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Biosafety and Biosecurity Relevant Life Sciences Work: Protection from Bio-Warfare and Bio-Terrorism

Zusammenfassung

Fortschritte in den lebenswissenschaftlichen Arbeiten haben in den vergangenen Jahren neue und verbesserte Ansätze zur Bekämpfung von Krankheiten und zur Beförderung von Gesundheit im Allgemeinen gebracht. Solche Forschungen sind weiterhin essentiell. Gleichzeitig können die Ergebnisse einiger dieser Arbeiten für nichtfriedliche Zwecke missbraucht werden; sie sind mit einem sogenannten Dual-Use-Charakter (doppelte Verwendbarkeit) behaftet, der es besonders schwer macht, den Nutzen zu ernten und gleichzeitig die damit verbundenen Risiken zu minimieren. Die relevanten Entwicklungen beziehen sich vor allem auf die Forschungsbereiche der Genomforschung, der synthetischen Biologie, der Systembiologie, der Bioinformatik, der Nanotechnologie und der Targeted-Delivery-Technologien. Auf internationaler Ebene kommen die Bemühungen sehr schleppend voran, Risikomanagementprogramme, die die Gefahren des Missbrauchs entschärfen könnten, abzufassen und zu etablieren. Die Entwicklungen in Wissenschaft und Technik standen stets im Mittelpunkt der 1972 vereinbarten B-Waffenkonvention (Übereinkommen vom 10. April 1972 über das Verbot der Entwicklung, Herstellung und Lagerung bakteriologischer (biologischer) Waffen und von Toxinwaffen sowie über die Vernichtung solcher Waffen) und mit den rasanten Entwicklungen in den Lebenswissenschaften in den letzten Jahren haben diese kontinuierlich an Relevanz gewonnen. Seit 2005 werden die Mitgliedsstaaten der Konvention speziell aufgefordert, ihre Aktivitäten in Richtung Risikovorsorge bzw. Risikomanagement bekannt zu machen, sodass optimale Verfahren (best practices) ausfindig gemacht werden können. Bis jetzt haben sehr wenige Staaten darauf reagiert, nämlich die Vereinigten Staaten von Amerika (USA), deren Risikomanagementsystem schon implementiert worden ist und die Niederlande, dessen Risikovorsorgeprogramm zwar abgefasst aber noch nicht implementiert ist. Jetzt hat auch Deutschland reagiert. In Antwort auf eine Anfrage der Bundesregierung an den Deutschen Ethikrat, hat der Ethikrat eine Stellungnahme dazu verfasst, mit Empfehlungen zu einem kohärenten Regelungssystem, das den Missbrauch von Forschung und Forschungsergebnissen in den Lebenswissenschaften minimieren und verhindern soll. Um auf der internationalen Ebene vorwärts zu kommen und bis andere Staaten diesen Beispielen folgen, sollten die Mitgliedsstaaten der BWC schon mit diesen drei detaillierten Risikomanagementprogrammen in einem Arbeitsgruppenformat beginnen, optimale Verfahren aus diesen Systemen ausfindig zu machen, die mit allen Mitgliedsstaaten als Wegweiser zur Risikovorsorge diskutiert werden können.

I. Introduction: life sciences work of relevance to biosecurity

Advances in science and technology over the past few years have initiated new and improved approaches to countering disease and promoting health in general. This progress in the life sciences is absolutely essential. At the same time, the rapidity with which the advances occur and the possibilities for misuse that they reveal give us a clear indication that we have reached a critical point in being able to deal effectively with the biosecurity implications of these developments.

Progress in *genomics* is enabling the ever increasingly rapid and cost effective analysis of genes and their regulatory elements as well as facilitating high through-put nucleic acid synthesis, which in turn is enabling the modification of even very complex microorganisms to meet designer specifications.[1] *Synthetic biology* is advancing beyond sophisticated engineering of microorganisms to perform new tasks by outfitting them with DNA-based biological circuits built from standardized biological

1 National Human Genome Research Institute, DNA Sequencing Costs. Data from the NHGRI Genome Seque 1093/nar/gks546.

2 *A. Prindle/J. Selimkhanov/H. Li et al.*, Rapid and Tunable Post-translational Coupling of Genetic Circuits, 508 Nature (2014), 387, doi: 10.1038/nature13238.

