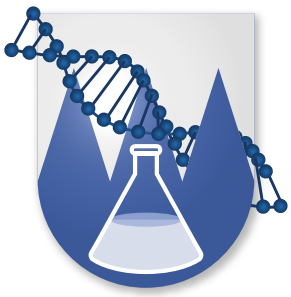

Spiez CONVERGENCE

Report on the first workshop
6–9 October 2014

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2 Official opening speaker

Executive Summary

Purpose

Spiez CONVERGENCE is a new workshop series organised by Spiez Laboratory, the Swiss Federal Institute for NBC-Protection. The series is dedicated to inform participants about significant advances in chemical and biological sciences, and to serve as a forum for discussion. The objective is to identify developments in chemistry and biology which may at some point have implications for the Biological Weapons Convention (BWC) or the Chemical Weapons Convention (CWC), and therefore may warrant further study. The series is designed as a Swiss contribution to a science and technology review.

The BWC and the CWC are arms control treaties strongly linked to developments in science and technology. The increasing overlap between chemical and biological sciences – generally referred to as convergence in chemistry and biology, or short 'Convergence' – has been noted by the treaties' States Parties in recent conference reports, and they recommended exploring its potential implications. 'Convergence' describes an integrative and collaborative approach in the life sciences that brings together theoretical concepts, experimental techniques as well as knowledge of different (science and engineering) disciplines at the crossroads of chemistry and biology.

Summary of Programme

This first Spiez CONVERGENCE brought together experts from academia, industry and policy making and started with an introduction to the concept of 'Convergence' from the perspectives of the CWC, the BWC and from an NGO perspective. This was followed by summaries of previous reviews conducted on the subject by the Organisation for the Prohibition of Chemical Weapons' Scientific Advisory Board (OPCW SAB) as well as by the Biochemical Security 2030 project (Bath University, UK). The scientific and technical presentations dealt with the subjects of 'chemistry making biology and biology making chemistry' and 'enabling technologies'. Expert speakers gave presentations on the following subjects:

- *Directed Evolution of Enzymes for Industrial Use*: using advanced computational methods and directed evolution to tailor enzymes which address a specific industrial need.

- *Genome Editing*: presentation of various gene modification tools commonly used in the field of synthetic biology.

- *Holistic Characterisation of Organisms*: history and current technology capabilities that allow for rational approaches in terms of modifying organisms and gathering information about the cellular machinery.

- *Industrial Biology*: engineering yeast to produce artemisinin, a potent anti-malarial drug. How the engineering process of yeast has been automated to optimise time to market for other chemicals.

- *Generating Data for Systems Biology*: methods for generating data for systems biology, including through genomics, transcriptomics, proteomics, and metabolomics, and examples of how that data is currently used.

- *CRISPR/Cas for Genome Editing*: using a bacterial defense mechanism known as CRISPR/Cas as a genome editing tool, from the basics of how the system changes DNA to how scientists have begun applying the tool in their research.

- *Between Biology and Chemistry, Toxins and the Relevance of Convergence*: overview of toxins – poisonous products of an organism which are incapable of reproducing themselves – and how they highlight the convergence between chemistry and biology due to their nature and coverage by both the CWC and BWC.

- *Biological Circuits and Biobricks in Systems Biology*: biological circuits, computers and memory in systems biology, and how multigene systems can mimic or affect metabolic pathways, thus enabling more sophisticated and precise manipulation of a living entity.

- *Antibody-Drug Conjugates and the Specific Delivery of Cytotoxic Payloads*: today's industrial production of Antibody-Drug Conjugates (ADCs) for the targeted delivery and release of cytotoxic payloads to cancer cells.

- *Applications of Nanoparticles in Biology:* surface-coated nanoparticles that perform functions common in biology, but rather unusual in chemistry, by mimicking folded biomolecules in a way that they exhibit the coexistence of regularly arranged hydrophobic and hydrophilic structures on a length scale on the surface.

- *Current and Future Impact of Additive Manufacturing (3D Printing) on Biology and Chemistry:* the concept of 3D printing (use of digital design data) to fabricate components via various approaches to layered material deposition.

- *Computing: Designing and Engineering of Biological Systems by Means of Computer Modelling and Programming Language:* the practice of combining computational methods with various engineering approaches in biology.

General Findings

The separation between biology and chemistry – as established in the BWC and CWC treaty regimes– has never been as pronounced in the chemical and biological sciences, thus an overlap between the disciplines is not a new development. However, certain scientific advances in this overlap continue to blur even further the boundaries between what constitutes biology and chemistry. This is reflected for example in how chemicals will be produced in the future: by traditional chemical methods, with the help of biological catalysts such as enzymes, or through the specially designed metabolic process of a self-replicating organism or an organism-like system. Drivers for pursuing a particular method of production will be based on economic, environmental and other factors. Organisms known in nature will be engineered to exhibit altered or new functions. Or their genetic functions may be reduced to a minimum 'chassis' type organism, which can serve as a building block for the design of new biological systems. Alternatively, organism-like systems with specific functionality may be chemically built from scratch.

How far and at what speed such advances will progress depends largely on developments in other disciplines acting as enabling technologies. These include data computation and management of large databases, nanotechnology, robotics, systems automation and many others. The resulting scientific and technological advances will open up new areas of application of chemistry and biology in society. The impact will largely be beneficial. But 'Convergence' also creates new opportunities and possible risks for chemical and biological arms control.

Applications of 'Convergence' will assist in developing new means of protection against toxic chemicals and infectious diseases: methods for their detection, diagnostics and identification, pre- or post-exposure medical treatment and countermeasures as well as decontamination. But 'Convergence' will also permit the production of known toxic chemicals, including toxins, by different new methods, and it may lead to novel toxic chemicals. Scientific advances will permit the engineering of known organisms that cause infectious diseases, in order to change how the disease progresses or can be treated. It will become possible to design and create new organisms based on the study of existing ones, which in turn may cause new forms or types of infectious diseases. 'Convergence' may enable new methods for distributing or administering toxic chemicals, or provide the necessary expertise to design new vectors or systems for the distribution of infectious organisms and their specific targeting.

It is important to emphasise in this context, that advances in science and technology will not transform themselves into weapons. Application of 'Convergence' to weapons development requires a weapons program. The development of a weapon based on a new biological or chemical agent requires a managerial decision followed by a

development and scale-up program, a testing phase and a doctrine for its use. How would such a program look like at state level? It would most certainly be very different from chemical weapons programs of the past.

'Convergence' may simplify certain technical procedures and at the same time reduce the necessary level of tacit knowledge required. It therefore might open up new opportunities for sub-state actors trying to develop or acquire some form of a biochemical weapon. This risk, however, is often overstated. The relative gains for sub-state actors from these technological advances remain unclear – especially if compared to the capabilities they already possess. Should certain technical steps become easier to undertake, the challenges for weaponization of a biological or chemical agent still remain considerable.

Toxic chemicals and infectious organisms will remain prohibited as weapons through the provisions of the CWC and the BWC. But the impact that 'Convergence' has on the provisions of the two regimes needs to be kept under review to avoid new gaps opening. Furthermore, new technical *opportunities* created by 'Convergence' might weaken the commitment of states to continue adhering to the regimes. But this is a question of political will. What are the forces that drive scientific progress and its practical application in society? Technology development follows directions that are determined by a desired outcome, even if not all intermediate steps are yet clearly understood. It is not likely – but also not impossible – that decisions could be made for deliberate small-scale breakout attempts from a regime.

Existing mechanisms for reviewing advances in science and technology to detect and assess key developments vary between the CWC and the BWC. The OPCW SAB meets once or twice a year to discuss a standing agenda, and every five years it undertakes more substantive reviews for the CWC Review Conference. This process is likely to capture some developments, most likely the ones affecting the chemical industry and those related to the protection against chemical weapons. The review process at the BWC is based on annual meetings of national experts, but shows little focus. It is currently not suited to evaluate and assess how 'Convergence' may affect the treaty.

Today the life sciences are advancing at an unprecedented pace. The amount of data and knowledge acquired should lead to non-linear progress in the future. Speakers from academia and industry convincingly showed in their presentations how the rate of progress in their domains is clearly outpacing treaty review cycles. Therefore, advances in the life sciences, in related technologies and industrial application require constant monitoring. Given the pace and complexity of current scientific and technological advances , today's review mechanisms, even if executed in best faith, may lack sufficient breadth, depth and quality of expertise to provide dependable results.

Outlook

Spiez CONVERGENCE cannot develop specific policy recommendations for the arms-control regimes and does not intend to do so. It also does not issue a consensus report. It is dedicated to assist its participants and readers with their own science and technology assessments, and to trigger, if possible, further discussions in other fora.

