ADVANCES IN SCIENCE AND TECHNOLOGY IN THE LIFE SCIENCES

IMPLICATIONS FOR BIOSECURITY AND ARMS CONTROL

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40 | UNIDIR UNITED NATIONS INSTITUTE FOR DISARMAMENT RESEARCH

ACKNOWLEDGEMENTS

Support from UNIDIR core funders provides the foundation for all of the Institute's activities. This research is part of UNIDIR's Security and Technology Programme, which is funded by the Governments of Germany, the Netherlands, Norway and Switzerland, and by Microsoft. Design and layout by Eric M Schulz.

The authors would also like to acknowledge Gigi Gronvall, Piers Millet, Alisha Anand, Giacomo Persi Paoli, John Borrie and Renata Dwan for their inputs.

CITATION

Warmbrod. K. L., Revill. J., Connell. N. 2020. "Advances in Science and Technology in the Life Sciences: Implications for Biosecurity and Arms Control". Geneva, Switzerland: UNIDIR. https://doi.org/10.37559/SecTec/20/SandT

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LIST OF ABBREVIATIONS AND ACRONYMS

AI	artificial intelligence
BWC	Biological Weapons Convention
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats

GLOSSARY

Artificial intelligence: A field of computer science in which computers demonstrate advanced functions often associated with human intelligence such as problem solving.

Bioeconomy: The segment of the economy involving the use or creation of products using biotechnology tools or biological materials.

CRISPR (clustered regularly interspaced short palindromic repeats): A biotechnological tool for editing genetic information. CRISPR systems are commonly used for DNA modification.

Gene drive: A type of biotechnology with the potential to make directed and highly specific modifications to the genetic make-up of an entire population.

Machine learning: A subset of artificial intelligence whereby computer algorithms learn and improve iteratively and automatically as they access data.

Megabase: A unit of measure for the length of nucleic acid molecules. One megabase has 1 million nucleotides (see nucleic acid).

Nanotechnology: Manipulation of materials at the atomic or molecular level, below the size of 100 nanometers.

Nanoparticle: A particle of matter smaller than 100 nanometers in diameter.

Nucleic acid: A molecule in living organisms carrying the organism's genetic information, which stores information and encodes the proteins that make cells and organs function. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are types of nucleic acid. Nucleic acids are made up of nucleotides including adenine, thymine, cytosine, guanine, and uracil.

Nucleic acid/DNA modification: The process of modifying nucleic acid by adding, removing, or changing the order of nucleotides. Modification can be accomplished with different molecular biology tools, such as a CRISPR system. Nucleic acid modification can affect DNA or RNA and are considered as editing genetic information.

Nucleic acid/DNA sequencing: The process of determining the order of nucleotides in nucleic acid. DNA sequencing refers to the order of nucleotides in DNA while RNA sequencing refers to the order of nucleotides in RNA. Nucleic acid sequencing can be considered as reading genetic information. Sequencing nucleic acids is often used to identify an organism or a specific individual.

Nucleic acid/DNA synthesis: The creation of nucleic acids naturally or synthetically. DNA synthesis occurs naturally in cells during DNA replication by means of enzymes. DNA synthesis can also be performed using molecular biology techniques to create artificial gene sequences. Nucleic acid synthesis can be considered as writing genetic information.

Precision medicine: Customization of treatments and therapy pathways for individual patients based on that patient's genetics, metabolic function, or other factors. Precision medicine makes healthcare decisions based on the unique context of each patient.

Synthetic biology: A field of research that uses molecular tools to create or alter biological systems.

EXECUTIVE SUMMARY

Multiple technologies in the life sciences are advancing and converging to generate considerable potential benefits to society, the global economy, and future generations. However, the same technologies also raise considerable safety and security issues. This report explores the unfolding life sciences landscape over the next decade, paying particular attention to the benefits and security implications posed by key technologies.

This report outlines trends in three broad areas that are facilitating advances in different areas of the life sciences. Specifically, it looks at the growing capacity to read, write and now edit DNA; the development of tools that enable the manipulation of biology at the nanoscale; and the increasing role of big data, machine learning and artificial intelligence. This report outlines how these trends are impacting five different fields of the life sciences: immunology, neuroscience, reproductive technologies, animal and plant agriculture, and infectious disease.

Research and development in these fields is overwhelmingly undertaken for peaceful purposes. However, in the same fields of research there are a number of ethical, legal, safety and security concerns, including concerns that developments in these fields could feed into new forms of biological weapons with different and potentially more damaging effects than those of the past.

Table A. ***Summary of safety and security implications of key fields***

Immunology	Improved understanding of immune response can contribute to improved therapeutics to treat disease; however the same knowledge could be exploited for hostile purposes in new biological weapons systems capable of more effectively overwhelming immune responses.
Neuroscience	Greater understanding of human neurology can advance the treatment of various psychiatric disorders. However, this also potentially expands the range of possible effects of biological weapons to include cognitive, behavioral or neurophysiological modification.
Human genetics and reproductive science	Advances in understanding of human genetics and reproductive science could play a role in treating infertility and genetically inherited disease. However, this technology has raised considerable ethical and safety concerns, in addition to fears that it could be exploited in the development of more sophisticated means of affecting human fertility and genetic inheritance.
Agriculture (plants and animals)	The new field of 'gene drive' technology enables scientists to change inherited characteristics of subsequent generations of a target species of animals or plants. To this end, gene drives have been proposed for a number of functions, including efforts to eradicate the malaria-carrying mosquito population. This too raises ethical and safety concerns, as well as concern over hostile exploitation.
Infectious disease	Research on infectious disease can improve disease response and aid the creation of new and better vaccines for infectious disease. However, some research in this area, such as the synthesis of horsepox virus and the modification of strains of highly pathogenic avian influenza, have raised a number of safety and security concerns.

Table B. *Matrix of possible implications emerging from broad trends impacting upon fields of research*

	DNA (read, write, edit)	Nanotechnology	Artificial Intelligence
Immunology	Engineering immunodeficiency or autoimmunity	Nanocarriers targeting immune system components	Predicting susceptibility
Neuroscience	*In vivo* neural editing	Neurotargeted nanoweapons	Mind control
Reproduction	Deletion or addition of genes to the germ line	Selection of specific spermatozoa	Fertility algorithms
Agriculture	Engineered crop diseases	Detection by engineered sensor-crops	Drones for forecasting and analysis of labour and pests
Infectious Disease	Creation of chimeric organisms	Nanobots for early detection of infection	Pandemic viral genetics

Ongoing developments in DNA editing, nanotechnology and big data/artificial intelligence and their application to the fields identified above could have far-reaching implications in terms of enhancing the creation, production and delivery of biotechnology-derived products. Areas of particular note are identified above in table B.

Advances in the life sciences take place in a wider context of increasing geostrategic tension and the rise of great power competition. This raises the possibility that States or even non-State actors might seek to mobilize the growing capacity of the life sciences with hostile intent.

However, the development of biological weapons is not inevitable. Significant biological weapons will likely require considerable resources and expertise. Moreover, much has already been done to prevent the hostile exploitation of the life sciences, including a patchwork of biosafety and biosecurity initiatives that States and stakeholders have undertaken over the course of the twentieth century, as well as mechanisms to prevent the development of biological weapons. These include Security Council resolution 1540, which is designed to prevent non-State actors, among others, from acquiring, developing or using weapons of mass destruction, and the Biological Weapons Convention (BWC).

The latter is particularly important at this current juncture. The BWC is comprehensive in its scope and covers agents beyond those used in Cold War biological weapons programmes through the intent-based prohibition in article I. However, advances in science and technology have both positive and negative implications for several articles of the BWC. These implications demand further attention from States Parties ahead of the Ninth BWC Review Conference, currently scheduled for late 2021.

INTRODUCTION

Multiple technologies in the life sciences have advanced and, in some cases, converged to provide great potential benefits to society, the global economy, and future generations. One reason for this is that biological research and technology is becoming comparatively cheaper, more accessible, and more widely disseminated. Expanded access will improve global science literacy; more people and resources will enter the global 'bioeconomy'—that portion of the economy that relies on biological materials and data—to foster its development and growth (Johns Hopkins Center for Health Security 2019; National Academies 2020). The bioeconomy is a significant driver of technological advances in the life sciences with an estimated USD 4 trillion impact over the next 10 to 20 years (Chui, Evers, and Zheng 2020).

In addition to rapid advances in biotechnologies, there are significant surges in development and innovation in artificial intelligence, nanotechnologies, miniaturization, robotics and quantum computing. The massive potential changes to human existence that will result from the overlap of the boundaries of the biological, physical, and digital worlds have been termed the 'Fourth Industrial Revolution'. Klaus Schwab, Founder and Executive Chairman of the World Economic Forum, wrote:

> Like the revolutions that preceded it, the Fourth Industrial Revolution has the potential to raise global income levels and improve the quality of life for populations around the world … In the future, technological innovation will also lead to a supply-side miracle, with long-term gains in efficiency and productivity. Transportation and communication costs will drop, logistics and global supply chains will become more effective, and the cost of trade will diminish, all of which will open new markets and drive economic growth. (Schwab 2015)

However, these same technologies also present risks and uncertainties. The history of biological research clearly demonstrates that accidents can and do happen around the world (Klotz 2020). In addition, biotechnology innovations and in some cases the basic technologies themselves can be—and have been—used for harmful purposes by State and potentially certain non-State actors. Finally, these technologies may exacerbate wider societal issues, potentially leading to greater inequality and, for example, disrupting labour markets (Murch et al. 2018).

