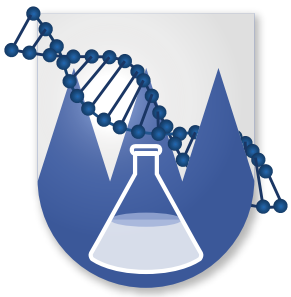

Spiez CONVERGENCE

Report on the fourth workshop
10, 13–15 September 2021

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Executive Summary

Switzerland started the Spiez CONVERGENCE conference series in 2014 to continue the discussions the Organisation for the Prohibition of Chemical Weapons' (OPCW) Scientific Advisory Board (SAB) had started on convergence in chemistry and biology. This fourth edition again offered a platform to the science, industry and arms control communities for monitoring and discussing how new developments in science and technology may affect the regimes governing the prohibition of chemical and biological weapons.

The COVID-19 pandemic led to the postponement of the 2020 conference for one year and to a change in the workshop format. Presenters and participants joined remotely, only chairs and rapporteurs gathered at Spiez to conduct the virtual proceedings. Whilst this format put time constraints on the conference programme, it allowed for a wide range of geographical participation.

Previous editions underscored how important it is to understand the state of maturity of a technology in order to evaluate its impact on arms control and security. Not everything that science and technology promise will eventually become reality; and new scientific discoveries do not equal new weapons. This conference reviewed technologies at various stages of maturity – from fundamental research to globally distributed technologies at industrial scale. In three half-day sessions, this year's conference discussed the subjects summarised below.

How advances in science and technology influence the synthesis and utilisation of chemicals and expand the potential of this "chemical space" at a fast pace, is a reoccurring observation at Spiez CONVERGENCE. Automated synthesis and screening, better algorithms and higher computing power allow identifying molecules with predicted characteristics. This may help with the development of new treatments and diagnostics.

An example for the utilisation of chemical molecules and the expanding potential of the "chemical space" is **Positron Emission Tomography** (PET). PET is an imaging technology that uses radioactively labelled chemicals as PET tracer. Glucose with one hydroxyl group substituted with ^{18}F is an example for such a chemical tracer. PET is a highly sensitive diagnostic method that can help to detect pathological changes before any morphological manifestations occur.

Biocatalysis is a second example for how advances in science and technology are expanding the "chemical space". The OPCW SAB keeps this subject under review because of the application of biologically mediated processes for the industrial production of discrete organic chemicals. Biocatalysts have many advantages; they offer reaction and stereo selectivity, are generally non-toxic and easily biodegradable. They also operate under similar and

generally modest reaction conditions for different types of chemistry. Biocatalysts do not pose particular concerns regarding the synthesis of known chemical warfare agents. They however provide access to molecular structures that are not easily produced otherwise through traditional methods and they play an increasingly important role in the manufacturing of certain chemicals, e.g. fragrances, which was presented during the workshop.

Genome Engineering is a recurrent theme at Spiez CONVERGENCE. This conference looked at advances in **Digital Genome Engineering**, using algorithms to facilitate assembly of DNA constructs from genome sequencing data stored in digital databases. New algorithms help streamline DNA synthesis. They optimise the native DNA sequence and maintain the coding for the target proteins without compromising functionality. In April 2021, the first computationally optimised semisynthesised cells were made, and full cell synthesis capability is projected by 2023. Today's computer algorithms enable the generation of entire genomes from scratch, providing new solutions to pressing challenges. However, a wide accessibility of genome synthesis increases the potential for accidents as well as for technology misuse.

Projects in synthetic biology require relatively long DNA strands of many thousand base pairs in length. Today, the synthesis of DNA is error prone, in average one error occurs in every 200 base pairs. Conventional error correction is laborious and under the title **Third Generation DNA Synthesis**, binary assembly error removal was presented as a solution. Currently at prototype stage, the method is based on three core technologies: a chip with thousands of pixels independently thermally controlled, phosphoramidite chemistry enabling thermally controlled synthesis of single stranded DNA, and on-chip assembly of single DNA strands into double-stranded DNA. Errors are recognised and removed during assembly based on the physical property that heteroduplex DNA strands melt at a lower temperature than a strand that has a correct match. Future plans include a plug-and-play bench-top instrument utilising "smart" consumables. The aim is to provide researchers with modular third-generation bench-top DNA synthesis capability. The potential associated with this technology goes far beyond that of genome cloning or genome editing (e.g. CRISPR), and so does its potential for misuse. The consequences of the growing access to tools of synthetic biology have yet to be fully understood, as well as the requirements for regulation and/or oversight.

In the area of **Nanoscience and Nanotechnology** this conference looked at the use of nanomaterials as drug delivery systems. A drug release mechanism was presented that responds to physiological or other stimuli and which has reached the stage of preclinical studies. Nasal or oral uptake of nanoparticles of glucose-sensitive polymers deliver insulin to diabetic patients. At high glucose levels, the nanoparticles degrade and release insulin. Another example of a drug delivery vehicle are green tea based drug carriers. Experiments have shown positive effects when anticancer drugs are delivered by green tea based nanocomplexes. Nanomaterials have also been studied as a method to fight microbial resistance to antibiotics. Salts of poly-imidazolium particles have shown to disrupt the membrane and break down the cell wall, which rapidly kills microbial pathogens and circumvents the development of resistance.

Artificial Intelligence (AI) has become an important technology for the synthesis and utilisation of chemical molecules. The combination of improved algorithms, increased computational power as well as open access to data is becoming a game changer and is making so far unknown molecules and entire "chemical spaces" accessible. A very promising field is the use of machine learning (ML). ML algorithms predict properties based on existing data to prioritise drugs for *in vitro* and *in vivo* testing. Curated data depositories are combined with trained algorithms to function as generative models, working like a medicinal chemist. Such a generative model could however also be employed to propose structures for toxic agents – an example based on the nerve agent VX was presented at the workshop. Using ML, the steps from molecular design to synthesis are becoming easier and they can be automated, with the downside, that such ML methods could be deployed to actively avoid control measures. The number of companies that are active in the field of AI is growing rapidly and so is the capital investment in this industry. The conference discussed an emerging risk in the AI industry due to a seeming absence of awareness about the misuse potential of AI as well as a lack of oversight.

Advances in **mRNA Technology** and **mRNA-Based Vaccines** have gained much attention during the COVID-19 pandemic, which fuelled the development of vaccines against SARS-CoV-2. Different mRNA platform technologies and their advancement enable faster development of therapeutics and vaccines. Additionally, they increase their efficiency and thus reduce the amount of RNA needed. Furthermore, they broaden the applicability of the approach. Genes of monoclonal antibodies can be encoded in the RNA and thus eliminate concerns on their modifications and artefacts from their production. mRNA-vaccines are game changers as their rapid design and development enables shorter times to production and easier adaptation to targets. The synthesis platforms allow fast and cell-free production, and are largely independent of the RNA sequence. These new types of synthesis and delivery platforms are being developed by collaborations of academic groups, companies and funders, and many opportunities exist, to optimise them further. Potentials for misuse arise from the encoding of complete virus genomes to launch an infection without the need for physical access to the virus as well as from encoding toxic proteins and delivery through the already established routes. While this was also possible using plasmids, the new mRNA platforms make delivery much more accessible.

Yeast-Based Synthetic Genomics can be used to *de novo* assemble, reconstruct and edit viral genomes at relatively low-cost. The idea is to create a synthetic cell that has a minimal set of genes for which all functions are known. The construction of such a cell poses several challenges. Yeast cells are used to "park" genomes and to perform genome engineering techniques, for example by using CRISPR. Yeast-assembly technology for example was successfully used to reconstruct SARS-CoV-2 in January 2020 within a short period of time, and a vaccine against African Swine Fever that takes advantage of a yeast-based platform is currently in development. Another area for the application of yeast-assembly technology is the development of bacteriophages – viruses that target bacteria with high specificity. The bacteriophages would then be deployed to treat infections with multi-drug resistant bacteria.

Universal Vaccines are an attempt to induce protection against all viruses within one viral species/genus/family, and against variants that could appear over time. Influenza is an example, where one form of the virus can after some time replace another, and where several forms of the virus can co-exist over long periods. Small mutations in the genome may change the virus, or different strains of one virus, or strains of different viruses combine and form a new subtype. A universal vaccine will try to target conserved parts of the virus and induce protective levels of antibodies. Universal vaccines are currently under development for Influenza, SARS-CoV-2, HIV-1 and Hepatitis C. Successful candidate vaccines will have a complicated development path, and a universal Influenza vaccine is possibly 5–10 years away.