3 *K. Adamala/J. W. Szostak*, Nonenzymatic Template-Directed RNA Synthesis Inside Model Protocells 342 Science (2013), 1098, doi: 10.1126/science.1241888; *D.G. Gibson/J.I. Glass/C. Lartigue et al.*,

parts.[2] Sub-fields of synthetic biology are now reaching into the realm of creating artificial life from chemical components.[3]

Advances in *systems biology* are revealing new potential targets for disrupting the careful balance of vital physiological functions.[4] This is a field of biology that seeks to understand the working of complex physiological systems within and between cells on a molecular level. An enormous amount of knowledge is accumulating through this work that pinpoints vital cellular targets and ways of affecting those systems; either positively, towards better health or negatively, towards disruption of the proper, balanced function of those systems.

Bioinformatics has to do with a whole array of enabling functions for modern life sciences work, including the storage and recall of genomics data, the directed design of gene segments and genes on up to entire genomes of microorganisms, directed design of therapeutic drugs as well as the modelling of the interactions between molecules.[5] Bioinformatics also enable the global distribution and exchange of knowledge. Indeed, bioinformatics plays a decisive role in all areas of life sciences work today.

Nanotechnology is the study of materials on a nano scale (a nanometer is one-billionth of a meter). It is most relevant for biosecurity in the creation of nanoparticles with a size between 1-100 nanometers. These particles can be designed to have specific size, form and physical-chemical properties that can promote improved delivery of bioactive substances such as pharmaceutical drugs across nasal and respiratory passages as well as the blood-brain-barrier for therapeutic purposes.[6] At the same time nanoparticles coupled with new methods for making substances more soluble across mucous membranes could be used to deliver biological warfare agents more effectively, for example in the form of aerosols.

Indeed, concerns about advances in science and technology that could lead to the creation of novel biological warfare agents are compounded by the recognition that new and improved ways of delivering bioactive substances are already at hand and will be developed further at a rapid pace.[7] As outlined above, nanotechnology has contributed greatly to improved delivery of bioactive substances over the aerosol route, the method that has always been preferred for delivering biological weapons.[8] However, the emerging interest over the past decade in developing viral vectors to deliver vaccines and for use in targeted cancer, drug and immunotherapy[9] has caused biosecurity concerns that this may be an effective way to deliver biological agents as weapons. The strategy is to outfit viruses with foreign genes encoding bioactive substances that will be delivered to a host after infection by the virus. The host activates those genes to direct the synthesis of the encoded substance, which then exerts its effects.

Viruses are very efficient in infecting cells and delivering genes, nevertheless, *non-viral vectors* (artificial viruses) are being actively developed to overcome some of the disadvantages of viral vectors such as safety, manufacturing problems, host immunity and limited carrying capacities.[10] The most recent developments in this direction are the so-called *nanorobots*.[11] These are nanoparticles composed of a polymer-based framework enclosing a bioactive substance e.g. DNA or protein. They are outfitted with surface molecules that can dock onto desi-

Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome, 329 Science (2010), 52; *M. A. Bedau/E. C. Parke/U. Tangen/B. Hantsche-Tangen*, Social and Ethical Checkpoints for Bottom-up Synthetic Biology or Protocells, Systems and Synthetic Biology 3 (2009), 65, doi: 10.1007/s11693-009-9039-2.

4 *K. Thiel*, Systems Biology, Incorporated?, 24 Nature Biotechnology (2006), 1055; *A. Aderem/J.N. Atkins/C. Ansong et al.*, A Systems Biology Approach to Infectious Disease Research. Innovating the Pathogen-Host Research Paradigm, 2 mBio (2010), e00325-10, doi: 10.1128/mBio.00325-10; *B.A Kidd/L. A. Peters/E.E. Schadt/J.T. Dudley*, Unifying Immunology with Informatics and Multiscale Biology, 15 Nature Immunology (2014), 118.