This report discusses the unfolding life sciences landscape over the next decade and addresses global challenges, such as the spread of infectious diseases and new potential threats related to the development of biological weapons. There are a number of challenges that trends in the life sciences—including so-called 'dual use'—present for multilateral governance and arms control frameworks.

This report first highlights some key developments in DNA sequencing, synthesis and modification;[1] in nanotechnologies; and in artificial intelligence and machine learning. It then illustrates the effect that these three innovative methodologies are having across several areas of research in the life sciences (immunology, neuroscience, reproductive technologies, agriculture, and infectious disease) showing how convergences can lead to both deep knowledge and remarkable innovation in medical, agricultural, and ecological solutions. In so doing, this report makes the case that ethical, safety and security governance is urgently required as we enter the Fourth Industrial Revolution.

1 Nucleic acid sequencing, synthesis and modification methods are now easily and inexpensively available to analyse, create and change the genetic material of most cell types, from virus and bacteria to human.

PART I. THE TECHNOLOGIES

Three broad methodological areas—DNA sequencing, synthesis and modification, nanotechnology and artificial intelligence—have advanced significantly in the past decade. Innovations in these three areas have been augmented by expanded distribution, increased access and decreased cost. The developments have played outsized roles in the Fourth Technological Revolution. Each will be discussed with respect to current and potential future impacts on arms control, disarmament and international security.

Genetic technologies

All genetic technologies ultimately rely on one or more of three core capabilities: genomic sequencing, nucleotide synthesis, and genome editing. Simply put, these technologies allow those with the necessary expertise to respectively read, write and edit DNA. While all of these capabilities have been used in the biological sciences for decades, recent advances have rendered them cheaper, more accurate, and more widely accessible. (Swings et al. 2018)

DNA sequencing

Technical advances in sequencing have allowed the complete sequencing of an entire human genome (i.e., all of an individual's DNA) in a few hours. For comparison, in 2013, there were several thousand human genomes sequenced; in 2019, there were well over 1 million sequenced. Furthermore, the cost of DNA sequencing has plummeted from approximately USD 1 million per megabase[2] in 2003 to USD 0.01 per megabase in 2019. The sequencing of a human genome, costing more than USD 10 million in 2003, now costs about USD 1,000; the time required to sequence a human genome has shrunk from years to overnight (National Human Genome Research Institute 2019). To put this in context, the sequencing of the DNA of the *Bacillus anthracis* strains used in the anthrax attacks in the United States in 2001 cost several thousand USD and took three months to accomplish (Rasko et al. 2011); currently, a typical microbiology researcher can sequence the same size genome for approximately USD 200 in an afternoon. Figure 1 below provides an illustration of the changes in speed and costs of genome sequencing between 1996 and 2014.

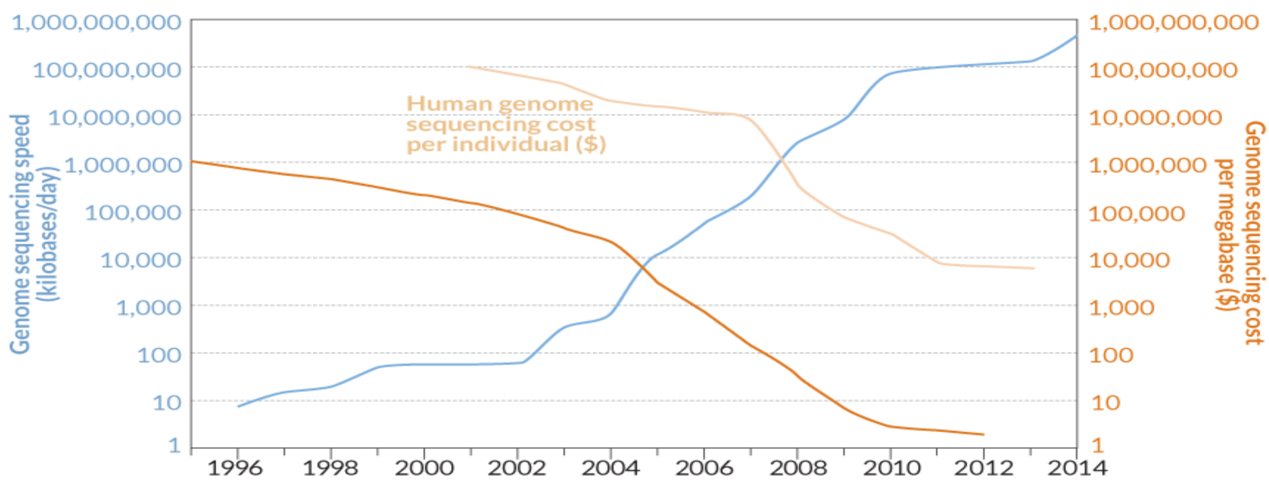


Figure 1. ***Changes in speed and costs of genome sequencing, 1996–2014 (Mole 2014)***

2 A megabase is composed of 1,000 bases, the molecular building blocks of DNA. The human genome comprises three billion nucleotide pairs.

Data accumulated by human genome sequencing will allow healthcare providers to customize treatments for patients with precision medicine and conduct genetic testing to confirm diagnostics. Sequencing the genomes of pathogens will also enable researchers to gain new knowledge about the mechanisms of disease, and may lead to the creation of better therapeutics (Norquist and Swisher 2015, Ostrov et al. 2019).

Massive amounts of sequencing data have permitted increased understanding of the molecular determinants of pathogenesis, that is, the manner of development of a disease. During outbreaks, the ability to sequence multiple genomes of pathogens with rapidity and precision has helped researchers to track transmission and the emergence of outbreaks, to assist with contact tracing, and to determine how specific mutations accumulated during an outbreak might have contributed to the speed of transmission (Wohl, Schaffner, and Sabeti 2016). Sequencing has been used during the COVID-19 pandemic to track the spread of SARS-CoV-2 from country to country and to better understand both transmission chains and the interaction between the virus and animal hosts (Bugembe et al. 2020; Goes de Jesus 2020; Meredith et al. 2020, Zhang and Holmes 2020).

The process of DNA sequencing is continually evolving. Current widespread methods that were developed in the 2010s under the heading 'third generation sequencing' relied on the convergence of microfabrication, high-resolution imaging and advances in computational power (Giani et al. 2020). Single molecules of DNA were directly sequenced without an amplification step. Over time, this approach led to longer segments being analysed in a single run. This development is important as longer segments are more easily assembled by overlapping sequences, and since 2010 larger and larger genomes have been sequenced in their entirety with great rapidity. In addition, nanopore-based technologies enable entire genomes to be read in a non-destructive manner, thus enabling sample conservation, unlike traditional methods that segment the genome (Kono and Arakawa 2019).

Single cell RNA sequencing technology has also been useful for more subtle analyses, such as identifying cell subpopulations or regulatory network components by examining the specific RNAs synthesized in individual cells. The next stage in sequencing technology is 'fourth generation sequencing', also called *in situ* sequencing or massively parallel spatially resolved sequencing. This combines advanced microimaging and next generation sequencing to define tissue heterogeneity. Fourth generation sequencing is useful in diagnostics and basic research to understand how cells control expression of their genes (Ke et al. 2016).

Security Implications of DNA Sequencing

Progress in the area of DNA sequencing has generated considerable benefits, such as rapid diagnosis of disease or analysis of samples of high complexity, leading to maturation of fields such as microbial forensics and personalized medicine. However, this information could also be exploited for the generation of powerful new strains of viruses, with increased transmissibility and virulence (National Academies 2015). In the area of human genetics, there is great concern that exploitation of population sequence analysis could even conceivably lead to the malicious targeting of specific populations or individuals with biological weapons (Khoury, Iademarco, and Riley 2016).