The content of this report is the result of the contribution of many authors but has been edited by Spiez Laboratory. It does not intend to fully reflect all views expressed by workshop participants and it does not represent the official position of the Swiss government.

The workshop series Spiez CONVERGENCE will continue, and the Spiez Laboratory organising team looks forward to the second edition in September 2016.

Introduction

‘Convergence’ describes integrative and collaborative trends in the life sciences that bring together theoretical concepts, experimental techniques and knowledge of different science and engineering disciplines at the intersection of chemistry and biology. Such interdisciplinary approaches often revolutionise scientific discovery and open up new areas of application of science and technology in society. The benefits of convergence can be huge, but it can also create new risks to safety and security, including the existing arms control regimes.

This was the first in a workshop series planned by Spiez Laboratory. The presentations and discussions reflected the points of views of the diplomatic, security and arms control communities; those of treaty implementers at national as well as international levels; and the views of the science advisory, research, industry and NGO communities. This broad spectrum of viewpoints helped to provide the context for the technical presentations and the subsequent discussion of their implications for arms control and security policy.

Key aspects of this context are the Chemical Weapons Convention (CWC) and the Biological Weapons Convention (BWC) – cornerstone multilateral disarmament and non-proliferation treaties. Their continuing relevance and credibility depend on their ability to adapt to changes in their implementing environments. Developments in security and policy, advances in science and technology, and changes in industry all can challenge these conventions and the ways in which they are being implemented in practice.

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Historically, chemical and biological weapons were considered together in humanitarian and arms control law. Even as our understanding evolved about what causes disease, this association remained close until, for pragmatic reasons, a separate regime was agreed for biological and toxin weapons in 1972. Completing the negotiations of the CWC took another three decades, amongst others because a verification system needed to be negotiated for the treaty to be dependable.

This regime split was the reflection of both technical and political realities. It was possible at the time because the lines between chemistry and biology were still more or less clear. Since their adoption, the two treaties have evolved in distinct and separate ways. The BWC relies today upon consultative mechanisms and exchanges among its States Parties at expert and diplomatic meetings in an intersessional process between five-yearly review conferences. A small Implementation Support Unit (ISU) supports this mechanism. The CWC, on the other hand, has created an international organisation (the Organisation for the Prohibition of Chemical Weapons or OPCW) that implements a formal verification and compliance management system.

Implementation of the CWC is organised around seven agreed core objectives (chemical demilitarisation, non-proliferation, assistance and protection, international cooperation, universality, national implementation, and organisational effectiveness). Much progress has been made already with eliminating chemical weapons stockpiles worldwide. As the eradication of all chemical weapons is getting closer to completion, more prominence is given to preventing the re-emergence of chemical weapons. To achieve and maintain a state of chemical weapons disarmament will require continuing implementation efforts at the national level as well as an effective verification system that adapts to new developments.

Convergence, as it manifests itself in the chemical industry, is one of these developments that call for review and adaptation. The OPCW Scientific Advisory Board (SAB) has addressed the impact of convergence through a temporary working group (TWG). Among the trends that the SAB has identified are the increased uses of biological and biologically mediated processes for the production of chemical products and the removal of technological barriers. The SAB expects that by 2020, biomediated processes will be responsible for more than ten per cent of the world's chemical production. It did not see any specific advantages in using biologically mediated processes to manufacture traditional chemical warfare agents, but such processes are highly relevant for other types of toxic chemicals, including peptides and bioregulators.

To achieve and maintain a state of chemical weapons disarmament will require continuing implementation efforts at the national level as well as an effective verification system that adapts to new developments.

Biologically mediated manufacturing is no longer a niche business – today it includes the production of small hydrocarbons, alcohols, amino and other organic acids, polymers and complex molecules such as peptides. The worldwide production of biofuels in 2013 was estimated at 60 million tonnes. The TWG concluded that it was important to continue monitoring the advances in production technologies, including the manufacturing of complex molecules by biologically mediated methods, and in key technology areas relevant for agent

production, delivery and protection, including nanotechnology. It is important to engage with experts working in these fields, and to assess the impact of these trends on the arms control regimes. But convergence poses certain questions already today: for example, States Parties have adopted different rules for whether they declare biologically mediated production of discrete organic chemicals (DOCs), resulting in uneven application of the CWC's provisions.

How relevant are these trends for the CWC? The convention already excludes certain types of chemical production from its DOC regime – facilities exclusively manufacturing hydrocarbons or high explosives are not declarable. How, then, should biofuel production be treated? The SAB has consistently stated that *any* production of a DOC should be covered by the rules of the CWC, whether production is by chemical synthesis or a biological process. Some States Parties disagree. But there is a broader question: which of the more than 140 million chemicals that have been registered by the Chemical Abstract Service (some 15,000 more are registered every day) are of relevance to the CWC? The CWC covers the traditional chemical warfare agents such as nerve and blister agents to toxic and precursor chemicals in industry all the way to toxins and bioregulators. With advances in delivery techniques and production methods, toxins and bioregulators may become more relevant.

Convergence is beginning to blur the lines that have hitherto separated the implementation environments of the CWC and the BWC.

Toxins are also the area where the CWC overlaps with the BWC. This overlap has had few practical implications so far. However, the recent investigation of alleged chemical weapons use in Syria and subsequently the elimination of Syria's chemical weapons programme, have also highlighted the importance of the toxin issue. The verification measures implemented in Syria have reminded us of certain shortcomings in the field of chemical analysis (biomedical sample as well as toxin analysis), the need to improve the reach-back capacity to scientific expertise, and more generally speaking the need to pay more attention to the risks posed by developments at the intersection of chemistry and biology.

In the BWC context as well, convergence has been recognised as a major trend in science and technology that affects its implementation. Reviews prepared by international science unions, assessments submitted by a number of States Parties and the background paper prepared by the ISU for the 7th Review Conference all identified convergence as a key challenge. Although convergence as such was not taken up in the current intersessional process, themes that are closely connected to it figured prominently in the intersessional work programme, both under the standing agenda item of reviewing advances in science and technology and with respect to specific agenda items. This includes: the advances in enabling technologies (2012), infec-

tious disease and toxin surveillance, detection, diagnosis and mitigation (2013), understanding of pathogenicity, virulence, toxicology and immunology (2014), and advances in production, dispersal and delivery (2015).

The discussions during the BWC intersessional process as well as the deliberations of the OPCW have shown the great benefits that convergence and, more generally speaking, the advances in the life sciences are expected to bring about. They reach from more effective medical countermeasures (for example bio-scavengers as pre- and post-exposure treatments of nerve agent exposure or new diagnostic tools such as biosensors embedded in smart phones) to new decontamination methods or detectors for toxic chemicals as well as biological agents. But convergence also creates new risks, which need to be assessed and managed.

The workshop highlighted how convergence is beginning to blur the lines that have hitherto separated the implementation environments of the CWC and the BWC. This is not, as was noted, an entirely new issue. The BWC States Parties have long recognised the need to cover all microbial or other biological agents and toxins, naturally or artificially created or altered, as well as their components, whatever their origin or method of production, as well as any synthetically produced analogues of toxins. The CWC, in turn, includes in the term "toxic chemical" all such chemicals, regardless of their origin or method of production. The drafters of both treaties took great care to ensure that there would be no legal gaps between the two regimes. The main attention of the workshop focused on the impact of convergence on the practical implementation of the two treaties and was felt to be the key area of concern. Convergence in the science base common to both treaties does not in itself call for legal adjustments such as an overarching framework to bring the two conventions together. It was argued instead that tending both treaties and keeping them apt was what was needed.

A first important effect of convergence is "time compression".

The workshop highlighted that although the overlap between chemistry and biology is not a new issue, convergence as we are experiencing it today is. It is an indication of a new multidisciplinary approach in the life sciences. This reflects the fact that when complex scientific issues are addressed more deeply, no single science discipline can comprehensively address them and multidisciplinary work will be in demand. But interdisciplinary work does not merely help solving complex problems – it can create new understandings and knowledge, and lead to new ways of undertaking research or manufacturing goods.

A first important effect of convergence is "time compression" – a dramatic reduction in the time it takes from scientific discovery to practical application in society. It is often stated that we are experi-

encing revolutionary change in the life sciences. There remain roadblocks, but experience has shown that once an obstacle is removed, progress in the life sciences is both very fast and far-reaching, leading to applications in entirely unexpected ways and fields.

Such revolutionary advancement also carries the potential of leaps in understanding, of non-linear progress. Surprise can happen in many ways – new understandings of how biological systems work, new tools that open up research opportunities at a scale hitherto unknown, manufacturing technologies that did not exist in the past, and even types of products that did not exist in the past. In an arms control context, this raises the question of whether the treaties and their implementation systems are capable of adapting quickly enough to such leaps.

