalized in the Rome Statute of the International Criminal Court (ICC).[41] The use of "poison or poisoned weapons," a prohibition first codified in 1899, is stipulated as a war crime.[42] Another paragraph is derived from the 1925 Geneva Protocol, making the use of asphyxiating, poisonous or other gases and all "analogous liquids, materials or devices" a war crime. The provision notably does not refer to the use of bacteriological weapons, which is prohibited in the Geneva Protocol, and makes no further reference to either chemical or biological weapons. Some commentators maintain that biological weapons are nevertheless included – relying on the premise that the term "poisoned weapon" was the first prohibition of both chemical and biological weapons.[43] However, most commentators conclude that biological weapons are not included in the Rome Statute.[44] The absence of a provision explicitly making the use of biological weapons a war crime under the Rome Statute is a striking gap in the international legal regulation of biological weapons and must swiftly be rectified.

2. Strengthen the BWC science and technology review procedure

Developments in science and technology play a fundamental role in the continued relevance of the BWC. These developments are, however, highly technical in nature, and the process through which BWC Member States identify science and technology developments and assess their implications must reflect this. Whilst the current intersessional work program of the treaty provides limited time and space to comprehensively deal with science and technology challenges, addressing these issues primarily within the policy work of the treaty further complicates efforts. More time and a different environment are needed.

A dedicated technical body such as an open-ended working group with its chair and vice chairs appointed for several years at a time would help insulate technical discussions from policy considerations. The group should be expert-

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41 Use of biological weapons will in many cases be covered by *other* provisions, such as Rome Statute of the International Criminal Court, article 8(2)b) (xx), prohibiting methods and materials of warfare that are of a nature to cause superfluous injury or unnecessary suffering, or are inherently indiscriminate, if and when an annex has been agreed to the provision. See Filippa Lentzos and Cecilie Hellestveit, "The Categorical Ban on Bioweapons: Challenged by Synthetic Biology?" in *High-Tech War and International Law*, ed. Guglielmo Verdirame, *et. al.* (forthcoming).

42 Rome Statute of the International Criminal Court, Article (2)(b)(xvii).

43 Michael Cottier,"War Crimes: Article 5," in *Commentary on the Rome Statute of the International Criminal Court, Observers' Notes, Article by Article*, ed. Otto Triffterer, 2nd edition (Oxford: Hart Publishing, 2008), 413.

44 Markus Wagner, "The ICC and its Jurisdiction – Myths, Misperceptions and Realities," in *Max Planck Yearbook of United Nations Law*, vol. 7, ed. Armin von Bogdandy and Rüdiger Wolfrum (Boston: Brill, 2004), 460.

led and inclusive, open to all signatories and to academies of science and other relevant organizations that could help in making these collective judgments. This would help ensure that discussions remain technical, that the conclusions reached are factual and that any recommendations made have a sound scientific basis. Clear topics for consideration include potentially pandemic pathogens, synthetic biology and neurobiology, as well as the increasing convergence of biology with other fields, particularly with chemistry, and the implications of this for arms control and international law.

The group should meet separately from the Meeting of Experts in a restructured intersessional process and feed its recommendations to the member states directly. It needs to be adequately resourced and a scientific secretary should be appointed to provide continuous professional support. It should have a mandate as an organ of the Convention carrying forward the science and technology review function envisaged from the start in Article XII, but on a more systematic basis.

3. Strengthen norms of transparency and public accountability

The life science community plays a crucial role in sustaining biological disarmament and non-proliferation. The health of the BWC rests on individual life scientists and the systems and safeguards where they work, on an awareness of dual-use problems and structures to encourage responsible behavior, on biosafety and biosecurity and all the elements of good practice for those engaged in relevant science and technology. Key to this is education. Not education in the sense of implanting facts and knowledge and instructing people in what to think, but education in the sense of eliciting understanding and teaching people how to think for themselves. It is about equipping life scientists with sensitivity to the risk that the knowledge gained from the experiments and research they carry out can be misused.

Education, however, is not an end in itself; in this case, it would rather provide an avenue by which to affect behavior. The ultimate aim is that life scientists behave responsibly, as well as provide a layer of oversight about the work carried out in their laboratories and in their specialized fields. The rapid pace and nature of change in the life sciences today means that anyone other than practicing life scientists is hard-pressed to have the sort of current, technical expertise required to provide adequate oversight. Education and awareness-raising efforts must, therefore, go hand-in-hand with the development of supportive structures and professional practices for flagging any suspect activities or worrying advances in the field.

Although life scientists may feel autonomous in their work, most remain susceptible to larger institutional and political pressures. Whether in academic medical centers, pharmaceutical companies or government facilities, they work in settings where norms, professional responsibilities and missions are bureaucratically defined. However, these scientific communities also respond to national norms concerning transparency and public accountability. BWC signatories must therefore view national implementation of the treaty within states, and transparency and compliance assurance mechanisms between states, as vehicles for promoting norms of transparency and public accountability and for fostering responsible science.

About the author

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