Gene and genome modification

Vast improvements in sequencing technologies have been accompanied by more precise tools and methods to modify genes. While genome modification has been practiced for decades, 2013 ushered in a remarkable new approach: Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR (Hsu, Lander, and Zhang 2014; Jinek et al. 2012). This methodology allows the simple and precise alteration of specific gene sequences through the use of a combination of RNA and proteins. The "guide" RNA directs the DNA-

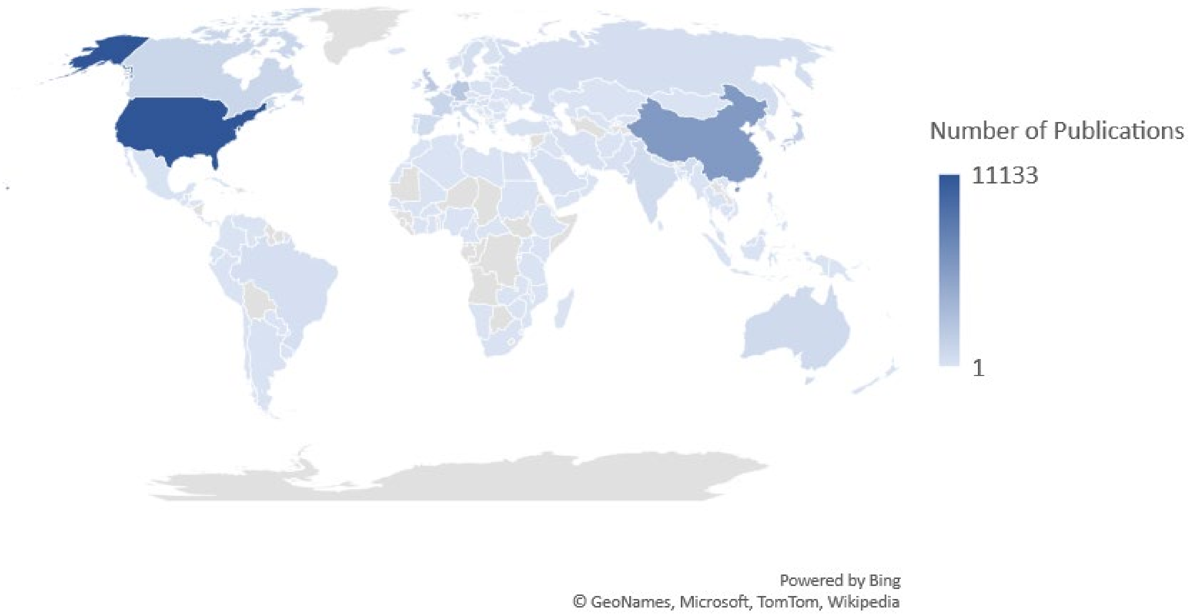


Figure 2. ***Map showing the intensity of scholarly publications referring to CRISPR by country.***[3]

editing proteins to a precise location in a chromosome, where they proceed to delete and/or replace the target site with new DNA sequences. The method was quickly commercialized—within months of the first publications—and is now universally available and applicable to any genome within any kind of cell, whether bacterial, animal or plant. Scientist around the globe are now exploring CRISPR technology, something illustrated in Figure 2 above, which shows the extent of scholarly publications discussing CRISPR.

CRISPR and other gene editing methods have the potential to revolutionize medicine by making it possible for scientists to target specific genes with highly specific modifications (Dominguez, Lim, and Qi 2016). Already, CRISPR has been used for general research purposes allowing rapid and precise alteration of genes in multiple experimental systems. Targeting and editing human genes opens-up the possibility of eliminating certain genetic diseases in individuals (Anzalone et al. 2019; Dunbar et al. 2018; Li et al. 2019). For example, CRISPR gene editing has been used in humans to treat sickle cell disease (Bourzac. K. 2017).

Security implications of gene and genome modification

New gene editing tools can be used to alter plants, animals, and insects, as well as somatic (non-inherited) and germline (inherited) or embryonic cells, including in humans. CRISPR is also used in the development of novel detection, diagnostic and therapeutic tools (Abbott et al. 2020). Moreover, in the burgeoning global bioeconomy, genetically modified organisms have been created to produce high-value compounds, such as therapeutic drugs, in a more flexible and sustainable manner (National Academies 2020). As such, gene and genome modification have positive implications for security.

However, the technology has also raised security concerns (Clapper 2016). Scholars have discussed the rapid advances, ease, and availability of CRISPR in genetic editing technologies as aiding the development of biological weapons by both State and non-State actors. It has been argued that States and non-State actors with limited resources would find the low cost and relatively easy access attractive for the development

3 This map has been produced by the authors using the search term "TITLE-ABS-KEY (crispr)" in the publication database SCOPUS. Of the 26,630 publications with CRISPR in the title, abstract or keywords, 1420 were of an undefined origin.

of biological weapons, while States with greater resources could assign these resources to potentiating existing weapons or creating entirely novel ones (Shwartz 2018).

In addition, the ability of gene editing to create 'gene drives'—in which novel genetic forms of plants, animals or insects can be inserted into and take over entire populations in a few generations—has added a new path to weaponization that could have devastating effects on food supplies or targeted groups of people. The advances in genetic editing, coupled with low cost and wide access, are causing alarm among some Biological Weapons Convention (BWC) analysts and experts (Gerstein 2016).

Gene and genome synthesis

The advent of efficient and affordable genome sequencing has laid the groundwork for the development of gene synthesis technologies that allow scientists to create artificial genes in the laboratory. Scientists have already synthesized entire bacterial genomes (Fredens et al. 2019) and yeast chromosomes (Callaway 2014); within the next decade, it is anticipated that developments in this field will empower scientists to synthetically create the entire human genome (Ostrov et al. 2019). Future directions of biotechnology will include increasing the accessibility and speed and lowering the cost at which nucleic acids can be sequenced, modified, or synthesized at scale, as discussed below. As nucleic acid technologies are further used in basic research, novel therapeutics, industrial enzymes, environmental remediation compounds, and other uses of biotechnology are emerging.

Security implications of gene and genome synthesis

The ability to synthesize nucleic acids quickly and inexpensively has applications in multiple industries. In the health care industry, for example, a novel therapy for cancer and other genetic disorders involves the synthesis of genetic material specific to a patient. Gene synthesis has made rapid development of medical countermeasures possible in the face of outbreaks including the COVID-19 pandemic; for example, some of the candidate novel vaccine platforms under consideration for COVID-19 require de novo[4] gene synthesis (WHO 2020). As such, gene and genome synthesis present a number of positive implications for health security.

However, the ability to more easily synthesize nucleic acids quickly and inexpensively, raises concerns over how this technology could be exploited in the production of biological weapons agents from digital data. To this end, several steps have already been taken to mitigate the risks associated with gene synthesis. The International Gene Synthesis Consortium is a group of international gene synthesis providers that adhere to a set of biosecurity guidelines to prevent the misuse of these technologies (International Gene Synthesis Consortium 2019). These guidelines include screening both sequences and customers, sending ordered products only to verified institutions, and putting safeguards in place to prevent the synthesis of sequences of concern (i.e., sequences that originate from organisms with known or possible pathogenicity for humans).

Unfortunately, Consortium companies comprise only approximately 80% of total global gene synthesis providers. The remaining 20% of synthesis providers could potentially be exploited for the synthesis of harmful products if they do not commit to the screening of sequences and customers. In the future there is a risk that the changing biotech landscape and the growing availability of gene synthesis technologies might further undermine the efficacy of these measures (Kobokovich et al. 2019).

4 De novo, "from scratch"

Nanotech

Nanotechnology encompasses the broad number of tools needed to work at the nanoscale (in the range of 1 to 100 nanometers).[5] The ability to manipulate materials at nanoscale has accelerated in the past decade due largely to multidisciplinary convergence, specifically between physics, chemistry, biology, and engineering. New nanotechnologies are crosscutting, showing growing promise as tools in both basic research and commercial enterprises in and beyond the life sciences. Nanotechnological applications within current and future enterprises have an astonishing range: consumer products, treatment of multiple surfaces, information, communication, heavy and light industry, food and food processing, medicines and medical research, drug delivery, and environmental modification—the electrical, chemical, and mechanical properties of nanoparticles have seemingly limitless applications.

New developments in nanotechnological devices have affected therapeutic, diagnostic, and preventative medical applications. A number of these advances in therapeutic and preventative capabilities stem from the utilization of nanostructures as a device for drug delivery. Inclusion of nanomaterials across multiple military applications is paving the way for both protective materials and devices as well as offensive capabilities (Kosal 2009).

Yet, despite their widespread use, the interactions of engineered nanomaterials with animals and the environment are not well understood (Leins 2020). Indeed, while certain nanoparticles have demonstrated toxicity in the immune system, nanoengineering capabilities can redefine toxicity, direct nanomaterials toward or away from specific components of the immune system, or contribute to reduction of immunotoxicity of existing compounds. Similarly, studies of environmental risk show toxic effects of bioaccumulation all the way out to so-called "gray goo" (the result of uncontrollable replication of nanoscale entities) first proposed by nanotechnology pioneer K. Eric Drexler (1986).

The nanotech revolution in drug delivery has affected the agricultural, health care and pharmaceutical sectors and is estimated to feed into 90% of future products on the drug delivery market. Three of the primary advantages are reducing toxicity, lowering cost and increasing target specificity. Many effective compounds are sitting unused because of delivery setbacks, so the impact of new nano-related delivery systems could be swift, widespread and highly profitable.