A second issue to consider are the drivers for convergence. Traditionally, the drivers for scientific progress were firmly in the hands and under the control of governments. Convergence happens within a different environment where governments are only one of the actors, and where government funding – although still a major driver in research and development – is increasingly complemented by resources and incentives emanating from the markets and from within industry and the research community.

Thirdly, convergence is creating a new environment for scientific collaboration and the application of scientific results in society. This more widely distributed environment, which is enabled by data sharing and collaborations over the Internet, open-source software, open access databases and other enablers, challenges some of the traditional regulatory mechanisms that the arms control community has been successfully applying in the past to prevent proliferation (for example: export controls of dual use materials, equipment, technologies and intangibles).

These changes are not limited to the domain of science, but the industrial landscape has begun to change as well. This poses additional questions: How will convergence affect the functioning of the two treaties at the level of practical implementation? Which are the challenges that National Authorities will face in their interaction with the different domestic actors? Will the CWC industry verification regime be able to provide the transparency needed to assess compliance at the intersection of chemistry and biology? Will it even get involved with facilities in this field given the CWC's declaration thresholds? Alternatively, how will the framework for discussing verification options under the BWC change? How would BWC verification (were it to be agreed) work at the technical level, and in which manner could it be developed?

Convergence is creating a new environment for scientific collaboration and the application of scientific results in society.

Answering these questions, it was argued, requires appreciating the context within which chemical and biological weapons issues have evolved, including perceptions about their future potential utility. Traditionally, chemical and biological weapons were considered as weapons of mass destruction. In today's and tomorrow's security environment, it is perhaps less the number of possible casualties that matters, more the potential of these weapons to subjugate and coerce. New types of war, attempts by sub-state actors to acquire and use chemical or biological weapons, the use of chemical or biological weapons in covert operations, their small-scale use to terrorise and subjugate – all these scenarios define the boundaries for the assessment of how advances in science and technology may affect CBW arms control.

The disarmament community must better understand what is actually happening in the relevant areas of science and technology, and it has to evaluate how these advances affect the regimes.

Because major drivers for convergence emanate from the science, technology and industry domain, responses need to be built on the premise that convergence calls for, and also creates opportunities for, engagement between the arms control community and the scientific, technological and industry communities, at both the national and international levels.

A condition for this engagement to be productive is effective communication. The disarmament community must better understand what is actually happening in the relevant areas of science and technology, and it has to evaluate how these advances affect the regimes. The two treaty communities need to continue exchanging information and assessments, including on directions and ways of managing the risks that convergence poses to their treaties. Despite the institutional and procedural differences, further and stronger interaction between the OPCW and the ISU should be encouraged.

The science and technology communities need to be conscious of the requirements that the two regimes have established, help with the evaluation of the risks posed by new developments in their fields, and contribute to the management of these risks. Industry needs to understand what is required from it to comply with the norms and regulations established, and how it can contribute to meeting the goals and requirements of the arms control agreements and related international norms and national regulations. NGOs can assist with developing effective communication between these different communities, and help developing risk evaluation and management strategies.

The workshop showed that there was a need for genuine two-way engagement. Awareness raising and outreach are important, but sustainable long-term solutions to the arms control risks that convergence may pose will require the participation of the research and industry communities as partners of governments in the risk management process.

Chemistry making biology – biology making chemistry

The first block of technical presentations and discussions was titled "Biology Making Chemistry and Chemistry Making Biology". This block highlighted the current state and promise of genome modification and bioinformatics tools.

Researchers are capable of making directed changes to organisms on a genetic level, but systemic rational design and comprehensive predictive capability is still a goal for future research. Using tools that are already available, including direct insertion of gene sequences and directed evolution, organisms and molecules can be guided to meet a specific purpose within a reasonable timeframe and with a degree of reliability that was not previously possible. A number of examples were presented and discussed for industrial-scale production of complex molecules with application in medicine and elsewhere.

The thematic block also looked at emerging technologies advanced by findings in both chemistry and biology, as well as in the information sciences and engineering disciplines. There was a particular focus on efforts to manipulate biological systems to produce a specific desired result, with an eye towards eventually being able to engineer complete systems to produce materials of commercial value. All of the described technologies are currently used in research, and while they have potential commercial applications, most of them have yet to reach the stage of large-scale and broad-based use. The workshop noted not only the swift progress and shrinking cost of the technologies, but also identified rate-limiting factors on more rapid development and commercial applications. Despite the incredible improvements thus far, researchers are still considerably far from being able to design rationally and build complex biological systems as a matter of routine.

Researchers are capable of making directed changes to organisms on a genetic level, but systemic rational design and comprehensive predictive capability is still a goal for future research.

It is clear, however, that the academic and industrial research communities are actively working to solve these problems. It is also clear that funding and infrastructure development are critical elements for continued development, and one significant source of funds today is organisations that see a market opportunity for these new technologies.

There are still significant hurdles to commercialise such nascent technologies, and the wide-scale impact may not be seen for some years. However, since the funding drivers are no longer only health-care but include commercial interests in other fields of application, from information technology to energy production and dealing with the effects of global warming, these changes are likely to occur.

Here follows a more detailed summary of the presentations and discussions.

Directed Evolution of Enzymes for Industrial Use

Advanced computational methods and directed evolution are used to develop enzymes tailored to address a specific industrial need. Every cell, from the simplest to the most complex, relies on chemical reactions that are accelerated by enzymes,[3] and every enzyme is more complex than any man-made catalyst available today. Despite their ubiquity and versatility and a general understanding of their functionality, very little is known about the molecular mechanisms that underpin their reactivity. Given recent advances, it is now possible to take advantage of the tools of nature and those of molecular modelling to take existing, non-optimal enzymes and tailor their properties to drive chemical reactions with high selectivity and yield. These advances are steps on the path to one day being able to create fully artificial enzymes to enable reactions that are currently not possible with naturally occurring enzymes.

In keeping with the spirit of convergence, one can imagine having a set of tailored enzymes or the tools to make them in a chemical laboratory.

The technique used around the world is directed evolution. This can be applied to naturally occurring enzymes that have demonstrated the desired functionality or artificial enzymes that, based on theoretical models,[4] are predicted to have the desired reactivity and selectivity. Regardless of the starting point, the genetic sequence that describes the enzyme can be inserted into a system such as *Escherichia coli*, either at a single or multiple site, and grown in culture in a well-plate to allow naturally-occurring mutagenesis to create variations to that genetic structure. This method generates a large number of candidate sequences (~2 weeks for 2000 variations), which can be removed from this system and analysed using any one of a variety of tools. For example, the variations can be assayed and ranked in efficiency using micro-fluid screening systems. Some of these variations will demonstrate improved function for the desired purpose compared to the native state enzyme, and some that will not. Those demonstrating the most promise can be used in another round of directed evolution to further optimise the molecule.

From an industrial perspective, this technology has the potential to increase efficiency and reduce waste in existing or new processes.

3 An enzyme is a protein that facilitates chemical reactions at a high rate in biological systems. The sequence for every protein in an organism is encoded within its genetic sequence.

4 This modelling starts with the calculation of the "transition state" through which the chemical reaction must pass, followed by computing how this state can be stabilised in space (the "theozyme") and computing a protein scaffolding that would support that theozyme in three-dimensional space. With this method, it is possible to use libraries of data significantly larger than what can be accomplished solely by directed evolution.

This has already been demonstrated as possible by Merck Company, which, in collaboration with Codexis, revised a process to incorporate an artificial enzyme instead of a man-made catalyst after only 11 rounds of directed evolution. Another area where this work may be useful is in treatment or deactivation of harmful materials either *in vivo* or as part of decontamination. Finally, in keeping with the spirit of convergence, one can imagine having a set of tailored enzymes or the tools to make them in a chemical laboratory. Rather than performing reactions using small molecules or a standard set of laboratory chemicals, researchers could draw from this library to perform the reaction, potentially reducing the number of steps, increasing yield, and reducing waste and the need for hazardous materials in the laboratory.

There remain a number of challenges in doing this work reliably, quickly, and effectively. For example, the modelling tools required are still in the relatively early stages of development. Current enzymatic modelling is limited with regards to modelling electrostatics, dynamics, and tertiary structure. Though creation of the theozyme takes only a few weeks, the directed evolution required for optimisation of the structure adds considerable time to the process.

Participants discussed if it would be possible to use this technology to activate as well as deactivate a nerve agent. This was described as potentially possible, either in an *ex vivo* manner to activate a previously inert binary mixture or *in vivo* in a similar manner to a prodrug.

Genome Editing

Genome editing can be defined as "the process of manipulating the function of a living cell or organism by directly modifying the chromosomal DNA sequence." There are three approaches to accomplishing this task:

- Gene knock-out – removal of a portion of the coding sequence for a genome;
- Gene knock-in – insertion of a new segment into a coding sequence for a genome;
- Gene surgery – modification of small sections of code such as single nucleotide pairs (SNPs), generally to correct minor errors.