Summary and Conclusions, the final session of Spiez CONVERGENCE, is always dedicated to a policy discussion. What is the impact of the new advances in science and technology that were just presented? The 2021 conference confirms one observation from 2014 – science and technology advances at a fast pace. Furthermore, the time it takes for new discoveries to find application in society seems to become shorter. This years conference highlighted important developments that cause fundamental changes in experimentation and manufacturing in the life sciences:

The “chemical space” is expanding, making new domains of unknown chemicals available with new and designed functionality. The way experiments are conducted is shifting further away from using wet chemistry and living organisms to employing algorithms, models, data libraries and computation. The availability of automation and distributed cloud services is a growing trend. Technologies that allow the delivery of bioactive molecules to a chosen target have been successfully developed.

Advances in life sciences and enabling technologies bring great benefits to humankind. However, there is virtually no single-use life sciences technology. Dependent on the intent, technological advancements can be misused to develop chemical or biological warfare agents, to find new methods for the production of known agents, to help defeat detection or verification, or to compromise existing countermeasures. The use of chemical weapons in the Syrian conflict and assassination attempts using nerve agents demonstrate that interest in chemical weapons is not an issue of the past. Arms control measures must therefore not obstruct scientific progress but assist in applying such progress towards beneficial purposes.

Advances in science and technology manifest themselves in capabilities. How these capabilities are deployed is directed by intent. Laws and international conventions provide the regulatory context, long-term values, norms and aspirations. Conventions are however not designed to adapt their implementation tools as quickly and as often as it may be necessary to keep up with the pace of scientific progress. There must be complementary measures coming from other communities and actors.

An important example is the increased dependency of the life sciences on open-source data and software, on cloud services, and on the internet for

access to materials, equipment and services. Who actually owns the data or decides over access? How can objectives and intent be recognised, if activities and transactions are separated and executed within complex programme structures that obscure the final product? How much does cybersecurity play a role in these processes?

Which actors are best placed to assess risks and benefits of new capabilities? Are these the subject matter experts because they understand the implications of their work, or the policy community who tends to focus on the risks rather than the benefits? An ongoing dialog is required between the policy community explaining its concerns about how existing norms could be undermined, and the subject matter experts to assess, whether and how a given technology could actually enable that.

Outreach, Awareness Raising, Ethical Guidelines, Codes of Conduct, Ethics Training etc. are initiatives that focus on a dialog about risks and benefits of new advancements. These initiatives generally aim to build consideration in the scientific community to take responsibility for its work and create a system of self-governance. Education and training initiatives however generally target individuals and self-governance is more than good behaviour of individuals. The challenge for the policy community is how it can engage more effectively with the wide spectrum of the scientific community and to find the right balance between the focus on institutions and the individual.

In order to further explore how advances in science and technology affect the norms and measures of chemical and biological arms control and how to properly respond, Spiez CONVERGENCE will continue to facilitate conversations between experts from the worlds of science, technology and industry as well as policy experts – next in September 2022.

Introduction

Spiez CONVERGENCE started in 2014, when Switzerland took up the recommendations of the OPCW's SAB on convergence in chemistry and biology, and decided to offer a platform for monitoring and discussing how new developments in science and technology may affect the regimes governing the prohibition of chemical and biological weapons.

This fourth Spiez CONVERGENCE conference took place under conditions imposed by the ongoing COVID-19 pandemic. Whilst a small number of conference session chairs, rapporteurs and presenters, and key support staff, travelled to Spiez to conduct the proceedings, other presenters and participants joined the proceedings remotely. The conference programme was more condensed than at previous events. At the same time, this format allowed for more in-depth cross-community conversations.

These conversations aimed to facilitate an informed discussion between different stakeholder communities from academia, industry and arms control about the impact that advances in science and technology have on arms control, with a focus on the 1975 Biological and Toxin Weapons Convention (BWC) and the 1997 Chemical Weapons Convention (CWC). How do these changes affect the norms as well as the implementation of the treaties? Which advances will change the environment in which the treaties function, and how? What are the challenges and opportunities that these advances pose to arms control, and what are their broader benefits and risks?

These discussions aim to facilitate an informed conversation between academia, industry and arms control about the impact that advances in science and technology have on arms control.

Both treaties are anchored in the science and technology that framed past weapons programmes. Today, science and technology support achieving and maintaining comprehensive global disarmament of chemical and biological weapons. But there are no rigid boundaries between the sciences concerned – they are transdisciplinary and convergent. As Jonathan E. Forman from Pacific Northwest National Laboratory observed in his keynote presentation, there is today an increasing "cross-talk" and interdisciplinary research. Chemistry and biology rank among the disciplines that are most involved in this convergence, enabled by the digital transformation of science, technology and the economy.

To adapt to advances in science and technology, both treaties rely on a general-purpose criterion – a legal construct that links definitions and prohibitions to the purpose a chemical or biological agent was intended for. At the practical level, national implementation as well as, in the case of the CWC, international verification need to adapt to changes in the implementing environment caused by advances in science and technology. Such adaptations must take into account risks as well as benefits emanating from the advances in science and technology.

Risk assessments address the full spectrum of agents, technologies and scenarios, from naturally occurring and re-emerging diseases to unintended consequences of legitimate chemical and biological activities to the deliberate use of such materials for hostile purposes. As pointed out by the second keynote speaker, Filippa Lentzos from King's College London, they must be conscious of the intents and capabilities of different actors, including States, insiders, and interested outsiders. Monitoring emerging capabilities and understanding their potential for beneficial applications, accidents or misuse are essential elements of science and technology monitoring and impact evaluation.

National implementation as well as international verification need to adapt to changes in the implementing environment caused by advances in science and technology.

Other contextual factors too influence perceptions about the relevance and impact of science and technology: the use of chemical weapons in Syria and recent assassination attacks using chemical agents mirror threats posed by agents from past programmes; the COVID-19 pandemic was a reminder of the destructive and disruptive potential of a natural disease outbreak, but at the same time testimony to the importance science and technology play in mitigating risks; an increasingly multipolar world poses challenges to the international rule-based system; the changing nature of armed conflict brings new actors to the fore who may be less constrained by legal and customary norms; heavy defence investment in the life sciences may raise questions about the harnessing of biotechnology for nefarious purposes.

Evaluating the impact of convergence, therefore, must be interdisciplinary and inclusive. This is why conversations involving scientists, the industrial community and arms control experts are important. Different actors and scenarios lead to the consideration of different types of risk, involving more (or less) sophistication in weapons design, and may call for different types of responses. This workshop, as its predecessors, set out to explore which proofs of concept, technological breakthroughs, or scientific game changers, by themselves or together, might shift or flip concepts and perceptions of chemical and biological warfare and challenge certain assumptions underlying CBW arms control. It did not attempt to put forward any firm conclusions or policy recommendations.

Findings of Previous Conferences and Themes of this Conference

Previous conferences (2014, 2016, 2018) understood convergence as an integrative and collaborative approach in the life sciences that brings together theoretical concepts, experimental techniques and knowledge of different science and engineering disciplines at the intersection of chemistry and biology.

The discussions have covered a wide range of subjects: from the synthesis of physiologically active molecules including (highly) active pharmaceutical ingredients (HAPI/API) to large molecules such as DNA, proteins and carbohydrates; from chemical and biological synthesis at laboratory scale to industrial-scale chemical and bio-manufacturing; from additive manufacturing of metal components to bio-printing of structures mimicking organic tissue; from genome editing using CRISPR technology to the application of gene drives to fight malaria; from OMICs and big data to the use of DNA for information storage and computing; from patchy particles to DNA origami with potential for the design of nanoparticles for drug delivery or as nanomachines. The maturity of the technologies reviewed ranged from fundamental research to technologies deployed at industrial scale and distributed globally.

Not everything that science and technology promise will become reality; tacit knowledge remains an important modulator; new scientific discovery does not equal new weapons; and the context is important.

These past discussions underscored the importance of understanding the state of maturity of a given technology when evaluating its impact on arms control and security. Not everything that science and technology promise will become reality; tacit knowledge remains an important modulator; new scientific discovery does not equal new weapons; and the context is important within which scientific discovery is taken forward from the lab bench to practical application.

This virtual conference was held in three half-day sessions – Synthesis, from Chemistry to Biology; Materials Science, AI and mRNA Technology; Response and Preparedness Technologies – with presentations and discussions on the following themes:

- Positron Emission Tomography
- Biocatalysis
- Digital Genome Editing
- DNA Synthesis
- Nanoscience and Nanotechnology
- Artificial Intelligence
- mRNA-Based Vaccines and Therapeutics
- Yeast-Based Synthetic Genomics
- Universal Vaccines

As in previous conferences, there followed a final discussion of how these scientific and technological advances affect the Chemical as well as the Biological and Toxin Weapons Conventions. This included both opportunities and challenges for the regimes. The focus of these discussions was on identifying trends and how to better understand the implications of emerging capabilities for arms control. However, it did not focus on formulating policy recommendations, drawing up warning lists of risky technologies, or blessing new technologies.