5 *L. Yao/J.A. Evans/A. Rzhetsky*, Novel Opportunities for Computational Biology and Sociology in Drug Discovery, 27 Trends in Biotechnology (2009), 531.

6 *S. Suri/H. Fenniri/B. Singh*, Nanotechnology-Based Drug Delivery Systems, 2 Journal of Occupational Medicine and Technology (2007), 16; *F. Andrade/D. Rafael/M. Videira et al.*, Nanotechnology and pulmonary delivery to overcome resistance in infectious diseases, 65 Advanced Drug Delivery Reviews (2013), 1816.

7 National Research Council, Globalization, Biosecurity, and the Future of the Life Sciences, (2006), National Academies Press, Available at http://www.nap.edu/catalog/11567.html (29.8.2014); *K. Nixdorff*, Advances in Targeted Delivery and the Future of Bioweapons, 66 Bulletin of the Atomic Scientists (2010), 24.

8 See GolbalSecurity.org, Weapons of Mass Destruction, Biological Warfare Agent Delivery. Available at http://www.globalsecurity.org/wmd/intro/bio_delivery.htm (29.8.2014); U.S. Department of Defense, The Militarily Critical Technologies List. Part II: Weapons of Mass Destruction Technologies, Office of the Under Secretary of Defense for Acquisition and Technology (1998). Available at http://www.fas.org/irp/threat/mctl98-2/mctl98-2.pdf (29.8.2014).

9 *P.A. Gilbert and G. McFadden,* Poxvirus Cancer Therapy 1 Recent Patents on Anti-Infective Drug Discovery (2006), 309.

10 *K.L. Douglas*, Toward Development of Artificial Viruses for Gene Therapy. A Comparative Evaluation of Viral and Non-Viral Transfection, 24 Biotechnology Progress (2008), 871.

11 *S.M. Douglas/I. Bachelet/G.M. Church*, A Logic-Gated Nanorobot for Targeted Transport of Molecular Payloads; 335 Science (2012), 831; *J. Elbaz/I. Willner*, DNA Origami. Nanorobots Grab Cellular Control, 11 Nature Materials (2012), 276; *S.C. Lenaghan/Y. Wang/N. Xi et al.*, Grand Challenges in Bioengineered Nanorobotics for Cancer Therapy, 60 IEEE (Institute of Electrical and Electronic Engineers) Transactions on Biomedical Engineering (2013), 667.

gnated cells, signalling the vector to open up and release its bioactive payload. Some nanorobots are being developed to be taken up by cells and upon a signal, release their bioactive substances inside the cell. Even though non-viral vectors have not been as efficient as viral vectors in delivering genes to host cells,[12] there is a great deal of interest in developing them further.

II. The International Governance Problem

Urgent attention is needed in dealing adequately and responsibly with the risks of misuse that are inherent in life science work of dual use character. Although there has been a substantial amount of thought put into minimizing the risks involved in this work, the governance proposals made to date are not in any way keeping pace with the developments.

In effect, all work with biological agents for non-peaceful purposes is prohibited by the Biological Weapons Convention (BWC)[13], which was agreed in 1972 and came into force in 1975. In Article I of the convention, each member state[14] agrees never to develop, stockpile or otherwise acquire or retain biological agents that have no justification for peaceful purposes. Thus, at the same time, the convention allows work with all biological agents for peaceful purposes. With this formulation, called the general purpose criterion, the convention prohibits biological weapons, but does not hinder scientific progress, and it is not a captive of the technological development of the 1970s. In this regard, all new technological developments in the life sciences to date are unequivocally covered by the convention, as has been determined at all Review Conferences of the BWC, including the last one in 2011.[15] This is the great strength of the convention.