A critical element for success in all of these techniques is the choice of restriction enzyme used to identify the site(s) that should be cut. In order to ensure that the edit is done selectively, the enzyme must be able to reliably identify a long enough strand of DNA to ensure that the site of the break is correct. Identifying options for restriction enzymes is an area of active research, but there are a number of enzymes available to perform this task today, including zinc finger nucleases, CRISPR/Cas, TALEN, and meganuclease.

Since its creation 9 years ago, these three tools have been used to add a function to a crop (herbicide-resistant cotton plant), remove functionality in a crop (non-pollinating corn to facilitate controlled

hybridisation), and modify functionality (change pigment expression in flowers). A number of collaborations are currently under way to detoxify a variety of plants, but one project of particular interest to this workshop is that of the use of gene editing to remove ricin from the castor plant. Removal of the toxin would also have obvious positive implications for the control of Ricin, a Schedule 1 chemical of the CWC.

There are a number of technical challenges to this work including the presence of seven isoforms of the gene that produces ricin, a need to develop a new vector for introducing the modified gene into the plant, and the inherent difficulties in predicting the impact of this genetic change on the plant as a whole. Given the complexity of the system, it is quite likely that some unintended consequences may be encountered. Though the genes responsible for the toxin have been identified, it is impossible to predict what other effects removal of these genes might have on the organism itself – a common problem in genome editing. As predictive capability increases, this will be less of a concern, but currently the state of the art requires iterative development and testing to achieve a given purpose.

A number of collaborations are currently under way to detoxify a variety of plants, but one project of particular interest to this workshop is that of the use of gene editing to remove ricin from the castor plant.

There were questions about whether it would be possible to use these techniques to increase (rather than remove) the number of copies of the gene sequence for one of the isoforms in the castor plant, to increase the concentration of ricin toxin. Though this was deemed technically feasible, it remains questionable whether and why someone wishing to acquire large quantities of ricin would not simply follow the low-cost and low-tech avenue of planting more castor plants.

Holistic Characterisation of Organisms

Genomics, transcriptomics, proteomics and metabolomics together provide a set of tools in synthetic biology that can be used to design organisms with desired properties. These tools have been applied in three different industrial projects: The production of lysine – a feed additive – using *Corynebacterium glutamicum*, production of xanthan – a thickener for use in food and personal care products – using *Xanthomonas campestris pv. campestris*, and production of acarbose – a medication used to treat type II diabetes – by *Actinoplanes sp*. For each of these projects it was critical to obtain information about the cellular machinery, from genome to metabolome, in order to rationally approach modifying the organism.

This type of characterisation usually begins with sequencing of the genome. Indeed, the pace at which bacteria are being sequenced has accelerated exponentially since the first was completed in 1995.

Genome sequencing has its roots in 1953 when the DNA double helix was identified and the series of publications from 1961 to 1977 from a variety of laboratories that elucidated the genetic code and introduced the first robust technology for sequencing. The so-called Sanger method was adopted as the primary method of DNA sequencing for the next 25 years. In 2008, automated sequencing tools were introduced, along with some new forms of sequencing technology, and the cost of running a full analysis has decreased faster than Moore's law would imply since that time. Today, sequencing is largely considered a routine step in the analysis of an organism. These sequences, and importantly, the annotations created along with them describing the functions of each gene encoded by the sequence, provide critical information for the researchers about current and potential functions of the bacteria.

The importance of understanding the relationship between the genome and the behaviour of the cell cannot be overstated.

The importance of understanding the relationship between the genome and the behaviour of the cell cannot be overstated. Genes provide the base code for a cell, but as every cell contains the same genetic sequence, genes are expressed differently in each cell depending on that cell's function, environment, and immediate context. The synthesis of protein is based on the code of a given genetic sequence and is facilitated by an mRNA transcript, which acts as intermediary. That protein then performs functions within the cell by synthesising, digesting, or otherwise interacting with smaller molecules in the cell, called metabolites. For each of these stages, there exists a limited set of molecules responsible for the performance of these activities, and these sets are called the transcriptome, proteome, and metabolome, respectively. It is the presence of and interaction between these sets of molecules that ultimately determine the behaviour and function of the cell. At any given time, even though the genome remains the same, the type and number of mRNA transcripts, proteins, and metabolites varies. Understanding the full set of potential options for any given organism provides important information that can support investigations of their dynamics and capabilities.

The true value of these largely mature technologies is that they make it possible to have a holistic picture of the pathway for the production of a given molecule, and this information can be used to optimise industrial-scale production processes.

As with genomics, the technology to support the analysis of these classes of biological molecules are available, though none are as advanced in development as those for genomic analysis. The true value of these largely mature technologies is that they make it possible to have a holistic picture of the pathway for the production of a given molecule, and this information can be used to optimise industrial-scale production processes.

Although these technologies are used to characterise and optimise functions that already exist within the organism, it is possible to use the data collected with these techniques to aid in the development of organisms with significantly modified functions using the tools of synthetic biology described above. One possible application would be to use a so-called "minimum chassis", where all genes, except those that describe functions fundamentally required for cellular health under the required conditions, remain. The genes required to produce the desired product are inserted, and enough of an organism is grown to support production at scale. One advantage of this approach would be that genes supporting, for example, temperature range tolerance could be removed, in essence creating a "self-destruct" function should the bacteria be removed from its production context. Though a great deal of work and understanding still needs to be developed, synthetic biology is expected to play a dominant role in developing newly designed production strains in the future, as these tools are enabling the field to enter the realm of engineering.

A key discussion theme was scientists' ability to predict any one domain of information from another. For example, if one knows the transcripts present in an organism, can one predict the proteins? The answer remains negative, as the correlation between the transcripts and the proteins is not that clear. Not every transcript will produce a protein, and signals within a cell may trigger the activation or deactivation of a transcript or protein. The system is interconnected and complex, and predictive capability is not yet strong enough to accurately predict behaviour across these levels. Biological complexity is still the primary challenge to predictive, rational design.[5]

Industrial Biology

A primary goal of industrial biology is to develop effective, scalable and robust processes that convert a renewable feedstock such as sugar, using a microorganism such as genetically engineered yeast, to a desired chemical compound at industrial scale.

A well-publicised example of such a combined chemical and biological production process to manufacture a desired product at industrial scale is the engineering of yeast to produce artemisinin, a potent anti-malarial compound. The only natural source of artemisinin is the sweet wormwood plant (*Artemisia annua*). The availability and cost of artemisinin was highly variable and dependent on the quality and amount of the crop grown each year. Given the compound's importance to the treatment of malaria, the Bill and Melinda Gates Foundation funded research in the hopes that it would result in a reliable, high-production-volume source of the molecule.

The steps that went into designing the modified organism included 22 genetic modifications to a yeast cell to engineer an organism that is now producing pharmaceutical grade artemisinin in a fermentation and production facility in Brazil. It is the primary source of the com-

5 See also the section on systems biology further below.

pound in the world. This work took 9 years and some 130 research and development (R&D) person-years to complete, with considerable financial backing. However, the time required to complete this effort was considerably less than that required for earlier biological modification projects.

After completion of this initial task, the company refocused its research efforts on farnesene, a compound that could be synthesised using the same pathways, taking advantage of an earlier precursor compound then that used to produce artemisinic acid by the yeast. To reduce time and costs, the company automated and miniaturised as many repetitive R&D processes as possible. For example, to streamline the sequence production, a "toolbox" of sequences that have specific effects (gene sequence promoters, tags, terminators, etc.) were identified and catalogued to allow for easier sequence development. In addition, considerable effort went into automating, through the use of software and robotics, the process of assembling these sequences via one-step syntheses in well plates. This is now a standard technique for most of the development work, and increases quality control, aids in records keeping and project tracking, and has increased the rate of sequence development significantly. This has also reduced the technical skill level required to perform the synthesis. These new organisms are characterised and the data stored in a library that supports continuing research efforts.

The timeline for development of a new product has been substantially reduced when comparing the initial production of artemisinin to today's capacities.

As it has been pointed out above, directed evolution takes time. With this system, enough sequences are created regularly to reduce the need for directed evolution for much of the work, though directed evolution remains a valuable tool to draw upon when needed. The odds of landing on a beneficial sequence are increased by the sheer number of variations constructed rather than by allowing for mutagenesis to take place. Though the infrastructure for automation was expensive to develop (~$200 M), the cost per sequence to develop has dropped exponentially with the implementation of this process, and the rate at which new sequences are developed has increased by magnitudes.