Positron Emission Tomography

A key observation of previous Spiez CONVERGENCE conferences has been that advances in science and technology are expanding the space available for the development, synthesis and utilisation of chemical molecules – whether they are small molecules or complex constructs. The potential for further expanding this "chemical space" is growing at an astonishing pace, enabled amongst others by automation of synthesis and screening methods, better algorithms and vastly increased computing power. Science is getting better at identifying novel lead molecules with predicted biological activity, creating novel synthetic pathways, and moving solutions from the bench top to industrial manufacturing. This session looked at Positron Emission Tomography, Biocatalysis and Digital Genome Editing.

Positron emission tomography (PET) is an example for the development of diagnostics to overcome the limitations of conventional methodology and detect diseases early. This is particularly important for diseases that show no early symptoms or morphological manifestation.

Detecting a disease at an early stage can help avoiding the disease progression as well as guide the choice of an effective therapeutic approach. Such diagnostics rely on detecting deregulations or metabolic fluxes, such as over-expressions of certain proteins, amyloid plaques (aggregates of misfolded proteins that form in the spaces between nerve cells), or changes in the uptake of carbohydrates. One diagnostic approach is the use of PET – today the most sensitive and specific imaging technology to detect and localise pathological changes well before any morphological manifestations occur. An example for a PET tracer is [^{18}F]FDG – a modified glucose where a hydroxyl group has been replaced by a ^{18}F atom. This molecule is trapped metabolically, which allows the imaging of areas with high-energy needs for example in cancer diagnostics.

Positron emission tomography (PET) is today the most sensitive and specific imaging technology to detect and localise pathological changes before morphological manifestations occur.

One current research priority is the translocator protein (TSPO), which plays a role in steroid production and mitochondrial metabolism. Its overexpression is an early sign of Alzheimer's, Paget's as well as Parkinson's disease. The gold standard for TSPO diagnostics uses PK1195, a ^{11}C tracer. It is widely used despite limited uptake and the fact that parts of the population show mixed or low affinity for TSPO because of polymorphisms. To overcome these limitations, a library of alternative tracers has been synthesised to replace the current gold standard.

A second research priority are tracers to detect certain cancer cells. One approach uses the pentose phosphate pathway (PPP) – a pathway parallel to glycolysis. The PPP has an oxidative (irreversible) phase in which glucose undergoes conversion to ribulose-5-phosphate, and a non-oxidative phase with several reversible carbon scrambling events. One of the molecules involved in this second phase is sedoheptulose-7-phosphate (S7P). The existence of an enzyme that phosphorylates the corresponding sugar (sedoheptulose kinase) shows that there is at least one entry point into the PPP that is independent of glucose. This opens up the possibility to develop tracers that accumulate in areas with elevated flux to the PPP (indicative of high-energy demand). A number of radiolabelled structures have been developed and are being screened for their utility as tracers.

There remain significant challenges for developing new PET tracers: the design of tracers, the development of precursors and the labelling strategy must meet high standards of radioprotection; the demands for purity and selectivity are very high; and there are constraints emanating from the short half-life of the isotopes used (examples: 20 min for ^{11}C, 110 min for ^{18}F). Whilst this is good news for patients – as adverse health effects can be kept very low – it requires collocating and synchronising the production of PET tracers with their use in diagnostics. Tracers are labelled at a late stage, just before being used as diagnostics. Work is under way to design 3rd generation PET tracers that overcome the limitations related to poor lipophilicity of 1st generation tracers, and the sensitivity of 2nd generation tracers to polymorphisms.

The development of new PET tracers will expand the diagnostic capabilities for the early detection of certain diseases. It will also help monitoring the effectiveness of treatments, including by micro-dosing of therapeutics or the treatment of long-acting poisons. Initial animal tests in this direction have been promising. At the same time, PET depends on the wider distribution of cyclotrons to ensure that tracers can be produced just-in-time for their clinical use.

Take-home points

- Detecting diseases at an early stage avoids disease progression and can guide therapeutic choices.
- Positron emission tomography (PET) is the most sensitive and specific imaging technology to detect and localise pathologies before morphological changes manifest.
- [^{18}F]FDG, glucose with a hydroxyl group replaced by ^{18}F, is used in diagnostics to image areas with high-energy needs, e.g. tumours.
- Research aims to improve tracers for neurodegenerative diseases and to overcome limitations due to polymorphisms.
- Challenges for PET tracer development: their design, the need for radioprotection, high purity and selectivity demands and the short half-life of isotopes.
- A broader use depends on a wider distribution of cyclotrons.

Biocatalysis

A second example of how the chemical space is expanding is the industrial use of biocatalysis. In CWC terminology, this relates to the "production by synthesis" of discrete organic chemicals (DOCs) using biologically mediated processes. The OPCW's SAB has raised this issue on several occasions: as early as before the 1st CWC Review Conference in 2003 and most recently in its report to the 4th Review Conference.

The SAB has observed that such processes have been upscaled for industrial production of organic chemicals in quantities declarable under the CWC. However, they do not appear suitable or offer any advantages for the production of traditional chemical warfare agents. Toxins and materials of biological origin, on the other hand, are amenable to such methods. OPCW Member States agree to keep the issue under monitoring, but have yet to agree on any guidance on how such manufacturers should be treated under the CWC.

Today, strong market forces are driving manufacturing towards green chemistry and biotechnology.

Biocatalysis is used, amongst others, in the manufacturing of ingredients and materials used in flavours and fragrances (F&F). Biocatalysis is also important to understand processes that affect product quality such as malodour formation or biodegradation, and to conduct analysis using biosensors or receptors.

Historically, these ingredients were extracted from natural sources such as different kinds of wood, fruit, flowers, herbs, and animals. More recently, many were made by organic synthesis. Today, strong market forces including concerns about the environment, climate and health, and pressures on resources and prices, are driving manufacturing towards green chemistry and biotechnology. Biocatalysis makes F&F manufacturing more independent from natural sources, helps to reduce the exposure to allergens and pesticides, and contributes to an increased use of renewable carbon sources.

New technologies with improved health, safety and environmental profiles have enabled this shift, making use of the myriad of biochemical pathways available. Biocatalysts have many advantages over chemical catalysts: stereo/regio/chemo-selectivity, their benign nature – non-toxic and easily biodegradable, the similar reaction conditions for very different types of chemistry, and their ability to provide access to molecular structures that are not easily accessible by chemical means. They are technically feasible, scalable, and cost efficient. Many efficient tools are in place for biocatalytic engineering, and the technology is increasingly penetrating the domain of specialty and bulk chemicals manufacturing.

Biocatalyst formats range from purified enzymes to immobilised enzymes and cells, homogenised plant tissues and microbial cells, microbial cell suspensions and the use of viable cells in fermentation and cell factories. *In vitro* biotransformation typically uses batch processes with water or organics as solvents. They can either be configured as one-step reactions or reaction cascades with multiple reaction steps in one pot, or through hybrid routes involving biological and synthetic steps. *In vivo* fermentation processes, on the other hand, involve substrate feeding into a fermentation broth or, in cell factories, the fermentation synthesis of more complex structures from simple carbon sources such as terpenes or glucose and glycerol.

A small number of catalysts and reaction formats enables diverse chemistry that meets concerns about green manufacturing, consumer protection and sustainable development.

An example is the manufacturing of "green notes" – green-grassy, fruity ingredients used as fragrances and flavours. Synthetic chemistry routes coexist with extraction from botanical sources, biotransformation or combinations of these methods. Traditional bioprocesses use sources such as linseed oil hydrolysate, homogenised soybeans or guava fruits, or baker's yeast. These are one-pot-cascade reactions utilising locally sourced raw materials. Fluctuating quality in the raw materials and undesirable side products result in high costs and low productivity. Low process stability and yields, and high catalyst loads, are major bottlenecks. To overcome these constraints, directed evolution is being used to engineer enzymes with higher selectivity, better stability, and using new substrates or allowing new product profiles. DNA shuffling or error-prone PCR can be used to speed up the directed evolution.

Such *in vitro* processes have resulted in higher productivity of green notes manufacturing with higher product yields and purity, lower costs, a larger palette of ingredients, and reduced waste streams. The catalyst supply is stable and the enzymes have constant activity and long shelf life.