At the same time, the problem with the convention in this context is that it has no effective way of assuring compliance. It was not politically possible at the time of negotiation of the BWC for the states parties to agree on a verification regime[16], and the text gives no indication of how to deal with the biosecurity risk of misuse of material and knowledge resulting from dual use work in the life sciences. Negotiations starting in 1995 over a Protocol to the BWC that would strengthen the convention with, among other measures, a detailed verification programme, failed in 2001 to be agreed upon.[17] In Article IV of the convention the states parties are charged not only with prohibiting biological weapons but also with *preventing* their *(mis)use*, again without providing any procedure for accomplishing this.

The evolution of the work of the BWC has taken place at different levels of undertakings. At the top level, the BWC itself contains legally binding obligations, or the things that States Parties MUST do. No new legally binding measures have been agreed since the treaty was signed and came into force. At the next level, the review conferences, which are generally held every five years, reach "additional agreements" as to how to implement the obligations of the BWC; these are considered to be politically (as opposed to legally) binding obligations, or the things the States Parties SHOULD do. Finally, the intersessional processes (ISPs), yearly meetings which have taken place since 2003 between the review conferences, have led to the development of "common understandings" on elements that might be useful; these are shared national positions on mechanisms that might strengthen the implementation of the BWC, or the things States Parties COULD do.[18] These common understandings are clearly the weakest form of agreements reached in the BWC process.

In this regard the states parties to the BWC have since 2003, within the ISPs, tried to "promote common understandings and effective action" on specific topics of greatest relevance to the BWC that could strengthen the convention. One topic that continues to be taboo is, however, verification of the convention; instead, states parties try to reach agreements on other topics, which have over the years included strengthening the implementati-

12 Fn. 10, 871.

13 United Nations 1972, Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, United Nations General Assembly Resolution 2826 (XXVI). Available at http://www.unog.ch/80256EDD006B8954/(httpAssets)/C4048678A93B6934C1257188004848D0/$file/BWC-text-English.pdf (29.8.2014)

14 As of August 2014, there are 170 States Parties and 10 signatories. 16 states have neither signed nor ratified the convention. For lists, see http://www.unog.ch/80256EE600585943/(httpPages)/7BE6CBBEA0477B52C12571860035FD5C?OpenDocument (29.8.2014).

15 United Nations 2011, Final Document of the Seventh Review Conference. The Seventh Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. UN Doc. BWC/CONF.VII/7. Available at http://www.un.org/ga/search/view_doc.asp?symbol=BWC/CONF.VII/7 (29.8.2014).

16 *M.I. Chevrier,* History of BTWC Disarmament, in: K. McLaughlin/K. Nixdorff (eds.), BWPP Biological Weapons Reader, 2009, 13. Available at http://www.bwpp.org/documents/BWPP%20BW%20Reader_final+.pdf (29.8.2014).

17 *D. Butler*, Bioweapons treaty in disarray as US blocks plans for verification, 414 Nature (2001), 675.

18 *P.D. Millett*, The Biological Weapons Convention: Content, Review Process and Efforts to Strengthen the Convention, in: K. McLaughlin/K. Nixdorff (eds.), BWPP Biological Weapons Reader, 2009, 19, 30. Available at http://www.bwpp.org/documents/BWPP%20BW%20Reader_final+.pdf (29.8.2014).

on of the convention, cooperation and assistance within the convention, surveillance of disease outbreaks, security and oversight of biological agents, codes of conduct and awareness-raising education of life scientists about dual-use biosecurity issues. Under the "effective action" part of the process, states parties are called upon to recommend specific actions that can, however, only be agreed on at the next scheduled Review Conference. The BWC is presently in the middle of its third ISP (2012-2015), which was established at the Seventh Review Conference (Fn 15). So far most observers agree that the States Parties have reached many common understandings, but have promoted little to no effective action.[19]