The response of the organisms to the environment of a fermenter is not predictable, and any new organism must be carefully tested to prevent failures at the pilot plant scale. The timeline for development of a new product has been substantially reduced when comparing the initial production of artemisinin to today's capacities. However, the cost and time required to produce a new viable, scalable method are still high. The current process requires considerable infrastructure and trained technicians to run it successfully. Directing the path of the research still requires the input of highly trained scientists as experience, technical knowledge, and intuition are critical for identifying new sequences and engineering approaches. Even though a great deal

of data has been acquired, the process of development is still largely one of trial and error.

During the discussion, the question arose whether moving to a minimal chassis as described in the previous section would be feasible for this kind of work. That model has not been followed as of yet, in part due to the sense that much of the internal machinery of the yeast cells plays a role in maintaining robustness in conditions required for fermentation at production scale. This may change as predictive capabilities improve. This led to a question about how short the window could ultimately be for development of an organism suitable for scale up. Although it may take years to get to that point, it should eventually be possible to do this work within a three weeks' timeframe.

Generating Data for Systems Biology

Systems biology attempts to create a link in understanding from genome through transcriptome, proteome and metabolome to the phenome. Much progress has been made in the former omics, close to the genome, but the link to the phenome remains the ultimate goal in understanding how biological systems work, and to increase the predictive capacity of life science research.

A key issue in increasing this predictive capacity in the life sciences is the generation of large amounts of reliable data. The technologies for obtaining data through genomics and transcriptomics research are maturing, but a significant amount of work remains to understand the linkages and to be able to create complete models of cells with predictive capabilities. We are dealing with a dynamic rather than linear system. For example, linking the phenome—the expression and higher-level functioning of the cell system as a whole—down to the genomic level is still out of reach at present. To understand dynamic systems, the data ideally should be time resolved at a sufficient scale, be deep enough to cover all the components of the system, broad and complete enough to cover the extent of the cell model, and cheap enough to be feasible. A key question was how to make sense of the data derived from complex dynamic changes.

The field of systems biology that deals with these questions is changing focus from an obsession with data generation to data use. Currently, only a fraction of the "big data" collected through experiments is in the public domain, put to work, or its meaning known. By way of example, think about a national rail network: we might know the layout of the routes but lacking a timetable we have no idea how all the connections work – it is the same for our understanding of the functioning of the cell. This is creating a bottleneck as scientists cannot as yet interpret and determine what this data actually reveals about the full functioning of the cell. Therefore, the goal is to extract relevant information that contributes toward modelling systems' molecular components, interactions, spatial relationships, and

dynamics over time. While technologies are maturing for assessing the first three attributes, they are only in the early stages of measuring simple systems or components as they operate over short periods of time. Currently, scientists are able to produce models for simple systems and components of complex systems, but are unable to fully model complex biological systems. Improving data collection and analysis will aid in creating these full models in four dimensions, with the end goal of constructing predictive models of biology—from molecules to ecosystems—which would enable the rational engineering of biological systems involving a cycle of prediction, validation and refinement. A key step is to develop stochastic/multi-scale modelling as at present single models of single systems do not always join up. Nevertheless, technologies are becoming more mature – we are not that far away from a charge of $1,000 to sequence an individual's genome.

Think about a national rail network: we might know the layout of the routes but lacking a timetable we have no idea how all the connections work – it is the same for our understanding of the functioning of the cell.

Regulating (in the traditional sense of the word, as a top-down approach) the potentially dual-use information that already exists in the public domain as a result of these developments is already too late, and may not be possible in any case. In choosing how to approach the problem, the input of the wider scientific community is necessary both to enable use of this information for peaceful purposes and to prevent the potential misuse. Peer review of the information is critical to identify flaws, inconsistencies and gaps so that the scientific community can use these findings for biological and biomedical research to tackle climate change, the ageing population, and new biological threats—all of which are now becoming drivers of research in addition to healthcare. We are also seeing a commercialisation of academic research. All this calls for stronger self-regulation from within the life science community.

A key discussion point was the challenges of modelling complete biological systems through rational design. Large amounts of high quality data are required, and there is a need for standardisation to enable comparison of different models as well to ensure reproducibility. Scientists are trying to identify key points in biological systems that will describe how the system works, so they can collect a more limited amount of data in more detail and more efficiently. Current models of these dynamic systems are static, which limits our understanding of how biological systems behave.

CRISPR/Cas for Genome Editing

CRISPR/Cas is a new genome-editing tool, which has had transformational effects in the field of genome editing. The CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system uses a bacterial defence mechanism and is composed of two parts:

guide RNA containing sequences matching previous viral invaders, and CRISPR-associated genes (Cas genes) that code for proteins to cut invading DNA. In nature, bacteria will actively incorporate DNA from previously unrecognised invaders into their CRISPR loci, the nuclease system that defends the bacteria against invading phages and plasmids. The CRISPR system targets and cleaves specific sequences of invading DNA, thus providing a barrier to horizontal gene transfers in which new DNA is incorporated into a genome through recombination or insertion.

RNA guide the targeting and destruction of DNA through the recognition of certain target DNA at the atomic level. There are three types of CRISPR systems. The workshop looked specifically at Type II systems. The Type II CRISPR systems require the presence on the target DNA of a protospacer associated motif (PAM) – a short DNA sequence immediately following the DNA sequence targeted by one of the Cas genes. It has been shown that Cas9, the gene necessary for cleaving invading DNA, will not bind to the correct target DNA sequence if the PAM motif is missing.

Creating site-specific breaks in DNA allows for DNA manipulation near the cleavage site – either gene knock-outs (deletion) or transgene insertion ("gene surgery"). This one-protein, one-RNA system makes the tool specific, versatile, scalable, and easy to design. Scientists can now build a single genome-editing tool that targets multiple sequences of a genome. Even though it is only two years old, researchers have already used CRISPR/Cas as a genome-editing tool in a wide range of cells – human, animal, insect, bacteria and plants. It has multiple applications as a research tool for reverse genetics, synthetic biology, creating animal and cell-based models of human diseases, viral delivery into tissues/organs and gene therapy. That said, more work is still needed on the gene therapy aspects. The specificity of CRISPR/Cas creates the possibility of probing gene function in specific cells and tissues, engineering specific mutations to mimic human disorder in animals, and gene corrections delivered virally to specific tissues or organs. RNA is the key to genetic and epigenetic engineering.

The CRISPR/Cas tool has proven to be a transformational technology: it is simple and accessible, allowing scientists to conduct targeted genome editing easily and in a scalable way.

The CRISPR/Cas tool has proven to be a transformational technology: it is simple and accessible, allowing scientists to conduct targeted genome editing easily and in a scalable way. Reflecting these benefits, a large number of research laboratories around the world have adopted the CRISPR/Cas tool in the two years since its introduction. Current research applications of CRISPR/Cas include experiments on monkeys inactivating the genes for two human diseases, which poses the question of potential applications in humans. Some participants pointed out that although CRISPR/Cas has not been devel-

oped for human applications at this time, other gene editing techniques are about to enter the first stages of clinical trials, making it possible that the world will see such studies in the future. The Intellectual Property Rights aspects of this technology, on the other hand, are very unclear at present.

Toxins and Convergence

Toxins are poisons produced by living organisms, but as chemicals they are incapable of reproducing themselves. They represent a good example for understanding the convergence between chemistry and biology, both because of their nature (toxic chemicals produced by living organisms) and because of their coverage under both the CWC and BWC. Growing research interest in toxins for applications in medical treatment, life sciences research, pharmaceuticals, and agriculture shows that technological advances are changing the way in which toxins are being produced and used. The effect that these developments will have on the future implementation of the two conventions remains to be assessed.

The high specificity and potency of toxins on their molecular targets make them very attractive tools in life sciences research – in cell biology for instance, and their phylogenetic diversity makes them ideal lead compounds for the development of new drugs. This is a strong driving force in toxin research. At present, four toxins – one of which is in clinical trials – are used as drugs in therapeutic use.

The technical capability for chemical synthesis of toxins exists, and synthetic biology approaches could also be used for toxin production and modification. Specifically, there is current research in synthesizing saxitoxin by exploiting the function of *sxt* genes, expressing the ricin A and B side chains through modifying *E. coli*, and chemically modifying conotoxins to develop new drug candidates. But there are still drawbacks to producing and using toxins as weapons: despite their potency, it is very difficult to produce them in large quantities (with the exception of ricin). Also, for proteins with multiple S-S bonds, the correct folding of the molecule remains an issue. Many toxins have poor thermal stability, and (as they are solids) they require special means of dissemination as aerosols. The OPCW's SAB suggested to keep under review the feasibility of using metabolic engineering and synthetic biology to obtain toxins, but this raises the question: how close are these technologies to practical means of toxin production and modification, and what actions or measures may be taken to manage the risks involved?

There are already certain concerns about verification challenges for the CWC, an example being the growing production and use of botulinum toxin for both therapeutic and cosmetic purposes.