Biocatalysis combines the strength of chemical and biological processes: *in vitro, ex vivo* and *in vivo* platforms, some of which open up access to more complex chemistries and structural diversity.

An example for an *in vivo* process is the manufacturing of terpenes. Terpenes constitute a vast and largely underexplored diversity with more than 50,000 structures. Supply from botanical sources is limited, prices are high, and market conditions volatile. This makes biosynthesis an attractive alternative to extraction from natural sources. An example is Patchouli essential oil, which is normally obtained by steam distillation of dried patchouli leaves. The annual world production of the key ingredient (patchoulol) is 1,200 MT, but the price of the botanical oil fluctuates significantly due to climate factors, fungal infections, market speculations and other factors. The chemical is not accessible by organic chemical synthesis. Isolation and characterisation of a synthase gene from *Pogostemon hyeneanus* has shown that one single enzyme converts the terpene precursor FPP into all major sesquiterpene constituents of patchouli oil, which opens the door for biocatalytic synthesis of an oil that matches the profile of a commercial essential oil produced by traditional extraction.

A third example is Ambergris (a rare and highly prized fragrance produced in the digestive system of sperm whales) and its key olfactory component Ambrox. Ambrox can also be made through chemical transformation from a natural diterpene found in Clary sage called Sclareol, and this diterpene in turn can be synthesised with the use of synthetic genes and enzymes.

Over recent years, several terpenes have thus become accessible via microbial production platforms. This has resulted in more stable supply and pricing, the use of renewable feedstock in the form of carbohydrates, more benign processes, improved quality and the absence of allergens, pesticide residues or adulterations. All in all, biocatalysis has opened up a large and mostly as yet unexplored chemical space for interesting molecules. It is playing an increasing role in the manufacturing of specialty and bulk chemicals. A small number of catalysts and reaction formats enables diverse chemistry that meets concerns about green manufacturing, consumer protection and sustainable development. It uses new building blocks and combines the strength of chemical and biological processes: *in vitro, ex vivo* and *in vivo* platforms that often fit well into existing industrial manufacturing platforms, some of which open up access to more complex chemistries and structural diversity than was possible in the past.

Research and development in this field is highly collaborative involving academia, contract research organisations and specific service providers. This creates opportunities, but also regulatory challenges in the field of cybersecurity. Furthermore, whilst biocatalysis may not pose a particular risk for manufacturing known chemical warfare agents, it does provide access to molecules that are not easily accessible by traditional chemical methods, which may include relevant chemicals and precursors that are not captured by control lists used in arms control. This may challenge concepts underlying export/transfer controls of sensitive materials – the Australia Group is a forum to discuss possible implications and mitigation strategies.

Take-home points

- Biocatalytic processes have been upscaled for industrial chemical production; generally they offer no advantages for producing traditional chemical warfare agents.
- Biocatalysts allow stereo/regio/chemo-selectivity and similar reaction conditions for different types of chemistry; they are non-toxic and biodegradable and facilitate access to molecular structures difficult to access chemically.
- Biocatalysis formats are purified or immobilized enzymes, cells, homogenised plant tissues or microbial cells, microbial cell suspensions, fermentation processes as well as cell factories.
- Synthesis routes can be one-step reactions, one-pot reaction cascades or hybrid routes combined with synthetic steps.
- Directed evolution engineers enzymes for higher selectivity and stability, expanding substrate or product profiles to overcome the constraints of natural sources.
- Industrial biocatalytic processes provide supply chain and pricing stability, utilise renewable feedstock, improve quality and meet concerns about green manufacturing, consumer protection and sustainability.
- Biocatalytic processes may provide access to relevant (precursor) chemicals that are not on control lists and by that pose regulatory challenges.

Digital Genome Editing

Reading DNA is a move from the physical to the digital world: extracting DNA, sequencing it and transforming sequences into bits of data made accessible by algorithms. Writing DNA reverses this direction, using algorithms to assemble DNA constructs from data.

The ability to read and write genomes has further accelerated in recent years. Since the elucidation of the DNA structure in the early 1950ies, the deciphering of the genetic code at the beginning of the 1960ies, and the first synthesis of a total gene at the end of the same decade, the field has moved through an ever-expanding array of methods to sequence, synthesise and edit genomes of different species, from bacteria to *Homo sapiens,* to reconstruct extinct viruses as well as build a minimal cell. Beginning in the 1980ies, the digital revolution provided the computing power and algorithms that enabled the growing size and complexity of this work. Today, over 420,000 genomes of microbes, viruses and eukaryotes are stored in digital databases worldwide. In principle, there are also techniques to reverse this process and use the data stored to (re)construct complex DNA structures. However, whilst our ability to synthesise short DNA strands has dramatically increased, correctly assembling large DNA constructs remains a challenge.

The lab manufacturing of synthetic cells is no longer a fantasy.

Modern computers can optimise the sequence of DNA to streamline synthesis without compromising functionality. Such strategies maintain the coding for the target protein(s) and optimise the synthesis of the DNA from genome data by creating sequences that avoid constraints found in native DNA. A first computer-generated bacterium genome (*C. ethensis* 2.0) has been designed, incorporating some 700 different genes. Error diagnosis has enabled perfection of this digital genome, identifying misannotations, overlapping genes, errors resulting from chemical synthesis and issues related to training the algorithm to perfect the digital genome design.

This optimisation was completed in April 2020. The chemical synthesis of *C. eth.* 3.0 was accomplished in December 2020, and by April 2021, the first semisynthetic cells were made. Full cell synthesis capability is projected for 2022–2023.

This *C.eth.* 3.0 genome was designed by a perfected algorithm with a minimal gene set of 1372 genes for propagation in the lab. The generation of semisynthetic cells was accomplished by shuttling the synthetic genome into a related bacterium, where genome segments are exchanged and replaced to produce semi-synthetic cells. Eventually through a progressive build-up of the synthetic genome, all of the native genome is replaced by synthetic genome segments.

Computer algorithms enable the generation of entire genomes from scratch, long DNA molecules can be assembled as parts of entirely synthetic cells with functions that can provide new solutions to pressing global challenges.

The lab manufacturing of synthetic cells is no longer a fantasy: today's computer algorithms enable the generation of entire genomes from scratch, long DNA molecules can be assembled as parts of entirely synthetic cells with functions that can provide new solutions to pressing global challenges. But as genome synthesis becomes widely accessible, the potential for accidents and technology misuse will also increase.

Take-home points

- Digital genome editing allows to create (write) genomes to be synthesised and assembled in the physical world, reversing the direction of DNA sequencing (reading).
- More than 420,000 genomes are stored in databases and could be used to (re)construct complex DNA structures.
- Although the synthesis of short DNA has drastically improved, their correct assembly to larger constructs remains challenging.
- Computer algorithms can design synthesis-optimised DNA to facilitate the assembly of whole synthetic genomes.
- Chemical synthesis of the digitally designed genome allowed the creation of semisynthetic cells, and full synthetic cells are expected to be available soon.
- While synthetic cells can potentially provide solutions to global challenges, the accessibility of genome synthesis and the potential for accidents and misuse risks increase in parallel.

DNA Synthesis

Today, synthesis errors occur once in every 200 base pairs on average. To make DNA longer, faster, and cheaper, achieving low error rates will be essential. With conventional approaches, the yield of correctly synthesised DNA drops to zero when DNA lengths exceed 1,000 base pairs. Many projects in synthetic biology, however, require DNA lengths of 5 to 30 thousand base pairs. Such long DNA will require simplifying synthesis as well as assembly.

Conventional error correction is laborious. Enzymatic error correction (EEC) can reduce errors in small DNA strands but for long DNA sequences would require prohibitive numbers of colonies. One way of addressing the issue of error removal is binary assembly error removal. This involves three core technologies, each of which requires further development: a thermal control chip made up of thousands of pixels that can each be controlled independently; advances in phosphoramidite chemistry to allow thermally controlled synthesis of single-stranded DNA on a chip; and on-chip assembly of single DNA strands into complex double-stranded DNA with error removal during assembly.

Each of the thousands of thermal pixels controls the temperature in the liquid above, thus creating "virtual wells" within a continuous flowing liquid.

On the thermal control chip, each of the thousands of thermal pixels controls the temperature in the liquid above, thus creating "virtual wells" within a continuously flowing liquid. These islands of heat are used for the synthesis of short DNA oligomers. Because each pixel has independent and precise thermal control, the chip enables the parallel directing of synthesis of many single-stranded DNA molecules. These DNA molecules are then selectively released from the surface for on-chip assembly into double-stranded DNA. Synthesis errors are detected and removed through thermal purification during the assembly into double-stranded DNA: heteroduplex DNA melts at a somewhat lower temperature than a strand that has an accurate match so raising the temperature to just below melting point of the homoduplex will thermally remove mismatching DNA sequences.