For example, one common mechanism for drug delivery is the manipulation of nanomaterials into a structure tailored for the delivery of larger materials to sites that in the past have been hard to reach, such as across the blood–brain barrier (Cena and Jativa 2018). These structures can successfully carry compounds like novel drugs to a specific location, increasing the therapeutic effect (Shende, Kasture, and Gaud 2018). The introduction of nanoparticle delivery systems can increase the effectiveness of some therapeutics while also opening the door to new types of therapeutics that were not feasibly made with other methods.

The increase in interest in the applications of nanotechnology for drug delivery has been accompanied by much vaunted promise and futuristic rhetoric. But lost in the early discussions were public health, safety and the environment. The Woodrow Wilson Center for Scholars released a report in 2008 describing the widespread use of nanoparticles in manufacturing, followed by a Consumer Products Inventory, that has to date cataloged over 1,800 manufacturer-identified products (Davies 2017). In recent years, there has been increased global interest in the concept of 'responsible nanosciences', and academic societies, companies, and international agencies have devised relevant codes of conduct.

5 Leins (2020) illustrates the concept of nanoscale in the following way: "a nano-sized object is to an apple what an apple-sized object is to the Earth. Or to give another example, one nanometre particle could fit approximately 80,000 times across the width of a human hair".

Security implications of nanotechnology

The impact of nanotechnologies on compound delivery and molecular machine design has significant consequences for human health and security. Nanotechnology-based drug delivery platforms could be used for the widespread and effective treatment or prophylaxis against biological weapon agents, including toxins. Among the multiple applications of nanotechnology are advances in the design of molecular machines. In addition to therapeutic applications, these machines can be used for chemical remediation, cryptography, and quantum computing circuitry. The United States Department of Energy's Advanced Manufacturing Office initiated the Atomically Precise Manufacturing programme (US Department of Energy 2018) in 2018 to promote research and development in these security-related fields.

Among the potential risks of advances in technologies and research in nanoparticle drug delivery methods is the use of information on delivery systems for hostile purposes. In theory, the information needed to build unique carriers for therapeutics could also shed light on new methods to disseminate harmful materials. As has been noted in a report from Spiez Laboratory, "it is possible that such nanoparticles could be delivered as aerosols and inhaled into the lungs for uptake through the blood brain barrier. They may therefore be suitable for the targeted delivery of high amounts of toxins or bioregulators" (Spiez 2018).

The specific application of nanotechnology to drug delivery has significant implications for the BWC.[6] In particular, advances in compound delivery highlight the importance of the second clause of article I, which addresses the prohibition of "weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict".

Big Data, Machine Learning and Artificial Intelligence

Machine learning, big data, and artificial intelligence are shaping much of the direction of biotechnological development. The term 'big data' refers to the accumulation and analysis of massive amounts of data collected from all walks of life, and is characterized by the "variety, volume and velocity" of such data (Mooney, Westreich, and El-Sayed 2015). Artificial intelligence (AI) is exhibited by any machine that can interpret data using algorithmic processes similar to those associated with human intelligence (Boulanin 2019). A machine or system that performs AI requires processing and representation of language and knowledge as well as machine learning (i.e., iterative algorithmic processing) (Chiolero and Buckeridge 2020). These fields are converging with an "extraordinary array of other technologies, from cyber to biotechnologies, affective computing and neurotechnologies to robotics and additive manufacturing" (Pauwels and Denton 2020). The convergence of artificial intelligence and machine learning with other emerging technologies means that the large amounts of data being gathered is accessible for pattern analysis and information extraction.

As the ability to sequence and analyse DNA has become easier and faster, huge amounts of information have been generated. For example, traditional genetic studies collected individual pieces of genetic data; as each sample was collected and analysed, it was added to the growing collection of information. With miniaturization, increased accuracy and speed, orders of magnitude more genetic information can be collected and combined into gigantic data sets, analysed for patterns and associations using machine learning to study disease and interventions. As the acquisition of data describing genomes and other biological data becomes more accurate and accessible, the amount of data generated also increases—modern biological studies are dominated by massive data sets.

6 Contributions from the 2016 review conference are not available; however, in 2011, drug delivery was raised in several contributions to the background paper. See BWC/CONF.VII/INF.3, https://www.unog.ch/bwc/7rc; see also BWC/MSP/2018/MX.2/2, annex II, https://documents-dds-ny.un.org/doc/UNDOC/GEN/G18/234/14/pdf/ G1823414.pdf.

In addition to genetic data, machine learning and AI are applied to non-sequenced data, such as images or health records, to solve other health related challenges (Erickson et al. 2017). For example, these kinds of analyses have been useful in the public health response to the COVID-19 pandemic (Dananjayan and Raj 2020). Machine learning has also had significant impact in biotechnology-related engineering and manufacturing (Xu et al. 2020, Yang, Wu, and Arnold 2019). The use of AI and machine learning is also contributing to advances in robotic surgery and drug delivery (Hamet and Tremblay 2017).

Security implications of big data, machine learning and AI

As computing and data collection spreads across fields such as medicine and public health, big data, machine learning, and AI are increasingly used to address a variety of challenges. In public health, big data is generated in large-scale environmental and clinical surveillance programmes. Microbial forensics capabilities are expanding as these technologies advance. Machine learning is already being used in fields such as bioforensics to identify non-natural agents, and agents that may pose a risk (Warmbrod, Montague, and Connell 2020; Vogel 2019). This functions can help address certain security issues.

While one of the benefits of these computational technologies is reduced reliance on humans by increasing speed and potentially reducing error, this is also a risk because it lessens oversight. Algorithms contain their own biases and can also be manipulated and, if not caught, this could result in the creation of dangerous products or cybersecurity weaknesses (Ney et al. 2017).

The manipulation and analysis of huge amounts of genetic data can lead to rapid advancement in our understanding of virulence and pathogenesis, from the side of the pathogen as well as the host. However, access to millions of human genomes—often with directly associated clinical data—means that bioinformaticists can begin to map infection susceptibilities in specific populations. This kind of information could also be used to develop ethnically targeted weapons (ICRC 2004). Machine learning applied to protein engineering has profound implications in terms of identifying possible bioregulators and toxins that could be used for hostile purposes (Xu et al. 2020).

PART II. THE FIELDS

These three expanding methodologies have made cross-cutting advances in multiple fields of the life sciences with significant impact. This section summarizes recent advances in five of these fields with emphasis on the aspects impacted by one or more of the above methodological areas. For example, in the field of neuroscience, nanotechnology has permitted the generation of novel ("nanoneuroscience") approaches to the delivery of therapeutics to the central nervous system.

Immunology

Regardless of whether a disease is exogenous, like viral or bacterial infections or endogenous, like cancer or autoimmune disorders, the immune response is key in how disease is resolved. While the immune system is usually protective, the system can also switch to an overreactive response and actually damage the host. Understanding of the complex regulatory networks of cell populations and signaling pathways that determine the magnitude and quality of an individual's immune response has important implications for human health, since these genes and pathways can be therapeutically targeted to treat disease.

Mathematical, statistical and computational modelling has been applied to clinical and experimental immunology. Systems-based analyses rely on data-driven approaches based on huge data sets that catalog the synthesis of all the genes, proteins and metabolites in cells. Several large scale, international consortiums have been founded in recent years to engage with such data. For example, the Immunological Genome project (2007-present) seeks to examine gene expression and its regulation across the entire immune system; Euroflow (2007-present) is standardizing flow cytometry tests for immune cancers; and the Human Immunology Project Consortium (2010–present) seeks to establish a new public repository of different types of data that characterize diverse states of the human immune system (Benoist et al. 2012).

Security considerations related to Immunology

Advances in immunology offer considerable societal benefits. However, progress in immunology also has dual-use potential. As pointed out in a UK (2014) working paper contribution to the BWC process: "Knowledge gained through research on host–pathogen interactions and mechanisms used to overcome the host immune response could also be exploited for harmful purposes, for example in designing novel biological weapons agents or engineering existing agents to increase their suitability for biological weapons use".

Neuroscience

Highly specific neurotoxins produced by bacteria have long been well characterized with respect to their access to nervous tissue and their mechanisms of action. The dramatic increase in knowledge of neurological control mechanisms has already led to the development of sophisticated drugs to modulate nerve function. Combining this knowledge with gene therapy techniques for the delivery of DNA-editing enzyme packages means that, in the near future, methods for altering gene expression in the neurologic system of humans will be developed for medical treatment of, for example, Huntington's Disease or various psychiatric disorders.

Security considerations related to Neuroscience

Advances in neuroscience have fostered increased concern over the possible creation of neurobioweapons (DiEuliis and Giordano 2017; Howell 2017; Ienca, Jotterand, and Elger 2018). Certain States have long had an interest in technologies that can incapacitate adversaries (Kirby 2006; Davidson 2007). A growing understanding of neuroscience potentially widens the range of possible means of incapacitation to include effects on "locomotion, sensation, cognition or indeed any other process that keeps us functioning properly" (Robinson 2006). Such capabilities might have appeal to governments seeking to "make a populace more subservient", counter insurgencies (Kemp et al. 2020) or "undermine the capacities of enemy forces" (Nuffield Council on Bioethics 2013). Misuse of advances in neurosciences, for example, by the military sector for purposes of cognitive, behavioural or neurophysiologic modification would expand the definition of weapons of war into unchartered territory.