The workshop discussions confirmed the current drawbacks of toxins as weapons, particularly given their poor stability and im-

pediments to producing them in large quantities, but also confirmed the view that there should be continuing discussion on whether new technologies will one day enable the cost-effective production of large quantities of toxins. There are already certain concerns about verification challenges for the CWC, an example being the growing production and use of botulinum toxin for both therapeutic and cosmetic purposes. There remain significant technical hurdles to synthesising toxins, particularly in large quantities. Verification of toxin production and, more importantly, investigations of the alleged use of toxins as weapons, would require the development and validation of methods of chemical analysis so that toxin analysis could be integrated into the work portfolio of the OPCW's system of designated laboratories. Despite the current barriers to large-scale toxin production, however, toxins pose a threat not just due to their potency, but also because they can be used in unique ways – such as poisoning food supply – to harm human life.

Biological Circuits and Biobricks in Systems Biology

Another important trend, and a reflection of the fact that biology is also converging with and changing into an information science, is the development of biological circuits (switches enabling binary calculations, memory elements), eventually leading to the possibility of biological computing. Groups of genes – known as pathways – are used in living systems as modular blocks responsible for all functions. Trying to mimic or affect these pathways with man-made, multi-gene systems (circuits) can enable more sophisticated and precise manipulation of a living entity. Four types of gene circuits were discussed in some detail at the workshop. The first, synthetic gene oscillators, are engineered gene circuits that cause regular or periodic expressions of a gene, such as genes that fluoresce in a periodic fashion under certain conditions. The second type is called a network-based memory switch, in which a gene circuit is built to produce a lasting response to a temporary stimulus. The third type of circuit, known as a genetic memory switch, involves encoding heritable memory into a genome through recombination, as a first step towards building complex circuits.

The expectation is that sophisticated gene circuits are the future of genetic manipulation of living systems.

Most of the discussion focuses on the fourth type of circuit, known as biological computing, where the presence or absence of specific inputs will determine the circuit's outputs. The work is premised on logic models; if certain inputs are present in a predetermined fashion, then they produce a specific output. To effect these changes, it is possible to use microRNA, which functions in RNA silencing as a natural "off" switch. This research has medical applications in targeting tumors – the biocomputing circuits can be designed to produce a response when they identify tumor cells by the presence or absence of certain molecular features. More broadly, these circuits have appli-

cations in bioproduction, environmental monitoring, diagnostics, and gene and cell-based therapies.

Sources of the "building blocks" for these circuits can be found in physical and virtual repositories, in nature, or they can be developed by in-house design or outsourced synthesis. Physical repositories, such as Addgene or the Registry of Standard Biological Parts, are timesaving, but with new low-cost DNA synthesis and DNA cloning techniques, only the DNA sequence of the building blocks is needed to procure and assemble them. The current bottleneck, it was observed, is not the DNA assembly itself, but lays in making sure that the circuit works as planned from phenotype to genotype, i.e. in obtaining the function that is desired. The expectation is that sophisticated gene circuits are the future of genetic manipulation of living systems. An analogy was drawn between biocircuit development computing: we are still at the DOS stage rather than what we see today in personal computing with the availability of applications for the current generation of a variety of operating systems for personal computers, tablets and smart phones. Compared to *in silico* computing, biocircuits are still at an early and basic stage of design. The current technology does not provide the desired level of control to make biocircuitry useful for commercial applications, but the problems are not intrinsically unsolvable. Some of the bottlenecks identified include the level of complexity faced in making even simple circuits, the difficulties in delivering DNA payload directly to cells, and the pains of moving through the national health, safety and environmental regulatory processes. It was observed that unless a perfect biological transistor were created to amplify and control effects, it was unlikely that a point would be reached where robust biocircuits can be easily created for all phenotypes. There is, however, an increasing interest from funders, which is expected to drive the field forward – especially if there were a few successes emerging from these research efforts.

Take-home points

The discussions under this thematic block of "chemistry making biology, biology making chemistry" highlighted a number of points that describe the current state of affairs, and that were important to inform the subsequent discussion of policy implications of convergence (see the last section of this workshop summary). Here is a brief recollection of key points:

- Genome editing tools are state of the art, and the understanding of biological functionality from genome to phenome is increasing, but at-will, rational design of biological functionality from first principles is not yet possible;
- Understanding and managing the complexity of biology and the responsiveness of dynamic biological systems are still the greatest challenges for rendering biology predictive;
- The life sciences are advancing quickly, including through the generation and collection of vast amounts of data (increasingly to common standards) and better modelling;
- A number of success stories for scaling up from laboratory to industrial scale production have shown the potential that is inherent in convergence for changing the industrial landscape;
- Regulatory policy in this area is evolving relatively slowly, and in an uneven fashion between different countries;
- Implications of this research on the implementation of the CWC and BWC remain unclear; there does not appear to be an immediate impact on either treaty so there remains time to develop appropriate responses, while bearing in mind that non-linear progress is to be expected; and
- The democratisation effect of synthetic biology and systems biology, with public access to information and tools and crowd sourcing of data collection and analysis, may be significant factors in research in the future, despite the role of tacit knowledge.

Enabling Technologies

The second thematic block of technical presentations and discussions of the workshop looked at enabling technologies. Many of the research tools addressed in the previous thematic block are also relevant in this context, as they clearly exhibit enabling characteristics. But their primary area of application, at this stage, is in the field of facilitating life science research itself. The focus of this thematic block was on those technologies that facilitate the practical application of new scientific discoveries in industry and society. This includes technologies necessary for the production of chemical or biological materials, and for their delivery (as medicines or in the field).

Antibody-Drug Conjugates (ADCs) and the Specific Delivery of Cytotoxic Payloads

Antibody-Drug Conjugates (ADCs) have been developed and tested for the targeted delivery of cytotoxic payloads to cancer cells. This research is conducted to find alternative ways of cancer treatment that would avoid some of the pitfalls of current oncological treatments. Despite recent breakthroughs, current oncology treatments have limitations in the process of targeting, penetrating and releasing cytotoxic agents into cancer cells. On the one hand, monoclonal antibodies are selective to the antigens, but lack the potency to attack the cancer cells; on the other hand, cytotoxic agents (typically peptides or small molecules) can be highly toxic, but lack the necessary selectivity. The consequence is systemic toxicity for the patient with side effects that need to be managed and that limit the applicability of the treatments available. To overcome this limitation, an approach has been developed which combines selectivity with toxicity, by linking antibodies and cytotoxic molecules together in the form of ADCs. This represented a step closer to the 'ideal' cancer treatment through its exploitation of antibodies that are chemically modified with a linker to be loaded with a potent cytotoxic compound and can bind to the target antigen, become internalised and then release the toxic agent, killing the cancer cells.

At this stage of development, ADCs are expensive drugs, but the approach is considered competitive based on their increased efficacy. Moreover, two such approaches have met with FDA approval and some 30 other ADCs are currently in clinical trials at different phases. The Swiss company Lonza, for example, has developed both the capacity to produce bulk quantities and the specialist skills and experience in both the chemical and biotech fields necessary to manufacture ADCs. In terms of capacity, reactor sizes can vary from small (6 to 60

litres) to large scale (up to 600 litres, batch sizes up to 3 kg). In terms of safety, given the high toxicity of the cytotoxins used in the ADCs, the production environment is characterised by high containment, the use of isolators and safety hoods, and rigid standard operating procedures must be followed.

Looking at the impact of these developments on the CWC and the BWC, the question was raised whether the high-containment production unit could be subjected to international inspections (amongst others given intellectual property issue), to which it was suggested that there was already experience with visits by licensing authorities and this may not be too difficult to apply to other types of inspections of the facility provided there was an agreed need and there were guarantees of IP protection.

The development and production of ADCs also raised questions with regard to the declaration and verification thresholds in the Chemical Weapons Convention (CWC). Current production levels remain well below these thresholds, but what about the potential for increasing batch sizes by using larger equipment? It was suggested that batch production could theoretically be increased, however, the emphasis was on quality rather than quantity. The amounts produced had to match market demands, and given the envisaged shift towards personalised medicine in the future, it was suggested that a more likely route would be small batch production of a diverse range of medicines tailored to the requirements of each individual patient.

Given the envisaged shift towards personalised medicine in the future, a more likely route would be small batch production of a diverse range of medicines tailored to the requirements of each individual patient.

Questions were also raised over the drivers of costs, to which it was indicated that the manufacturing process is a minor part of the price of the drug, rather the costs are created by economics of product development and clinical trials. Other questions concerned best occupational health and safety practices and sharing of such practices. Companies apply inter alia, occupational health surveillance for staff, medical checks and monitoring of the air and surfaces. Whilst there was some sharing of best practices and exchanges of know how in these areas nationally, interaction was limited and there remained a reluctance to share more broadly with competitors.