This technology is at the prototype stage: the ability to create virtual wells in a flowing liquid has been demonstrated for a limited number of pixels, the thermally controlled synthesis approach has been shown to accurately synthesise single stranded DNA with all four bases, and a crucial step in the error-removal assembly has been demonstrated.

Future plans include the use of a modular platform that utilises "smart" consumables such as single-use application-specific cartridges for parallel DNA synthesis, a plug-and-play benchtop instrument, and user interfaces, design algorithms and portals implemented in the cloud. Instruments planned further down the line are to address demands for rapid iteration of gene designs and prototyping, shorter synthesis turn-around times, greater lengths and complexities of the DNA, highly parallel synthesis and access to high-fidelity DNA. This will provide researchers with modular third-generation bench-top DNA synthesis capability for rapid synthesis with high accuracy, implementing different functionalities. This can be interfaced with cloud-based synthesis services and machine learning tools to accurately predict key parameters.

The (mis)use potential associated with synthetic cells or long, highly accurate bench-top synthesis of DNA, goes far beyond that of today's genome cloning or editing (CRISPR).

The (mis)use potential associated with synthetic cells or synthesis of long, highly accurate bench-top synthesis of DNA, goes far beyond that of today's genome cloning or editing (CRISPR). Algorithms are becoming better in changing naturally occurring sequences to make them amicable for *in silico* platforms, and access to these technologies is getting easier. Commercial access to large DNA constructs is going to lower the level of human expertise required as well as the need for wet-lab infrastructure. The consequences of the growing access to tools of synthetic biology has yet to be fully understood.

Current oversight strategies are based on screening and limiting access to certain DNA sequences that can be associated with known threats. This is likely to become harder as the communities that have access to DNA synthesis grow massively. Screening for "problematic" sequences remains a challenge even with regard to natural genomes, and synthetic DNA constructs that do not replicate natural DNA sequences but are optimised for other functionalities

pose yet another level of complexity. Control measures may have to focus on who can get access to DNA synthesis rather than on particular DNA sequences, which poses the question of who would implement such controls?

Screening for "problematic" sequences remains a challenge, but synthetic DNA constructs that do not replicate natural DNA sequences pose yet another level of complexity.

It was noted that today there is very little oversight in synthetic biology activities, and the barriers to DNA synthesis market access are low. Much of the industry operates under self-regulation, which may not be sufficient to mitigate the risk potential inherent in this fast-evolving field. Also, there are differences in legislation in various countries. It was discussed that thus, there may be a need to rethink the existing regulatory framework to guard against misuse. At the same time, it may be possible to integrate biosecurity measures into cloud-based services to mitigate some of these risks.

Take-home points

- Synthetic biology depends on the synthesis of DNA, which is so far limited to shorter fragments due to synthesis errors.
- Binary assembly error removal aims to overcome the conventional error correction by removing them already during assembly.
- Short DNA molecules are synthesised in parallel at thousands of thermal pixels.
- Selective release of single-stranded DNA and assembly to double-stranded DNA allows for thermal selection of accurate DNA strands.
- This technology could become a third-generation benchtop DNA synthesiser with high speed and accuracy.
- Growing access to DNA synthesis challenge current screening-based oversight strategies and functionality-optimised DNA complicate them further.
- Existing regulatory frameworks leave little oversight in synthetic biology and much of the industry operates under self-regulation.

Nanoscience and Nanotechnology

Previous Spiez CONVERGENCE conferences have already looked at the developments in nanoscience and nanotechnology and their relevance to chemical security and arms control. A number of areas of interest have been identified, including the synthesis of pharmaceuticals, green chemistry and energy; applications of nanomaterials in bioimaging and biosensing for both diagnostics and drug screening; the use of nanomaterials for controlled tissue regeneration, and the use of nanomaterials as drug delivery systems.

One area discussed in this conference was the development of drug release mechanisms that respond to physiological or other stimuli, such as insulin delivery to diabetic patients triggered by increased levels of glucose in the blood. Nanoparticles made up of glucose-sensitive polymers protect the insulin and enable nasal or oral delivery, and at high glucose levels degrade to release insulin. This avoids invasive methods to treatment, mimics the physiological secretion of the peptide hormone, and avoids the need for blood sugar monitoring by the patients. Experiments in rats have shown the feasibility of this approach. Today, this work has reached the stage of preclinical studies.

Nanoparticles of glucose-sensitive polymers protect the insulin and enable nasal or oral delivery, and at high glucose levels degrade to release insulin.

Another example for nanomaterials as drug delivery vehicles is the development of green tea drug carriers. Incorporating epigallocatechin gallate (EGCG) – a green tea constituent with anti-cancer, anti-microbial, anti-inflammatory, anti-microbial and anti-aging activities – into a drug carrier could result in a combined effect of carrier and administered drug. Certain EGCG derivatives have been synthesised that self-assemble into nanocomplexes. These can be used as carriers for therapeutic proteins. Oligomers formed from EGCG and acetaldehyde, carrying a payload of a therapeutic protein, show increased inhibition of cancer cell growth. EGCG polyethylene glycol nanocomplexes show a prolonged circulation by avoiding rapid renal clearance, protect the proteins from proteolysis and allow passive tumour targeting. The therapeutic effects as well as the distribution of a Herceptin nanocomplex have been studied in mice and have shown significant accumulation in tumour, instead of liver and kidney; they have penetrated into the tumour, and showed greatly prolonged circulation in blood. Similarly, successful experiments have been conducted with other therapeutic small molecules such as Sunitinib, and showed similarly positive effects of delivering anticancer drugs by green tea based nanocomplexes: higher therapeutic effects, lower dosages required, lower administration frequency, and fewer side effects.

Another field of application of nanomaterials is microbial resistance to antibiotics. Overuse and abuse of broad-spectrum antibiotics, the emergence of "superbugs" such as Methicillin-resistant *Staphylococcus aureus* (MRSA), or biofilms on surfaces of implanted devices account for a growing number of hospital-incurred infections, and are responsible for a huge health and financial burden. Development of novel antimicrobials is essential. For example, certain poly-imidazole particles have been synthesised, the salts of which have been shown to destroy fungi cells thus preventing them from developing resistance. More generally, macromolecular antimicrobial agents have a broad spectrum of activity by membrane disruption as well as lysis of biofilms, rapidly killing microbial pathogens and preventing the development of resistance. They are non-toxic, do not irritate the skin, are biodegradable and eco-friendly, and are scalable low-cost products. They offer several advantages over conventional antibiotics in such areas as treatments of MRSA or tuberculosis, or as disinfectants or preservatives in personal care products.

Macromolecular antimicrobial agents have a broad spectrum of activity by membrane disruption as well as lysis of biofilms, rapidly killing microbial pathogens and preventing the development of resistance.

More broadly speaking, nanomaterials and nanosystems are increasingly finding applications in drug delivery, nanomedicine, as alternative biomaterials and cell culture substrates, as biosensors and nanoprobes, in paper-based assays, as molecular diagnostics, and in food and drug screening. They are being used to grow stem cells in regenerative medicine. Microfluidic reactors are used in *in vitro* toxicology studies including high-throughput screening and predict toxicity better than animal models. As demands for such applications evolve and the technology matures, demands for the synthesis of new nanomaterials will increase too.

Take-home points

- Nanomaterials can be used for stimuli-induced drug release.
- Glucose-sensitive polymer nanoparticles for nasal or oral delivery release insulin at high blood-glucose levels.
- Nanocomplexes of epigallocatechin gallate (EGCG) and therapeutic proteins show increased therapeutic effects with fewer doses and administration frequencies, and reduced side effects.
- Macromolecular antimicrobial agents can help to overcome antibiotics resistance by killing microbial pathogens rapidly and preventing the development of resistance.
- Such agents are non-toxic, do not irritate the skin, are biodegradable and eco-friendly, and are scalable at low-costs.

Artificial Intelligence

Artificial intelligence (AI) is widely expected to expand the available space of chemistry and make hitherto unknown or unreachable molecules accessible. The accuracy of algorithms to predict functionality from the sequence of biochemical building blocks has made much progress, for example with regard to determining a protein's 3D shape from its amino-acid sequence (the protein folding problem). Whilst the deployment of AI for drug discovery and for understanding structure-dose-response relationships is not new, the combination of much-improved algorithms and vastly expanded computational power is becoming a game changer.