Human genetics and reproductive science

Despite the exciting possibilities that CRISPR offers, modifying genes in humans is potentially dangerous. Gene therapy was lethal in one case and modifying genes in germline cells may lead to unintended consequences (Sand, Bredenoord, and Jongsma 2019; Somia and Verma 2000). Concern over technical problems associated with the method, such as off-target edits or effects and the generation of malformed proteins by the altered sequences, has led to wide-spread condemnation of certain experiments involving the modification of germline cells (Harper and Schatten 2019). Recent work from the Francis Crick Institute suggests that off-target and unintended editing events were consequences in human embryos edited with CRISPR (Anderson et al. 2018; Fu et al. 2013). Several international entities are reviewing the ethical issues related to these developments (Kemp et al. 2020).

Security considerations related to human genetics and reproductive science

There is some evidence that past biological weapons programmes considered affecting fertility in certain target populations through, for example, "developing an anti-fertility vaccine which could be selectively administered—without the knowledge of the recipient" (Gould and Folb 1990). For the large part, such programmes appear to have been ineffective; however advances in reproductive science and fertility could enable effective biological weapons targeted at fertility. As discussed above, understanding human genetics and the relative diversity within and among populations could also lead to the potential development of biological weapons targeting specific genes that predominate in certain groups.

Agriculture (plants and animals)

The risks of synthetic biology are no longer confined to the laboratory or to use at the level of the individual, but now could threaten extensive damage in human, plant, and animal populations, and in the environment. In addition, a medicinal or environmental cure, even after extensive analysis to anticipate all possible outcomes, might lead to an unintended negative consequence. Biotechnologies with the predicted ability to cause even small changes in large-scale environments should be carefully evaluated before their eventual real-world use.

The new field of 'gene drive' technology arising from the advances in genetic technologies discussed above is a particular concern. Gene drives are a class of genetic elements that bias inheritance patterns of a targeted host species such that all or most offspring in subsequent generations will contain the gene drive's sequence (National Academies 2016). As such, a gene drive engineered into a host organism will continue to propagate its own genetic elements in a manner that is not subject to normal natural selection pressures. Derived from naturally occurring bacterial defence systems, gene drives are not a singular type of biotechnology—there are many different drive systems currently under investigation. The ability of gene drives to self-propagate without human intervention following their release into the environment could be a cause for concern, depending on the nature of the gene drive.

Still, there are many beneficial proposed applications of gene drives, for example in decreasing the burden of malaria in Sub-Saharan Africa by driving down the malaria-carrying mosquito population (Scudellari 2019). Gene drives have been proposed as a more environmentally friendly method of invasive species management since their use would eliminate the need for distribution of toxic pesticides over large geographic areas. In addition, gene drives could be used to address the impacts of climate change on vulnerable plant and animal species by making genetic modifications to increase their resilience to environmental changes.

Security considerations related to Agriculture (plants and animals)

Enthusiasm for gene drive use in the wild may have been dampened by increasing awareness of several risks associated with the use of gene drives. In addition to the potential for agricultural gene-drive technology to feed into a new generation of anti-crop biological weapons, a primary concern is the potential for gene drives to create off-target effects in target species. Cascading or self-amplifying effects could ensue, such as a drop or increase in associated predator or prey species. Many ecosystems, particularly island ecosystems, are quite sensitive to even small changes in predator–prey cycles or the loss of a certain key species. The effects of small changes on macroenvironments are difficult to predict. Furthermore, there are few ways to monitor who is conducting this kind of research unless the work is published or activities are declared. Finally, there are no countermeasures to a released gene drive that are not themselves gene drives. Reversal drives and immunization drives are an active area of research, which may lead to effective measures to counteract the original gene drive. (Johns Hopkins Center for Health Security 2020)

Infectious disease

The power and the hazards of DNA synthesis are illustrated by the recent published description of the *de novo* synthesis of horsepox virus (Kupferschmidt 2017). Small pieces of the genome were ordered from a DNA synthesis company and stitched together to form the complete chromosome of the virus. While this virus was not the first to be synthesized *de novo*—the first was poliovirus in 2002 (Cello, Paul, and Wimmer 2002)—it is certainly the most complex. Horsepox virus (which is not known to harm humans) is, like its close relative smallpox, no longer present in nature. The stated rationale for the work was to create new, better vaccines for infectious disease and cancer (Kupferschmidt 2017). Producing smallpox virus in a similar manner would be strictly prohibited under World Health Organization and other regulations in place in many States (WHO 2019). The existence of such research illustrates the clear pathway to pandemic virus synthesis in laboratories and highlights the different and relative risks of each of these technologies while pointing to the urgency of universal governance considerations. Risks will continue to change as technology advances to improve usability, regulatory limitations are enacted, and attribution methods—through which to identify those responsible for viral synthesis—are developed.

Vaccination is a primary tool for the prevention and control of infectious diseases and DNA synthesis already plays an important role in the development of new vaccines, especially through vaccine platforms[7]. Traditional vaccination campaigns immunize one person at a time, with direct involvement from healthcare providers. New synthetic biology capabilities have the potential to change this paradigm through for example self-replicating vaccines that could enable small doses of a vaccine to produce larger stimulus once inside the body. This approach could greatly decrease the burden on healthcare systems. However, the technologies that are being developed to address these problems could also be misused to seek harmful outcomes. For example, increased dosage of certain RNAs could lead to toxicities (Murphy, Redwood, and Jarvis 2016; Nuismer et al. 2018).

Security considerations related to infectious disease

Modifying the genomes of pathogens may create organisms with increased or altered ability to infect or spread among humans. For example, in 2011 two laboratories modified strains of highly pathogenic avian influenza to study the genetic sequences that determine host range. The stated intent of the experiments was to collect sequence information that would aid influenza trackers to identify a potentially pandemic strain of avian influenza. The reconstituted influenza strains were not tested directly in humans but were shown to infect ferrets, which serve as an established experimental model for human infection. (Duprex et al. 2015; Frank et al. 2016). The risks of escape, theft or release of highly infectious agents associated with this kind of work raise both biosafety and biosecurity concerns. The risks and benefits of potential pandemic pathogen research—along with models of governance—continue to be examined and debated across scientific and policy communities around the world.

7 A vaccine platform is a single methodology designed to create multiple target vaccines, employing an underlying, nearly identical mechanism, device, delivery vector, or cell line.

PART III. IMPLICATIONS

The last decade has ushered in radical advances across the life sciences that have been propelled in part by wider technological developments in areas such as nanotechnology (The Royal Society and IAP 2016). At the same time, the decade has witnessed a shift from patterns of inter-State cooperation to increased competition among States along with a resurgence of geostrategic tensions (Wan 2020).

Biological weapons have not been used in conflict in recent memory. However, the ongoing consequences of the SARS-CoV-2 pandemic serve as a reminder of the power of biology. This raises the possibility that, in a changing security context, States might seek to mobilize new capabilities in the life sciences for hostile exploitation in the form of next-generation biological weapons capable of a spectrum of effects:

> During the century ahead, as our ability to modify fundamental life processes continues its rapid advance, we will be able not only to devise additional ways to destroy life but will also become able to manipulate it—including the processes of cognition, development, reproduction, and inheritance. A world in which these capabilities are widely employed for hostile purposes would be a world in which the very nature of conflict had radically changed. (Meselson 2001)

A major driver of the current revolution and massive expansion in the life sciences is convergence—the collaboration and crossover of research and development, leading to synergistic ideas and solutions to many of the medical, ecological and societal problems facing our increasingly complicated planet with its uncertain future. Accompanying these novel approaches to problem solving are potential dangers. In this report, three methodologies (DNA technologies, nanotechnologies and artificial intelligence) were selected for examination of their trajectories and interactions across a number of fields. Table 1 presents a matrix of potential consequences of the intersection of these methodologies and fields.

Table 1. *Matrix of potential consequences*

	DNA (read, write, edit)	**Nanotechnology**	**Artificial intelligence**
Immunology	Engineering immunodeficiency or autoimmunity	Nanocarriers targeting immune system components	Predicting susceptibility
Neuroscience	*In vivo* neural editing	Neurotargetted nanoweapons	Mind control
Reproduction	Deletion or addition of genes to the germ line	Selection of specific spermatozoa	Fertility algorithms
Agriculture	Engineered crop disease	Detection by engineered sensor-crops	Drones for forecasting and analysis of labour and pests
Infectious disease	Creation of chimeric organisms	Nanobots for early detection infection	Pandemic viral genetics

The set of technologies discussed above will have a number of far-reaching implications in terms of enhancing the creation, production and delivery of biotechnology-derived products.