Patchy Particles: Applications in Biology

Patchy particles have been so called because of the surface properties they exhibit. The work on such particles builds on the recognition that folded biomolecules exhibit a feature not typical for smaller chemical molecules, namely the coexistence of hydrophobic and hydrophilic centres on the surface of the same molecule. Mimicking this configuration on surface-coated nanoparticles, it was possible

to generate materials that performed functions that were normal in biology, but are not as common in chemistry. The work described here related to nanoparticles, specifically how gold particles coated with hydrophobic and hydrophilic compounds could be used to imitate certain biological functions. Using one-step synthesis, it is possible to generate nanoparticles coated with arrangements of hydrophobic and hydrophilic compounds on a length scale similar to biological materials. This, it was argued, is important, as the specific arrangements of such surface compounds have fundamental consequences for solubility, adhesion, catalysis, and molecular recognition of particles.

In chemistry, recognition on a molecular level is usually achieved through a 'lock and key' mechanism, wherein researchers sought to generate structures that contain rigid cages of a particular shape and size so that only molecules of a matching size and shape can fit in. In biological systems, however, molecular recognition functions differently, relying on what could be described as selective open cages. One can imitate this mechanism by using gold nanoparticles coated with arrays of hydrophobic and hydrophilic compounds, as a result of which these nanoparticles have been shown to have the ability to penetrate cell membranes. Such nanoparticles could either be designed to carry small payloads of highly active drugs (for example certain peptides), or the nanoparticle itself could act as a drug by interacting with viruses. Specifically, it offered a means of mimicking the heparan sulphate cell membrane receptor to trick viruses into opening-up and releasing their DNA before entering the target cell. This technology is important given the limits of Anti-viral drugs which attack the virus inside the target cell but at the expense of exhibiting detrimental cytotoxic effects. Virucides, it was argued, would be better, not least as they can disable a virus before it enters the cell, with potentially less side effects for the patient. More importantly, the nanoparticles could be used outside the body before the virus is taken up.

Using one-step synthesis, it is possible to generate nanoparticles coated with arrangements of hydrophobic and hydrophilic compounds on a length scale similar to biological materials.

The efficacy of this approach has been demonstrated through identifying common receptors targeted by a variety of viruses and using the technology to mimic such receptors in order to destroy these viruses, effectively creating a novel decontamination technique. Such a virucidal approach could be used to treat virus-contaminated water, or to applying virucides on surfaces which humans touch regularly, such as door handles. There is also potential of using this technology to better understand the underlying causes of the thermal instability of vaccines in order to find ways of stabilising them for transport (for example by adding sucrose to increase the viscosity so as to prevent small DNA releases), which practically speaking could potentially revolutionise the laborious logistical process of vaccine delivery to remote areas, for example in Africa.

This research raised a number of questions. From a scientific perspective it led to queries about the possibility of DNA – even edited DNA – delivery into a cell, something which was being considered. It raised questions over the stability of nanoparticles and the wider effects on tissues potentially caused through their use as virucides. Concerning the former, it was suggested that particles have demonstrated stability of up to 3 years in laboratory conditions. In relation to the latter, there was a degree of uncertainty in terms of the knock-on effects and unexpected bindings that could occur, although it was argued that even if nano-virucides were internalised within the body they may still be safe in clinical treatment.

Additive Manufacturing (3D Printing)

The third issue in this thematic block was the current and future impact of additive manufacturing (3D printing) on biology and chemistry. Additive manufacturing is the use of digital design data to fabricate components via layered material deposition. It was pointed out that this is not a new concept, rather it dates back to 1984. However, whereas in 1984, there was a single company using a process called stereolithography, there are currently more than 50 companies around the world using seven different processes, of which 'powder bed fusion' and 'directed energy deposition' represented the state of the art. Such cutting-edge methods enabled the printing of a plethora of exotic and high performance materials, including plastics, metals, ceramics, composites and biological materials, with metal products demonstrating the equivalent properties to products produced by traditional machining, although comparison was difficult because of the limits of data and methods for assessing 'strength'. Many companies are working in the field of additive manufacturing today, but few, it was observed, are able to build structures larger than 0.02 m^3, although one company was able to build up to 12.73 m^3. Moreover, in order to obtain properties comparable to traditionally manufactured items, printed products required post-processing to improve strength, through for example treatment by hot isostatic press (HIP) to reduce porosity. Other factors to keep in mind in consideration of the implications of additive manufacturing were the high initial costs for machine and materials, and the time consuming nature of 3D printing.

The technology offers a means to subvert traditional controls on process equipment made of high performance and corrosion resistant materials controlled by the Australia group.

Despite such limiting factors, additive manufacturing remained an area of relevance to the conventions for several reasons. Firstly because of the potential of 3D printing for building customised reaction vessels, such as micro-reactors and the related processing equipment, which although limited in volume sizes (at the moment: 10 ml or less) could nevertheless eventually allow someone outside a chemistry laboratory or plant to print production equipment configured specifically for a particular end product. The technology thus offers a means to subvert traditional controls on process equipment made of high per-

formance and corrosion resistant materials controlled by the Australia group. The technology also offered the potential for automatic production of human tissue and organs with at least one company (Organovo) able to generate 3D-printed tissue culture systems that is now undergoing advanced, pre-clinical pharmaceutical testing. The technology thus potentially offered actors the possibility of lower production costs and materials used and, significantly, a smaller footprint for production.

With regard to governance of 3D printer manufacturers, there was a suggestion that there had been a code of conduct put in place, although the extent and efficacy of such a code (or codes) was unclear. There also was the question of the extent to which this offered anything new per se from a security perspective, and whilst it raised issues for export controls, sending recipes electronically for printing may not be substantially different from traditional outsourcing. However, it was an elegant prototyping tool and could allow for the construction of previously difficult to manufacture equipment, such as 'tubes within tubes within tubes'.

Another issue was the envisaged time before substantially larger printing capacity would be available – years rather than months. Yet another query related to the ability of 3D printers to work with different materials and different moving or separate component pieces, to which it was suggested that at this stage, two to three different materials can be printed at the same time, and separate components could be printed individually and subsequently assembled.

Designing and Engineering of Biological Systems by Means of Computer Modelling and Programming Language

The practice of combining computational methods with engineering approaches in biology dates back to 2000, and soon after generated a number of predictions over the rapid synthesis and assembly of organisms on demand. More than a decade later such predictions have largely yet to materialise, in part because of the underlying complexity of biology. Nevertheless there have been developments and a number of computational methods, software tools and programming languages have recently emerged in the life science community which have served to compress the laboratory time required for converting design of a recombinant vector to its delivery. This has accelerated the pace of generating recombinant possibilities, and, given the pace at which synthesis technology is moving, one could speculate as to whether traditional cloning approaches will become obsolete in 5–10 years from now.

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Computational tools have been used to predict peptides and proteins from DNA sequences that nature did not use for expression. The goal of this type of research, for example the Synthetic Proteome

project, was to make useful peptides and proteins from non-coding DNA sequences. The initial experience with the use of computational methods to predict proteins from pseudogenes indicated that non-coding genome is an 'untapped goldmine' of therapeutic peptides and industrially useful proteins. However, moving from parts to pathways, it appears that to be commercially successful, a lot of fundamental biology still needs to be in place, particularly from the perspective of generating "contextual and modularity data". It was suggested that in the foreseeable future, the research community will most likely predict and perfect behaviour of biological parts like promoters, transcription factors and the ribosome binding site, and a "Registry of Standard Biological Pathways" would eventually replace Standard Registry of Biological Parts, as it offers a much better use-case.

But what are the implications and concerns generated by this sort of work? From a safety and security perspective, it was suggested that it could be useful to track molecules (peptides and proteins) that have failed clinical trials due to toxicity issues as these are readily available toxicity data in the public domain with a potential for misuse. There was less concern over the implications of 'computer-aided garage biology' leading to harmful outcomes as this remained an enormous challenge at the technological and biology levels at this stage. The design of an engineered yeast chromosome, for example, took more than 5 years, even after ensuring generous funding, advanced technological support and highly sophisticated skill sets. Thus it was not certain whether we will ever see a biofoundry that manufactures living organisms as a function of computer models. However, it was suggested that security and safety concerns would become more serious once (a) the cost of chemically synthesising DNA and proteins drops down significantly, (b) stable non-native modules of genetic circuits are routinely assembled, and (c) table top DNA / protein synthesis machines become affordable.