AI is now being deployed in the pharmaceutical industry (design of new molecules, repurposing of existing drugs, predicting toxicity and drug-drug interactions), in the chemical industry (predicting the environmental impact of chemicals), in consumer product manufacturing (cleaning products, cosmetics and avoidance of animal testing, reducing environmental impact), and in agriculture (biodegradation and reducing toxicity to non-target species, development of more cost-effective treatments in animal health). There are hundreds of companies that deploy AI for drug discovery, with billions of dollars invested.

A promising field of application is the use of machine learning (ML) to repurpose drugs that have already been approved, for use against new and emerging diseases. Based on existing data regarding the transcriptome, the proteome, clinical data, and knowledge about structure-activity relations and disease pathways, ML algorithms are deployed to make property predictions to prioritise drugs for *in vitro* and *in vivo* testing and ultimately clinical trials for potential repurposing. An example for a drug design from existing public domain data was the development of a Yellow Fever virus treatment. The data set for the algorithm was built from PubMed and ChEMBL data and a best model was generated that was used to virtually screen the data, followed by *in vitro* testing of potential candidates. This resulted in a new compound for Yellow Fever treatment.

The combination of much-improved algorithms and vastly expanded computational power is becoming a game changer.

With many more high-quality models built from curated data depositories, it is now possible to combine and train algorithms so they function as generative models – "thinking" like a medicinal chemist. This will increase the success rate in finding new lead molecules and optimise the search for molecules with desired properties.

An example was the development of new analogues of Ibogaine, a potent drug for neuroplasticity that has hallucinogenic properties and acts on the hERG potassium channel. An analogue that had been independently synthesised and tested was tabernanthalog. Would algorithms propose this same molecule by computation alone, given that the computation required multiple activity models and parameter optimisations to be combined? An original model was trained on the ChEMBL database, followed by training primed models on target compounds following what is called a hill climb maximum likelihood estimator (MLE) training method. The answer was yes: tabernanthalog was indeed among the top 50 structures generated by the algorithm.

Such a generative computational approach can also be deployed to generate target structures with properties similar to known toxic agents.

Such a generative computational approach can also be deployed to generate target structures with properties similar to known toxic agents. To demonstrate this capability, a test was conducted to generate structures that would show similarity to VX, using toxic dose (LD_{50} in rats) and acetylcholine esterase (AChE) inhibition data available from public databases. VX and other known CW agents as well as new molecules appeared among the top 5000 scoring compounds, including compounds that showed presumably enhanced lethality and AChE inhibition.

This approach opens the door for creating what might be called a "Generative Design Cookbook", made up of

- ML models that use publicly available datasets and open-source generative software to generate target structures
- Additional ML tools to model parameters such as environmental and metabolic stability and to optimise other properties
- Retrosynthesis tools (commercially available or open-source) to synthesise these structures
- Identification of suitable "chemistry starting points" for the manufacture of these target structures
- The deployment of robotic systems for large-scale synthesis.

"Looped intelligence" systems have already been developed that design and test certain types of chemicals using autonomous (mobile) laboratories which connect AI models that design target structures with robotic equipment to synthesise these compounds, and AI tools to evaluate the output; researchers then interpret the data and adjust the models to refine their goal definition before the cycle is repeated. The goal is to overcome obstacles that material sciences face, for example with regard to generating molecules from first principles, or when optimising desired properties is time consuming.

There remain certain bottlenecks. For example, algorithms remain prone to predictive failure when extrapolating from known domains into the unknown, and current algorithms are still too slow. However, in the future quantum machine learning (QML) is expected to outperform classical computers as the size of training data sets increases. A performance evaluation of a 53 Qubit machine hub for *M. tuberculosis* inhibition data of nearly 19,000 compounds significantly outperformed the classical computer baseline in both computation time and accuracy.

Another bottleneck is validation: not many experiments in the public domain have validated computational structures, and machine learning has not strayed far away from known drugs. Whilst approaches have been devised to validate generative models outputs, the best way is still to actually synthesise some of the molecules and test them. This is not done systematically today.

There also remains a worrying lack of awareness about these issues in the communities that are pursuing these technologies, and little oversight, despite the rapidly growing number of companies that are active in AI.

Despite these issues, ML technology today is capable of generating massive numbers of synthetically reasonable molecules. It can enhance design accuracy and drastically reduce the number of target structures that need to be synthesised and screened. In addition, the steps from molecular design to synthesis are becoming easier and can be automated. ML will speed up development and allow the exploration of larger chemical spaces. This will increase the ability to devise and manufacture molecules that are more effective and selective functionally, as well as safe for humans and the environment. On the dark side, ML could of course also be deployed to develop strategies and materials to actively avoid detection and control measures, for example by devising alternative pathways for known agents or target structures for new ones.

How such emerging risks can be managed in light of pressures towards open-source software and data has yet to be addressed in more depth. There also remains a worrying lack of awareness about these issues in the communities that are pursuing these technologies, and little oversight, despite the rapidly growing number of companies that are active in AI. There also remains a degree of naivety in the communities that all this research is only done for the common good – the notion of potential misuse is largely absent. Principles of "ethical AI" are being discussed, but their focus is on building trust in products and organisations, inclusiveness, transparency, and non-discrimination rather than how to manage misuse potential.

Take-home points

- Artificial intelligence (AI) for drug discovery and to understand structure-dose-response relationships is becoming a game changer due to much-improved algorithms and vastly expanded computational power.
- AI is deployed in the pharmaceutical and the chemical industry, in consumer product manufacturing and in agriculture.
- Machine learning (ML) algorithms make predictions based on existing data to prioritise potential drugs for re-purposing.
- Algorithms are able to propose molecules with properties similar to known chemical agents.
- This approach can generate structures of toxic molecules similar to VX, based on toxicity and AChE inhibition activity data.
- "Looped intelligence" systems can design and test chemicals in autonomous laboratories by combining AI models and robotics for chemical synthesis.
- Remaining bottlenecks are predictive failures, the required computation time and need to validate model outputs by chemical synthesis.
- ML can enhance design accuracy and reduce the number of structures for synthesis and screening by providing reasonable molecules.
- While there is the risk to deploy ML to actively avoid detection and control measures, the level of awareness for misuse potential is worryingly low in the growing AI and ML communities.

mRNA-Based Vaccines and Therapeutics

RNA vaccines have gained prominence during the COVID-19 pandemic. They mimic infections and induce T and B cells responses without additional adjuvants (ingredients that help create a stronger immune response). The RNA of these vaccines needs to reach the cytoplasm but not the nucleus of the target cells. There is no integration into the genome and thus no mutagenicity, and protein is expressed transiently and post-translationally modified by the target cells.

The development of RNA platforms has reached a stage where fast, cell-free production processes that are independent of any particular RNA sequence are available. These platforms use molecular engineering techniques to optimise functionality, and both manufacturing and purification processes are easy to standardise, fast and scalable, and at low cost. The demands on quality control for each individual manufacturing and purification step, on the other hand, are high.

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Amongst the platforms currently available for vaccine manufacturing are uridine mRNA, nucleoside-modified mRNA, self-amplifying mRNA and trans-amplifying mRNA combining mRNA and replicase. Whichever RNA format is chosen, delivery requires formulation of the mRNA using lipids, such as by embedding mRNA between lipid bilayers, lipid nanoparticles that encapsulate the mRNA, or polyplexes in which the mRNA is bound to a polymer and then forms a nanoparticle. Such formulations can enhance antigen expression and immunogenicity, and result in protection after a single vaccine dose. Work is ongoing to further improve immunogenicity of these vaccines, with modifications of the targeted antigen/protein, the RNA vector, and by changing the lead formulation and the delivery system (for example by moving towards the use of lipo-nanoparticles to enhance bio distribution to the lymph nodes after intramuscular administration, or opening up other application routes such as subcutaneous or intradermal injection).

The development of these new types of vaccine platforms is not pursued by individual companies, but by broader collaborations of academic groups, companies and funders. This approach has shown its effectiveness in the search for effective protection against Coronaviruses, including SARS-CoV, MERS-CoV and most recently SARS-CoV-2. The vaccines can target different structural proteins – an example being the spike (S) protein of SARS-CoV-2 that has been favoured as a target of the current mRNA vaccines as it mediates receptor binding and cell entry, and is the primary target of the immune system.