Preventing the hostile exploitation of the life sciences

While the above discussion highlights some of the considerable dangers posed by life science and perhaps some life scientists, the hostile exploitation of the life sciences is not inevitable. Significant biological weapons will still likely require considerable resources and expertise. Moreover, much has been done to prevent the hostile exploitation of the life sciences.

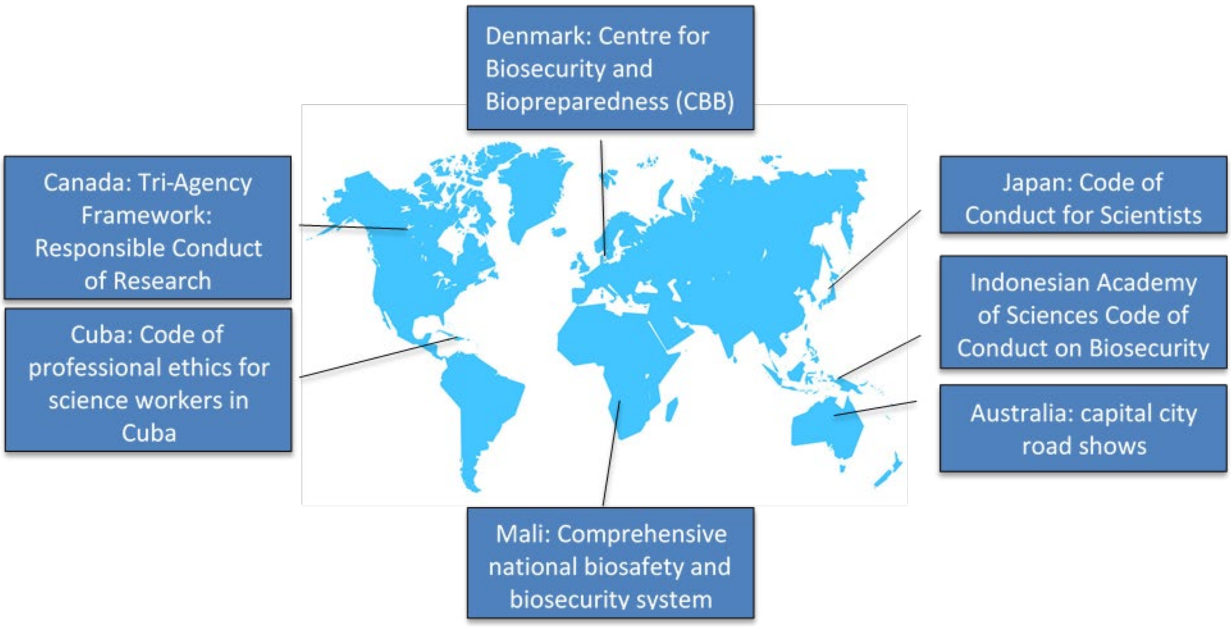
At the international level there are mechanisms in place to prevent the development of biological weapons. These include Security Council resolution 1540 (Security Council 2004) and the BWC. The BWC is particularly important and notably comprehensive in its scope, covering agents beyond those used in Cold War biological weapons programmes through the intent-based prohibition in article I. As such, no new developments fall outside of the BWC definition of biological weapons.

Nonetheless, developments in biotechnology will have positive and negative implications for several articles of the BWC. Illustrative examples of implications for articles of the Convention are outlined in Table 2 below and these suggest that there is a need to monitor developments in the life sciences and better understand the implications in the context of the BWC. One way to assist in this process could be through in-depth analysis and exchange on science and technology in—and between—future BWC meetings, including the 2021 Review Conference.

Table 2. ***Implications for articles of the BWC***

Article I	Although article I is comprehensive in scope, it will be important to monitor developments that could improve the perceived utility of biological weapons, including by broadening the spectrum of effects far beyond traditional understandings of biological weapons.
Article III	The digitization of biological data and the growing capacity to read, write and edit DNA present considerable intangible challenges to existing export control regimes and practices (National Academies 2018).
Article IV	Some of these technologies raise considerable ethical, biosafety and biosecurity concerns. As such, some States may need to re-evaluate whether they are indeed taking "any necessary measures to prohibit and prevent the development, production, stockpiling" of biological weapons.
Article VI	Some of these technologies, but particularly big data and DNA sequencing, provide a much greater range of possible evidence with which to confirm or deny the validity of alleged breaches of the BWC.
Article VII	Advances in several fields of the life sciences are fundamentally enhancing the speed and efficacy of responses to natural disease outbreaks. The same technologies could also be important in providing assistance to States exposed to a danger as a result of a violation of the BWC. The enhanced ability to provide assistance under article VII could also dampen the effects of biological weapons.
Article X	The digitization of biological data fundamentally changes the way in which scientist can exchange information, collaborate and cooperate for peaceful purposes.

Figure 3. *Illustrative examples of biosecurity-related activities around the world*



At the international level it is notable that efforts are well underway to enhance the oversight of dual-use research. As part of the Human Gene-Editing Initiative of the US National Academies of Sciences, Engineering, and Medicine, the security implications, regulatory issues and ethics of human gene editing were discussed at international public meetings in 2016 and 2017 (National Academies 2016, 2017). A review of oversight and governance perspectives from eight States (Singapore, China, Malaysia, the United Kingdom, Belgium, Spain, Canada and the United States) revealed a range of guidance mechanisms in place. The motivation for moving forward in this kind of work is often to maintain national technological advantage while also providing benefits to the general population. Powerful economic or regulatory forces can also be at play. Overall, the States surveyed agreed that germline gene editing with reproductive intent should continue to be prohibited.

At the national level there has been a patchwork of biosafety and biosecurity initiatives that States and stakeholders have already undertaken over the course of the twenty-first century (see figure 2 for some examples). Some of these initiatives are targeted at particular phases of the life science 'research life cycle' (National Academies 2018). Academic research institutes and other research bodies have Institutional Biosafety Review Committees to identify possible risks in research at the early conceptual phase; certain biotech research funders have collectively agree to review grant applications for dual-use content at the funding stage (Health and Human Services 2013); private sector practices for screening gene synthesis have been developed for the research conduct phase (International Gene Synthesis Consortium); and a collection of journal editors collectively agreed to review publications for biosecurity-sensitive content at the point of dissemination (National Academies 2018).

Scientific activities outside of traditional academic or industrial laboratory settings have contributed to increasing awareness of safety and security concerns among the public and within the scientific community itself. For example, the International Genetically Engineered Machine (iGEM) competition, brings together teams of young people from around the world to compete in the design and building of novel biological systems in living cells.[8] Integral to the evaluation criteria of the entries to iGEM are issues related to safety and security, and all proposals are reviewed at multiple points by internationally certified biorisk management professionals and by teams of professional scientists volunteering as judges. The iGEM leadership directly engages with teams on biosecurity related issues (iGEM 2020). In this way, the competition helps to foster a generation of young scientists around the world that is steeped in an appreciation of the fundamental issues of the dual character of technological advancement. Similarly, the community laboratories movement (do-it-yourself or 'garage' biology) around the world has led to the creation of supra-national networks that have developed their own ethical frameworks (Landrain et al. 2013).

In addition to such measures, scientists themselves have engaged in a multitude of international, national and local biosecurity- and biosafety-related initiatives. Through codes of conduct, awareness-raising and education—often using novel and creative methods of training (Elhadidy, El-Tholoth, and Brocard 2019)—these measures are designed to foster a biosecurity- and biosafety-conscious culture among a wide range of stakeholders working in and around the life sciences (Shinwari 2015). In addition to awareness of the BWC and promoting its implementation, global cooperation among scientists—including emphasis on the responsible conduct of scientific activities—could contribute greatly to developing standards of biorisk management and feed into an international "web of prevention" (Rappert and Macleish 2007).

8 http://iGEM.org.

REFLECTIONS

Multiple technologies in the life sciences are advancing and converging to generate considerable potential benefits to society, the global economy, and future generations. However, the same technologies also present considerable safety and security issues. The challenges posed by advances in the life sciences are not going to get easier to address as time goes by—rather, ongoing developments in key areas of technology are only going to complicate policymaking around the life sciences.

In the broader security context, it will be increasingly important for States and other stakeholders to engage in dialogue that builds a better understanding of the positive and negative implications of advances in biotechnologies, but also sets in motion steps to mobilize scientists in pursuit of the many peaceful benefits of science and technology while minimizing the ethical, safety and security concerns raised by the "Fourth Industrial Revolution".

BIBLIOGRAPHY

Abbott, T. R. et al. 2020. "Development of CRISPR as an antiviral strategy to combat SARS-CoV-2 and Influenza." *Cell* 181 (4):865–876 e12. doi: 10.1016/j.cell.2020.04.020.

Anderson, K. R. et al. 2018. "CRISPR off-target analysis in genetically engineered rats and mice." *Nature Methods*15 (7):512–514. doi: 10.1038/s41592-018-0011-5.

Anzalone, A.V. et al. 2019. "Search-and-replace genome editing without double-strand breaks or donor DNA." *Nature* 576 (7785):149–157. doi: 10.1038/s41586-019-1711-4.