For example, the topic of the review of developments in science and technology of relevance to the convention has been intensively dealt with as one of three standing agenda items in this present ISP. Within this process the mandate is to (1) review the most relevant developments, (2) consider the implications of these developments and (3) recommend risk management measures that can mitigate (minimize) the risks that these developments carry. There has up to now been much activity in the way of dealing with the first two elements, but very little consideration of the governance issue (Fn 19). Nevertheless, the member states have been called upon to communicate their efforts and experiences in implementing measures for strengthening biological risk management, voluntary codes of conduct and education and awareness-raising about dual-use biosecurity issues in the life sciences. Only a few states have responded to this call with the drafting of biosecurity-oriented risk management policies giving detailed descriptions of procedure; these policies include the oversight system of the USA[20], which has been implemented, and the proposed oversight and awareness-raising system of The Netherlands, which is in the implementation process.[21]

III. Germany's Response

Now Germany has acted in this context. In 2012 the Federal Government of Germany commissioned the German Ethics Council to draft an opinion as to whether the existing regulations and other measures such as codes of conduct were sufficient to minimize the risk of or even prevent the misuse of developments in life sciences work. The German Ethics Council took this opportunity to analyze the issue of freedom versus responsibility in life science work in the context of biosecurity. It came to the conclusion that additional biosecurity regulatory measures were needed, and made recommendations to the German government in 2014 toward a coherent regulatory system for minimizing/preventing the misuse of advances in life sciences work.[22]

The recommendations contain a balanced set of measures that allow scientists working in the field to demonstrate that they act responsibly in carrying out their research programmes, with sufficient regulations to guide them in taking the steps needed in this process in order to minimize misuse of their work. Education of life scientists about dual-use-biosecurity issues is placed first in the recommendations, reflecting the recognition that this is considered to be an essential biosecurity governance measure; that only when life scientists understand the issues will they be able to recognize the potential risks and be convinced of the necessity for minimizing those risks. Indeed, Peter Hale, founder of the Foundation for Vaccine Research stated in an interview in *Science*Insider that the Opinion "for the first time, contains a set of substantive recommendations that will hopefully inform/inspire debate and action in other countries" and that "The report should be required reading for governments around the world".[23]

19 *K. Nixdorff*, The 2013 Meeting of Experts to the BWC, with a Focus on the Standing Agenda Item Review of Science and Technology Developments, Policy Paper 2, Biochemical Security 20130 Project (2013); *M. Dando*, To What Extent Was the Review of Science and Technology Made More Effective and Efficient at the 2013 Meeting of BTWC States Parties? Policy Paper 5, Biochemical Security 20130 Project (2014). Both papers are available at http://biochemsec2030.org/policy-outputs/ (20.2.2015).

20 United States, United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern (2012). Available at http://www.phe.gov/s3/dualuse/Documents/oversight-durc.pdf (29.8.2014).

21 Royal Netherlands Academy of Arts and Sciences, Improving Biosecurity, Assessment of Dual-Use Research (2013). Available at https://www.knaw.nl/shared/resources/actueel/publicaties/pdf/advies-biosecurity-engels-web (29.8.2014).

22 Deutscher Ethikrat, Stellungnahme, Biosicherheit- Freiheit und Verantwortung in der Wissenschaft (2014). Available at http://www.ethikrat.org/dateien/pdf/stellungnahme-biosicherheit.pdf (29.8.2014). English Version available at http://www.ethikrat.org/files/opinion-bihttp://www.ethikrat.org/files/opinion-biosecurity.pdfosecurity.pdf (21.1.2015).

23 *M. Enserink,* ScienceInsider, German Ethics Council: Government Should Regulate Dangerous Research, ScienceInsider (2014). Available at http://news.sciencemag.org/europe/2014/05/ (29.8.2014).

Until other states follow these examples, a way forward at the international level would be for the States Parties to the BWC to start analyzing these three detailed risk management systems in a working group setting, with conclusions and recommendations about best practices reported to the next Meeting of States Parties as guidelines for those states that as yet have no risk management programme in place.

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