An example of the preclinical steps of a specific vaccine development presented at the conference included the encoding of the pre-fusion stabilised, full-length S protein in a nucleoside-modified mRNA, which was formulated with lipid nanoparticles and tested in mice for functional antibody response to a single dose. It resulted in high and sustained levels of antigen-binding antibodies as well as pseudovirus neutralisation over time, and high functional T-cell responses. An infection model using non-human primates (NHP) was deployed to test the effectiveness of boost immunisation challenged by subsequent virus exposure of the nasal and tracheal tracts after 52–55 days. No clinical signs of post-boost infections were observed and no viral RNA was detected in the bronchoalveolar fluid or in nasal swabs. The tests showed that the vaccine candidate induced strong and specific immune response in mice and NHP, with high antibody titres and strong T-cell responses and protection of the lower respiratory tract. This provided key support for clinical trials. In conclusion, there are today highly efficient and flexible mRNA platforms available to develop very potent vaccines that induce strong and protective immunogenicity at low doses. Many opportunities exist to further optimise these vaccine platforms, through adaptations in vector design, developments of better delivery systems and formulations, and through co-delivery of vaccines with immunomodulatory molecules.

The development of these new types of vaccine platforms is pursued by broader collaborations of academic groups, companies and funders.

But the application of mRNA technology does not stop at vaccines against Coronaviruses. The technology also lends itself to new approaches in other areas of disease prevention and therapy. A single immunisation with a nucleoside-modified RNA delivered by lipid nanoparticles, for example, has been shown to elicit protection from Zika virus infection in mice and NHP, including a durable neutralising antibody response in NHP. This vaccine was developed in less than 6 months.

mRNA technology using lipid nanoparticles is also being considered as a passive immunotherapy – a technique that avoids causing inflammation. Such a therapeutic concept can address the limitations of the use of monoclonal antibodies – one of the fastest growing classes of pharmaceutical products that however come with high development and production costs. mRNA encoding monoclonal antibodies would allow low weight and volume therapeutics to be made available at reasonable costs. An example is VRC01 – a broadly neutralising antibody in the treatment of HIV-1. An experimental system was developed based on mRNA that encodes VRC01 and is delivered by liquid nanoparticles (LNP). Mice injected with this treatment showed high VRC01 titres after a single injection for several days, and repeated weekly injections of a humanised mice model with an impaired immune system with no B cells resulted in a high and maintained level of human IgG titres throughout the treatment period.

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A viral challenge experiment was also conducted, using the same humanised mice model. A single dose of VRC01 or mRNA LNP was administered, and the immune response was challenged after 24 hours with an HIV-1 strain. The viral RNA levels one and two weeks after the challenge were found to render protection against the challenge. In short, the mRNA LNP treatment resulted in a rapid and massive VRC01 protein production without any signs of side effects, and the VRC01 was functional and rendered protection to humanised mice from HIV-1 infection.

Another example of the use of mRNA technology in therapy is the treatment of lymphedema. This is a rare genetic disease involving the lack or malfunction of lymphatics, leading to the build-up of fluid in soft body tissues. It is also a common secondary disease after the dissection of lymph nodes for example after breast cancer treatment. A key growth factor that can be targeted to treat the condition is the vascular endothelial growth factor C (VEGFC). It has been shown that intradermal injections of mRNA encoding this growth factor, delivered by lipid nanoparticles, induces lymphatic growth in mice. The treatment also significantly reduced the clinical manifestations of experimentally created lymphedema and thus reversed the condition in a mouse model.

In summary, mRNA LNP has been shown to be a versatile platform that offers a wide range of applications from vaccines and cancer treatments to monoclonal antibody therapy and protein replacement. The technology will undoubtedly enhance the capabilities and options for fast development and production of vaccines against emerging infectious diseases, as well as support other treatments. It will not replace all traditional vaccines (for example, vaccines using sugars as antigens cannot be replaced with this) but it is a game changer that will make better vaccines available for a range of different pathogens.

mRNA LNP is a versatile platform that offers applications from vaccines and cancer treatments to monoclonal antibody therapy, protein replacement and genome editing.

One of the risks to bear in mind is the possibility of using mRNA and lipid nanoparticles to launch a virus infection without access to the actual virus. This is not itself new – plasmids can be used in a similar manner – but the new mRNA platforms make delivery much easier. Another area to beware of is RNA printing. It is easy today to synthesise a gene of interest and make the corresponding RNA. In theory, RNA printing is accessible today. In practice, it may be as close as a couple of years. The implications of the spread of this capability, as well as related cyber security issues, will need to be considered.

Take-home points

- RNA manufacturing and purification processes are sequence-independent, easy to standardise, fast, scalable, and cheap but with high quality control requirements.
- mRNA platforms are highly efficient and flexible, their delivery requires formulations with lipids or polymers.
- mRNA vaccines induce strong and protective immunogenicity at low doses.
- mRNA encoding monoclonal antibodies are considered as a passive immunotherapy.
- The mRNA LNP is a versatile platform for applications from vaccines and cancer treatment to monoclonal antibody therapy, protein replacement and genome editing.
- Potential risk areas are inducing viral infection without the virus itself and RNA printing as well as cyber security related issues.

Yeast-Based Synthetic Genomics

The final theme on response and preparedness was devoted to developments that may enhance protection against chemical and biological agents. This question was touched upon in some of the previous discussions, including with regard to mRNA platforms and nanotechnology.

A relatively low-cost technology that can be deployed to reconstruct and edit viral genomes is **yeast-based synthetic genomics**. Work in this field was inspired by the concept of a "minimal cell" – a synthetically constructed cell based on the assumption that all gene functions are known, that it can autonomously replicate, and that it has the minimal set of genes needed to be viable. Such a synthetic cell could be used for functions such as the production of fuel or other tasks, including tasks unobtainable by conventional molecular biology methods.

To develop such a cell with a synthetic genome, it made sense to start with a natural genome. Initial attempts to transplant the smallest known genome that could replicate in medium *(Mycoplasma genitalium)* failed. But *Mycoplasma mycoides,* a bacterium that lives in and has evolved alongside livestock, could be transplanted. It is associated with contagious bovine pleuropneumonia (CBPP), a contagious and potentially lethal lung disease in cattle. In 2010, a team of the J. Craig Venter Institute synthesised a modified version of the *M. mycoides* genome and implanted it into a DNA-free bacterial shell of *Mycoplasma capricolum,* thus creating a synthetic cell that was self-replicating.

The publication of the first cell controlled by a synthetic genome in 2010 signalled a paradigm shift from reading to writing genomes.

The construction of such a cell poses several challenges, one being how to boot the genome. This has been accomplished by transplantation of mycoplasma genomes: Intact genomic DNA from *M. mycoides* subsp. *capri* was transplanted into *Mycoplasma capricolum* cells by polyethylene glycol–mediated transformation, resulting in cells that carry the transplanted genome and are phenotypically identical to the *M. mycoides* donor strain.

Yeast cells can be used to “park” genomes in between such genome transplantations. Yeast cells stably maintain and have a high storage capacity for DNA / genomes. The genome to be modified is inserted into yeast cells where genome engineering is performed (for example using CRISPR techniques). The resulting genome is isolated and transplanted into the recipient cells, and after resolution, the engineered bacteria cells are ready for further engineering steps or as final product.

It took a mere 7 days until recombinant SARS-CoV-2 reconstructed virus could be rescued on 12 February, long before the WHO declared the global pandemic on 11 March 2020.

The publication of the first cell controlled by a synthetic genome in 2010 signalled a paradigm shift from reading to writing genomes. Current research in this new field is inspired by possible applications in the area of infectious disease control, including with regard to such pathogens as Coronaviruses or swine fever, as well as therapeutic approaches that avoid antibiotic resistance.

As part of the fight against the COVID-19 pandemic, the SARS-CoV-2 virus was reconstructed. This was done using yeast assembly technology followed by *in vitro* production of the RNA and virus rescue via transfection of cells. The time frame of this research was astonishingly short: the new Covid virus was identified and confirmed on 7 January 2020, and a first genome sequence was released 3 days later; five more sequences were released the following day. SARS-CoV-2 DNA orders were placed in mid-January and received at the beginning of February, and the viral RNA became available on 5 February. It took a mere 7 days until recombinant SARS-CoV-2 reconstructed virus could be rescued on 12 February, long before the WHO declared the global pandemic on 11 March 2020.

A next step in the application of this technology is the development of attenuated vaccines. This vaccination method is well established, known to work well and fast, and is of interest with regard to emerging variants of the SARS-CoV-2 virus.

Another area of interest is the development of a vaccine against African Swine Fever virus (ASFV), the causative agent for a disease that is spreading across Europe and for which no vaccine is currently available. An efficient reverse genetic system for ASFV is under development, involving oral infection of pigs with ASFV genotype II followed by virus enrichment by gradient centrifugation of serum, followed by DNA isolation, and processing of the DNA isolate through a 10-day cloning protocol. This includes the cloning of sub-genomic fragments of ASFV, PCR-based screening for yeast transformants, multicopy plasmid induction into *E. coli,* the reassembly of the full-length ASFV genome and the engineering of the ASFV genome. This is work in progress, and there is hope that a ASFV vaccine will become available soon.