Benoist, C et al., and the Immunological Genome Project. 2012. "Consortium biology in immunology: the perspective from the Immunological Genome Project." *Nature Reviews Immunology* 12 (10):734–740. doi: 10.1038/nri3300.

Biological Weapons Convention. 2012. "Final document of the Seventh Review Conference."

Boulanin, V. 2019. "Artificial intelligence: A primer." In *The Impact of Artificial Intelligence on Strategic Stability and Nuclear Risk: Euro-Atlantic Perspectives*, edited by V Boulanin. SIPRI.

Bourzac. K. 2017. "Gene therapy: Erasing sickle-cell disease." *Nature* 549: S28–S30.

Bugembe, D.L. et al. 2020. "Main routes of entry and genomic diversity of SARS-CoV-2, Uganda." *Emerging Infectious Diseases* 26 (10). doi: 10.3201/eid2610.202575.

Callaway, E. 2014. "First synthetic yeast chromosome revealed." *Nature*.

Cello, J., A.V. Paul, and E. Wimmer. 2002. "Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template." *Science* 297 (5583):1016–1018. doi: 10.1126/science.1072266.

Cena, V., and P. Jativa. 2018. "Nanoparticle crossing of blood-brain barrier: a road to new therapeutic approaches to central nervous system diseases." *Nanomedicine (Lond)* 13 (13):1513–1516. doi: 10.2217/nnm-2018-0139.

Chiolero, A., and D. Buckeridge. 2020. "Glossary for public health surveillance in the age of data science." *Journal of Epidemiology and Community Health* 74 (7):612–616. doi: 10.1136/jech-2018-211654.

Chui, M., M. Evers, and A. Zheng. 2020. "How the Bio Revolution could transform the competitive landscape." McKinsey. https://www.mckinsey.com/~/media/McKinsey/Business Functions/McKinsey Digital/Our Insights/How the Bio Revolution could transform the competitive landscape/How-the-Bio-Revolution-could-transform-the-competitive-landscape.pdf.

Clapper, J. 2016. "Worldwide threat assessment of the US intelligence community." https://www.dni.gov/index.php/newsroom/congressional-testimonies/item/1845-statement-for-the-record-worldwide-threat-assessment-of-the-us-intelligence-community.

Dananjayan, S., and G.M. Raj. 2020. "Artificial intelligence during a pandemic: the COVID-19 example." *International Journal of Health Planning and Management*. doi: 10.1002/hpm.2987.

Davidson, N. 2007. "'Off the rocker' and 'on the floor': the continued development of biochemical incapacitating weapons." *Bradford Science and Technology Reports*.

Davies, J.C. 2017. *Oversight of next generation nanotechnology*. Princeton, NJ: Woodrow Wilson International Center for Scholars.

DiEuliis, D., and J. Giordano. 2017. "Why gene editors like CRISPR/Cas may be a game-changer for neuroweapons." *Health Security* 15 (3):296–302. doi: 10.1089/hs.2016.0120.

Dominguez, A.A., W.A. Lim, and L.S. Qi. 2016. "Beyond editing: repurposing CRISPR-Cas9 for precision genome regulation and interrogation." *Nature Reviews Molecular Cell Biology* 17 (1):5–15. doi: 10.1038/nrm.2015.2.

Drexler, K.E. 1986. *Engines of creation*.

Dunbar, C.E. et al. 2018. "Gene therapy comes of age." *Science* 359 (6372). doi: 10.1126/science.aan4672.

Duprex, W.P. et al. 2015. "Gain-of-function experiments: time for a real debate." *Nature Reviews Microbiology* 13 (1):58–64. doi: 10.1038/nrmicro3405.

Elhadidy, M., M. El-Tholoth, and A. Brocard. 2019. "Implementation of active learning approach to teach biorisk management and dual-use research of concern in egypt." *Applied Biosafety*. doi: 10.1177/1535676019836998.

Erickson, B.J. et al. 2017. "Machine learning for medical imaging." *Radiographics* 37 (2):505–515. doi: 10.1148/rg.2017160130.

Frank, G.M. et al. 2016. "Infectious Diseases Society of America and gain-of-function experiments with pathogens having pandemic potential." *Journal of Infectious Diseases* 213 (9):1359–1361. doi: 10.1093/infdis/jiv474.

Fredens, J. et al. 2019. "Total synthesis of Escherichia coli with a recoded genome." *Nature* 569 (7757):514–518. doi: 10.1038/s41586-019-1192-5.

Fu, Y. et al. 2013. "High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells." *Nature Biotechnology* 31 (9):822–826. doi: 10.1038/nbt.2623.

Gerstein, D. 2016. "Can the Bioweapons Convention survive Crispr?" *Bulletin of the Atomic Scientists*.

Giani, A.M. et al. 2020. "Long walk to genomics: history and current approaches to genome sequencing and assembly." *Computational and Structural Biotechnology Journal* 18:9–19. doi: 10.1016/j.csbj.2019.11.002.

Goes de Jesus, J. 2020. "Importation and early local transmission of COVID-19 in Brazil, 2020." *Revista do Instituto de Medicina Tropical de São Paulo* 62.

Gould, C., and P. Folb. 1990. *Project Coast: Apartheid's chemical and biological warfare programme*. UNIDIR.

Hamet, P., and J. Tremblay. 2017. "Artificial intelligence in medicine." *Metabolism* 69S:S36–S40. doi: 10.1016/j.metabol.2017.01.011.

Harper, J.C., and G. Schatten. 2019. "Are we ready for genome editing in human embryos for clinical purposes?" *European Journal of Medical Genetics* 62 (8):103682. doi: 10.1016/j.ejmg.2019.103682.

Health and Human Services. 2013. "Framework for guiding funding decisions about research proposals with the potential for generating highly pathogenic avian influenza H5N1 viruses that are transmissible among mammals by respiratory droplets." https://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf

Howell, A. 2017. "Neuroscience and war: human enhancement, soldier rehabilitation, and the ethical limits of dual-use frameworks." *Millenium* 45 (2):133–150.

Hsu, P.D., E.S. Lander, and F. Zhang. 2014. "Development and applications of CRISPR-Cas9 for genome engineering." *Cell* 157 (6):1262–1278.

ICRC. 2004. *Biotechnology, weapons and humanity*.

Ienca, M., F. Jotterand, and B.S. Elger. 2018. "From healthcare to warfare and reverse: how should we regulate dual-use neurotechnology?" *Neuron* 97 (2):269–274. doi: 10.1016/j.neuron.2017.12.017.

iGEM. 2020. "Safety Committee: values and risks workshops." https://2020.igem.org/Safety/Workshops.

International Gene Synthesis Consortium. https://genesynthesisconsortium.org.

Jinek, M. et al. 2012. "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity." *Science* 337 (6096):816–821. doi: 10.1126/science.1225829.

Johns Hopkins Center for Health Security. 2019. *The US bioeconomy: maximizing opportunities for economic growth and national security with biology*.

Johns Hopkins Center for Health Security. 2020. *Gene Drives: Pursuing Opportunities, Minimizing Risk*.

Ke, R. et al. 2016. "Fourth generation of next-generation sequencing technologies: promise and consequences." *Human Mutation* 37 (12):1363–1367. doi: 10.1002/humu.23051.

Kemp, L. et al. 2020. "Bioengineering horizon scan 2020." *eLife* 9. doi: 10.7554/eLife.54489.

Khoury, M.J., M.F. Iademarco, and W.T. Riley. 2016. "Precision public health for the era of precision medicine." *American Journal of Preventive Medicine* 50 (3):398–401. doi: 10.1016/j.amepre.2015.08.031.

Kirby, R. 2006. "Paradise lost: the psycho agents." *CBW Conventions Bulletin* 71:1–36.

Klotz, L. 2020. "The pandemic risk of an accidental lab leak of enhanced flu virus: unacceptably high." *Bulletin of the Atomic Scientists*.

Kobokovich, A. et al. 2019. "Strengthening security for gene synthesis: recommendations for governance." *Health Security* 17 (6):419–429.

Kono, N., and K. Arakawa. 2019. "Nanopore sequencing: Review of potential applications in functional genomics." *Development, Growth & Differentiation* 61 (5):316–326.

Kosal, M. 2009. *Nanotechnology for chemical and biological defense*.

Kupferschmidt, K. 2017. "How Canadian researchers reconstituted an extinct poxvirus for $100,000 using mail-order DNA." *Science*.

Landrain, T. et al. 2013. "Do-it-yourself biology: challenges and promises for an open science and technology movement." *Systems and Synthetic Biology* 7 (3):115–26. doi: 10.1007/s11693-013-9116-4.

Leins, K. 2020. *Magnifying nanomaterials*.

Li, N. et al. 2019. "Replication-defective West Nile virus with NS1 deletion as a new vaccine platform for flavivirus." *Journal of Virology* 93 (17). doi: 10.1128/JVI.00720-19.