A number of questions were raised regarding the suggestion that it would be useful to track molecules that have failed clinical trials due to toxicity issues. It was pointed out that there must be tens of thousands of compounds that failed tests for various reasons – including toxicity – and in most cases these were locked away in proprietary libraries but nevertheless could pose a risk; however, others pointed out that there was already an abundance of ways of poisoning people and unless such compounds offered a less expensive, more accessible or qualitatively different means of causing harm, there would be few relative advantages to this route. Other participants picked up on the importance of the life sciences becoming an information science and the implications of more distributed research, development and production, which could present a very different footprint of a chemical or biological weapons programme and may call for different control approaches. As one participant queried, it still remains to be seen whether the democratisation of biology and the deskilling offered by enabling technologies present a real game changer.

Take home points

As in the previous thematic block, the presentations and discussions under the title “enabling technologies” highlighted a number of key points:

- Market conditions and demands are the determining drivers that influence how industrial production is evolving that builds on convergence;
- Nanotechnology is an increasingly important area of multidisciplinary work; it is being applied to developing systems that are entirely synthetic in nature but mimic certain biological functions – this may open new opportunities in medical treatment, decontamination and other fields;
- New types of technology (such as 3D printing) can revolutionize manufacturing by bringing distributed production closer to the end user, and enable production of goods that at the moment are difficult (and hence expensive) to manufacture;
- New tools and research may lead to the discovery or design of biomolecules that do not exist in nature – these may have potential as therapeutically or industrially useful biomolecules;
- As enabling technologies are more widely distributed and relatively cheap (or getting cheaper), this poses challenges to traditional ways of proliferation control measures such as export controls.

Policy Implications

The impact that convergence has on the arms control regime governing chemical and biological weapons needs to be kept under review so as to ensure that *no gaps open up* in the combined legal coverage of the CWC and the BWC. The workshop has shown primarily with respect to any weaknesses in *implementation* that the impact of convergence on the arms control regime is what needs to be assessed. Furthermore, the workshop highlighted concerns that new opportunities created by convergence might weaken the commitment of states to continue adhering to the regimes.

Convergence also can create new opportunities for sub-state actors to acquire capabilities to employ some form of a biochemical weapon. There was broad agreement, however, that these risks are often overstated. The relative gains that sub-state actors could reap from these new technologies, if compared to the capabilities they already possess, remain unclear. Also, the challenges of weaponisation remain considerable with regard to mastering the required science, developing the entire spectrum of technical skills needed to develop and to use biochemical weapons effectively, as well as acquiring the tacit knowledge that is needed to move from a novel agent to an effective weapon.

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Nevertheless, the life sciences are advancing at an unprecedented pace, and the amount of data and knowledge acquired is such that non-linear leaps in science and technology should be expected which could lead to a genuine sea change. The wide and rapid impact that the removal of a single obstacle can have, became apparent during the workshop when the use of CRISPR/Cas in genomic editing was discussed.

The advances in the life sciences and related technologies and industrial applications, therefore, need constant monitoring. More importantly, the risks to the arms control regime need to be assessed and policy responses need to be designed to manage them.

Such risk assessments differ somewhat from traditional (safety) risk assessments that are based on the quantitation of event probabilities and impacts. The advances in the life sciences create many opportunities that will be difficult to predict or quantify; some new technol-

ogies may be capable of manufacturing things we have not been able to make in the past (additive manufacturing / 3D printing could serve as an example).

The farther the distance in time grows from the chemical and biological weapons programmes of the Cold War area, the more one must ask what a novel chemical or biological weapon might look like. Would risk evaluation actually recognise the intended use of certain chemical or, perhaps more importantly, biological agents? What would a new biochemical weapons programmes look like? Would it be widely distributed, perhaps even between several countries? How would the different activities that make up such a programme be outsourced to customs manufacturers who don't necessarily know the intended end product? How does one deal with the possibility of renting production capacity, or of proliferation networks setting up semi-legitimate front companies to obscure their activities? In short, what sort of footprint would a future CB weapons programme exhibit, and how would the implementation and compliance mechanisms of the two conventions detect non-compliance attempts?

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Some of the answers to these questions flow from answers to other, related questions: what would be the aim of such a future CB weapons programme? Would it aim at the acquisition of a weapon of mass destruction as in the past, or (more likely) the acquisition and use of chemical or biological agents in smaller amounts for other purposes (terror, destabilisation, manipulation), in ways that make it easier for a perpetrator to deny responsibility for the attack?

These are difficult questions, but they are not new. The same issues were raised when the BWC, and decades later the CWC, were being negotiated. Today as then, the answer lies in understanding the context. Compliance assessments, evaluation of verification data and the enforcement of national implementation requirements need to be based on a clear understanding of how chemistry and biology are done in different countries and circumstances. They need to be undertaken in partnership with the science and industry communities, and in synchrony with the compliance measures that a responsible science and industry community itself applies.

One aspect of understanding the context is to appreciate the forces that drive scientific progress and its practical application in society. Decisions about the directions that certain technology developments take are not automatic, nor are they blind. Technology development (perhaps more than scientific advancement) follows directions that are determined by desired outcomes. That is so, even if the intermediate steps are not as yet clearly understood. It is admittedly more

complex to establish (verify) intent in the field of biology as compared to chemistry. There are also other factors that can complicate the picture, from what might be called "institutional irrationalism" that can occur in governmental decision-making, to deliberate but small-scale breakout attempts from the regime that can be more easily denied.

In the final analysis, evaluation of developments in their context (and evaluation of that context) is essential for any form of compliance management. Science and technology advances do not by themselves mutate into new types of weapons. The development of a weapon that employs a newly discovered biochemical agent involves choices in auxiliary technology development, policy as well as managerial decisions on how to establish and execute a programme, the development of the doctrines and tactics to employ the new weapon, and many other steps. Understanding drivers, intents and incentives are important aspects of compliance assurance.

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But are the advances in the life sciences and related industrial applications outpacing the progress made in diplomacy to adapt the regimes, or even in national implementation of the requirements emanating from the arms control regimes? There certainly is a risk that a lack of political will to adapt treaty implementation to a fast-changing research, development and production environment could result in a loss of treaty relevance, effectiveness and sustainability.

Some of the relevant industries are, of course, applying their own internal voluntary measures to ensure that their products and services are not used to illicit ends. But these self-controls cannot be considered a fool-proof system. A pertinent example is the difficulty that states and the industry have to prevent and control the production and distribution of illicit drugs and related precursors and solvents. Strong incentives and drivers on the market create significant obstacles for effective measures to curtail and prevent illicit drugs trafficking.

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Comparably strong incentives and drivers may not exist with regard to chemical and biological weapons acquisition. Nevertheless, smaller companies often lack capacity to implement compliance assurance systems, companies under severe economic pressure may take irresponsible decisions, and there are limits to what a company can know about some of its business partners (for example when renting out production capacity to clients, or supplying biochemical products to customer specification). For example, the recent trend towards

wider use of generics as medicines has resulted in an explosion of biochemical manufacturing capacity with many bigger companies relying on outsourcing of the production of many specialty products.

There is also the question of whether in fact all countries and industries with relevant research, development and production activity actually apply all the necessary controls. There are significant differences between countries in how they apply and enforce the requirements under the two regimes. One example is the uneven application of transfer control requirements for dual use goods. At the same time, export controls are another example for how a partnership between governmental agencies and industry can be developed effectively through outreach, awareness raising, information sharing and collaboration, thus complementing regulatory mechanisms.

All these considerations lead to the recognition that a closer and more profound interaction between the arms control community and the life science community (including its associated industries) is needed. The mechanisms for this interaction, and for science and technology monitoring and evaluation, have evolved differently under the two conventions. On the one hand, there is the OPCW's SAB that, after an initial phase of finding the right balance and mechanisms, including the use of temporary working groups and correspondence mechanisms, is today generally seen as dependable and effective. On the other hand, there is the intersessional mechanism of the BWC with its standing agenda item on science and technology and additional, more focussed annual topics that deal with specific advances in certain areas of life science research.

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Both mechanisms have their pros and cons. Irrespective of the particular model chosen, flexibility and the ability to reach back into the science and technology communities to tap into their specific expertise are essential. It is important to reach out to these communities, to marshal their support, to ensure compliance with the provisions of the two treaty regimes. This can include formal and representative mechanisms, such as the SAB (if the risks of politicising can be curtailed), but for certain conversations, less formal interactions such as the current workshop are important to ensure transparency and confidence.

More generally speaking, science and technology monitoring and evaluation should be a two-way process that involves the arms control community as well as the life science community. The people who "do the work" are often the best detectors of compliance issues, but they need to be aware of the regime requirements, be empowered to resolve problems, and have the authority to contribute. This requires engagement and trust between the two communities.

To ensure that the conclusions and recommendations that emanate from this interaction are in fact taken up by the legal and political mechanisms of the two conventions, it is important to "embed" this science and technology review and advice into their legal and policy environment. This is where the crux of the problem lies – in the ability and will of the political actors to adapt treaty implementation to changing requirements and to this end engage in partnerships with science and industry.

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