Madden, L.V., and M. Wheelis. 2003. "The threat of plant pathogens as weapons against US crops." *Annual Review of Phytopathology* 41 (1):155–176.

Meredith, L.W. et al. 2020. "Rapid implementation of SARS-CoV-2 sequencing to investigate cases of health-care associated COVID-19: a prospective genomic surveillance study." *Lancet Infectious Diseases*.

Meselson, M. 2001. "Averting the hostile exploitation of biotechnology." *Chemical and Biological Weapons Convention Bulletin* 48.

Mole, B. 2014. "The gene sequencing future is here." *Science News*.

Mooney, S.J., D.J. Westreich, and A.M. El-Sayed. 2015. "Commentary: epidemiology in the era of big data." *Epidemiology* 26 (3):390–394. doi: 10.1097/EDE.0000000000000274.

Murch, R.S. et al. 2018. "Cyberbiosecurity: an emerging new discipline to help safeguard the bioeconomy." *Frontiers in Bioengineering and Biotechnology* 6:39. doi: 10.3389/fbioe.2018.00039.

Murphy, A.A., A.J. Redwood, and M.A. Jarvis. 2016. "Self-disseminating vaccines for emerging infectious diseases." *Expert Review of Vaccines* 15 (1):31–39. doi: 10.1586/14760584.2016.1106942.

National Academies of Sciences, Engineering, and Medicine. 2015. "Human Genome Editing Initiative." https://www.nationalacademies.org/our-work/human-gene-editing-initiative.

National Academies of Sciences, Engineering, and Medicine. 2016. "Gene Drives on the Horizon". https://doi.org/10.17226/2340.

National Academies of Sciences, Engineering, and Medicine. 2017. "Assessing the biosecurity implications of genome editing technology: a workshop." https://www.nationalacademies.org/event/10-11-2017/assessing-the-biosecurity-implications-of-genome-editing-technology-a-workshop.

National Academies of Sciences, Engineering, and Medicine. 2018. *Governance of Dual Use Research in the Life Sciences: Advancing Global Consensus on Research Oversight: Proceedings of a Workshop*. https://doi.org/10.17226/25154.

National Academies of Sciences, Engineering, and Medicine. 2020. *Safeguarding the bioeconomy*. https://doi.org/10.17226/25525.

National Human Genome Research Institute. 2019. "The Cost of Sequencing a Human Genome." https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost.

Ney, P. et al. 2017. "Computer security, privacy, and DNA sequencing: compromising computers with synthesized DNA, privacy leaks, and more." https://www.usenix.org/conference/ usenixsecurity17/technical-sessions/presentation/ney.

Norquist, B.M., and E.M. Swisher. 2015. “More genes, more problems? Benefits and risks of multiplex genetic testing.” *Gynecologic Oncology* 139 (2):209–10. doi: 10.1016/j.ygyno.2015.10.013.

Nuismer, S.L. et al. 2018. “Controlling epidemics with transmissible vaccines.” *PLoS One* 13 (5):e0196978.

Ostrov, N. et al. 2019. “Technological challenges and milestones for writing genomes.” *Science* 366 (6463):310–312. doi: 10.1126/science.aay0339.

Pauwels, E., and S.W. Denton. 2020. “Hybrid emerging threats and information warfare: the story of the cyber-AI deception machine.” In *21st century Prometheus: managing CBRN safety and security affected by cutting-edge technologies*, edited by M. Martinelli and R. Trapp.

Rappert, B., and C.A. Macleish. 2007. *Web of prevention: biological weapons, life science and the governance of research*.

Rasko, D.A. et al. 2011. “Bacillus anthracis comparative genome analysis in support of the Amerithrax investigation.” *Proceedings of the National Academy of Sciences* 108 (12):5027–5032. doi: 10.1073/pnas.1016657108.

Robinson, J.P. 2006. Near-term development of the governance regime for biological and chemical weapons. *Science Policy Research Unit*.

Rogers, P., S. Whitby, and M. Dando. 1999. “Biological warfare against crops.” *Scientific American* 280 (6):70–75. doi: 10.1038/scientificamerican0699-70.

Sand, M., A.L. Bredenoord, and K.R. Jongsma. 2019. “After the fact-the case of CRISPR babies.” *European Journal of Human Genetics* 27 (11):1621–1624. doi: 10.1038/s41431-019-0459-5.

Schwab, K. 2015. “The fourth industrial revolution: what it means, how to respond.” *Foreign Affairs* (12):2015–2017.

Scudellari, M. 2019. “Self-destructing mosquitoes and sterilized rodents: the promise of gene drives.” *Nature*.

Security Council. 2004. “Security Council Committee established pursuant to resolution 1540 (2004).” https://www.un.org/en/sc/1540/.

Shende, P., P. Kasture, and R.S. Gaud. 2018. “Nanoflowers: the future trend of nanotechnology for multi-applications.” *Artificial Cells, Nanomedicine, and Biotechnology* 46 (sup1):413–422. doi: 10.1080/21691401.2018.1428812.

Shinwari, Z. 2015. *Dual-use education concerns in biotechnology: Pakistani perspective*.

Shwartz, M. 2018. “Target, delete, repair: CRISPR is a revolutionary gene-editing tool, but it’s not without risk.” *Stanford Medicine*.

Somia, N., and I. M. Verma. 2000. “Gene therapy: trials and tribulations.” *Nature Reviews Genetics* 1 (2):91–99. doi: 10.1038/35038533.

Spiez Laboratory. 2018. “Spiez CONVERGENCE: report on the third workshop.” https://www.labor-spiez.ch/pdf/en/rue/Spiez_CONVERGENCE_Report_on_the_3rd_ workshop_2018.pdf.

Swings, T. et al. 2018. "CRISPR-FRT targets shared sites in a knock-out collection for off-the-shelf genome editing." *Nature Communications* 9 (1):2231. doi: 10.1038/s41467-018-04651-5.

The Nuffield Council on Bioethics. 2013. "*Novel neurotechnologies: intervening in the brain*".

The Royal Society and IAP. 2016. "The Biological and Toxin Weapons Convention; considerations for a science advisory mechanism."

United Kingdom. 2014. "Advances in science and technology: Evasion of the host immune response by pathogens" BWC/MSP/2014/MX/WP.4.

US Department of Energy. 2018. "DOE: atomically precise manufacturing 2018, Phase I Release II." https://www.nano.gov/node/1957.

Vogel, K. 2019. "Big data and biodefense: prospects and pitfalls." In *Defense against biological attacks*, edited by S. Singh and J. Kuhn.

Wan, W. [ed]. 2020. "Nuclear Risk Reduction: Closing Pathways to Use." UNIDIR. https://doi.org/10.37559/WMD/20/NRR/01

Warmbrod, K.L., M. Montague, and N.D. Connell. 2020. "Microbial forensics: detection and characterization in the twenty-first century." In *21st century prometheus: managing CBRN safety and security affected by cutting-edge technologies*, edited by M. Martinelli and R. Trapp.

Wegrzyn, R. 2020. "Preemptive expression of protective alleles and response elements (PREPARE)." https://www.darpa.mil/program/preemptive-expression-of-protective-alleles-and-response-elements.

Whitby, S., and P. Rogers. 1997. "Anti-crop biological warfare: implications of the Iraqi and US programs." *Defense Analysis* 13 (3):303–318.

WHO. 2019. "WHO Advisory Committee on variola virus research: report of the twentieth meeting."

WHO. 2020. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/ m/item/draft-landscape-of-covid-19-candidate-vaccines.

Wohl, S., S.F. Schaffner, and P.C. Sabeti. 2016. "Genomic analysis of viral outbreaks." *Annual Review of Virology* 3 (1):173–195. doi: 10.1146/annurev-virology-110615-035747.

Xu, Y. et al. 2020. "Deep dive into machine learning models for protein engineering." *Journal of Chemical Information and Modeling* 60 (6):2773–2790. doi: 10.1021/acs.jcim.0c00073.

Yang, K.K., Z. Wu, and F.H. Arnold. 2019. "Machine-learning-guided directed evolution for protein engineering." *Nature Methods* 16 (8):687–694. doi: 10.1038/s41592-019-0496-6.

Zhang, Y.Z., and E.C. Holmes. 2020. "A genomic perspective on the origin and emergence of SARS-CoV-2." *Cell* 181 (2):223–227. doi: 10.1016/j.cell.2020.03.035.

ADVANCES IN SCIENCE AND TECHNOLOGY IN THE LIFE SCIENCES

IMPLICATIONS FOR BIOSECURITY AND ARMS CONTROL

This report outlines a number of trends that are facilitating advances in different areas of the life sciences, including immunology, neuroscience, human genetics and reproductive science, agriculture and infectious disease. Research and development in these fields is overwhelmingly undertaken for peaceful purposes and potentially provides many benefits to society, the global economy, and future generations. However, the same areas of research raise a number of ethical, legal, safety and security concerns, including concerns that developments therein could feed into of new forms of biological weapons with different and potentially more damaging effects to those of the past.

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