A further area of interest is a yeast-based platform for the development of tailor-made bacteriophages for the treatment of infections with multiple-drug-resistant (MDR) bacteria. Bacteriophages are viruses that target bacteria with high specificity. Using this property, phages (or cocktails of them) have been used in the past (and in some countries still are being used today) to treat bacterial infections. However, the discovery of antibiotics and their widespread use has all but stifled the development of phages treatments. With the spread of antibiotics resistance, phages are attracting interest again as an option for therapies. Synthetic biology research in this direction is under way, focussing amongst others on the cloning of DNA as a tool to engineer phages into effective treatments of MDR bacterial infections.

With the spread of antibiotics resistance, phages are attracting interest again as an option for therapies as well as vaccines against bacterial infections.

Take-home points

- Yeast-based synthetic genomics allow reconstructing and editing of viral genomes at relatively low costs.
- The first self-replicating synthetic cell in 2010 was made by transplanting a modified *M. mycoides* genome into a DNA-free *Mycoplasma capricolum* bacterial shell.
- One key challenge of synthetic cells is how to boot the genome.
- Yeast cells allow the storage and genetic modification of bacterial genomes for transplantation.
- SARS-CoV-2 was reconstructed within 7 days with yeast assembly technology, in vitro production of RNA and virus rescue via transfection of cells.
- Yeast-based reverse genetics open possibilities to develop attenuated vaccines (e.g., against SARS-CoV-2 or African Swine Fever).
- Research is underway to engineer bacteriophage treatments against multiple-drug-resistant (MDR) bacterial infections using the yeast-based platform.

Universal Vaccines

Universal vaccines for respiratory diseases was another topic discussed in the session on protection against chemical and biological agents. Universal vaccines have to address two key challenges: the diversity of viruses, and the fact that viruses change (mutate) over time. There is a large diversity in the families, genera and species of viruses causing respiratory diseases.

Influenza is an example for how one form of the virus can after some time replace another, and that several such forms can coexist over long time periods, caused by antigenic drift (small mutations in the genome) and shift (larger rearrangement's of parts of a viral genome). The H1N1 subtype of Influenza A, a variant of which caused the 1918 outbreak resulting in some 40 million deaths, was globally replaced around 1957 by what appears to have been an H2N2 subtype. However, it remerged in 1977 only to be replaced around 2009 by another H1N1 subvariant. Alongside these subtypes, a H3N2 subtype of Influenza A appeared in 1968 and is present until today, whilst Influenza B has been around since the 1940s and is probably present until today.

Universal vaccines have to address two key challenges: the diversity of viruses, and the fact that viruses change (mutate) over time.

Universal vaccines, then, are an attempt to induce protection against all viruses within one viral species/genus/family, and against variants over time. To be able to do this, universal vaccines target conserved parts of the virus. Universal vaccines are at present under development for Influenza, SARS-CoV-2, HIV-1 and Hepatitis C.

The influenza virus, for example, comes in four forms: Influenza A, B, C and D. Only the A and B forms cause respiratory disease in humans. The virus is made up of a lipid envelope and its RNA genome, the latter consisting of eight genomic segments (hemagglutinin HA with H1 to H18; neuraminidase NA with N1 to N11; an M2 ion channel and conserved internal proteins). Conventional influenza virus vaccines stimulate the production of antibodies that block the attachment of the virus to the cell, usually by interacting with the exposed globular head domain of the virus. By blocking this domain, the vaccine interrupts virus uptake by the cells. But given the fast evolution of different virus sub-strains over time, which involve precisely this head domain of the virus, traditional vaccines always lag one or two steps behind the evolution of the virus. This can severely undermine vaccine effectiveness.

Universal influenza vaccines target instead conserved parts of the virus, such as internal proteins, the M2 ion channel, neuraminidase, or the stalk domain which mediates the fusion of viral and endosomal membranes during virus uptake by endocytosis. The hemagglutinin stalk is conserved among groups 1 and 2 of influenza A as well as influenza B, making it a possible target for a universal influenza vaccine. A high degree of conservation is also typical for the stalk of the different SARS-CoV-2 variants.

A condition for developing an effective universal vaccine is, of course, that it can induce protective levels of antibodies. For a universal influenza virus vaccine, one could for example, target the conserved stalk domain, exploiting pre-existing immunity to full-length H1HA and boosting it with chimeric hemagglutinins (cHA) of the different globular subdomains. Phase I clinical trials of such a vaccine have been conducted and show promising results. Work is also under way to more systematically measure the binding breadth that could be exploited to develop universal influenza vaccines. At this stage, cHA as well as headless/mini-HA vaccines that target the HA stalk are in different stages, from preclinical tests to phase I and II clinical trials; vaccines targeting the HA head have reached the clinical trial stage; vaccines targeting internal proteins had progressed to clinical trials but one phase II trial failed whilst another phase III trial was stopped for lack of efficiency. The situation with the development of vaccines targeting the ion channel is unclear, and alternative types of vaccines as well as alternative platforms are also being pursued; some have reached the stage of clinical trials.

Universal influenza vaccines target conserved parts of the virus.

Regarding Coronaviruses, the large variety with four genera (alpha to delta) and multiple subspecies and variants raises questions about whether to target a particular virus with its relevant variants (such as SARS-CoV-2 and its relevant variants), or a subgenus such as the Sarbecovirus, or a genus such as the Beta-Coronavirus, or the entire subfamily of Coronaviruses. Then, there is the question of which target area to select for the development of a broadly-protective vaccine. Several target proteins could be considered, and whilst current mRNA vaccines against SARS-CoV-2 target the spike protein, there are potential targets such as envelope proteins, matrix proteins, nucleoproteins, and other targets in the spike protein, that could be exploited.

Research and development towards universal vaccines has attracted attention as it could significantly reduce the disease burden of certain virus families, enhance universal preparedness for pandemics, and in some cases, it would remove the need for annual vaccinations or even eradicate an entire virus genus. There are a number of potential targets for developing such universal vaccines. However, each candidate vaccine has likely a long and complicated development path – a universal influenza vaccine is perhaps 5 to 10 years away, and work on identifying suitable targets for universal Coronaviruses vaccines has only just begun. New vaccine platforms and technologies can help to move faster towards universal vaccines, but the underlying scientific issues related to the workings of the immune system and the interaction of the viral protein with its host counterpart are highly complex and more research is needed.

New vaccine platforms and technologies can help to move faster towards universal vaccines, but the underlying scientific issues are highly complex.

Beyond the technical challenges of vaccine development, the workshop also looked at the need to engage with policy makers, medical professionals and the public, when it comes to acceptance as well as equitable (geographical) distribution of vaccines. Some funders like the Gates Foundation and some governments include aspects of short and long-term social impact and global access in their contractual arrangements. That could also include principles such as responsible research and innovation. However, smaller funders often do not have the capacity to include such longer-term considerations in their funding strategies.

Take-home points

- A large diversity of virus families, genera and species cause respiratory diseases.
- Influenza demonstrates how one virus form can replace another over time, and that several forms can coexist.
- Universal vaccines target conserved parts of the virus.
- They aim at inducing protection against all viruses within one species/genus/family, and against variants over time.
- Conserved targets are internal proteins, the M2 ion channel, neuraminidase, or the stalk domain.
- What is an appropriate target: a particular virus and its variants, a subgenus (Sarbecovirus), a genus (Beta-Coronavirus) or all Coronaviruses, as the variety of Coronavirus genera is large?
- Universal vaccines could reduce the disease burden, enhance pandemic preparedness, replace the need for annual vaccinations or eradicate entire virus genera.
- New vaccine platforms and technologies can support universal vaccine development, but the underlying scientific challenges are complex.

Summary and Conclusions

This conference had set out to facilitate an informed conversation between different stakeholder communities of the CWC and the BWC about the impact that advances in science and technology have on the two treaties and their implementation. It wants to draw attention to what is happening in the world of science and technology, and to consider how these developments may affect chemical and biological weapons arms control and security.

Science and technology affect these regimes in different ways: they can challenge the scope of prohibitions, change the implementation environment, offer new tools for implementation and verification, and provide new defences against chemical and biological weapons. They can also affect perceptions and incentives regarding the utility of chemical and biological weapons.

Most noticeable were two aspects: the expansion of the chemical space, combined with a further shift from conducting experiments using wet chemistry and living organisms to employing algorithms, modelling and computation.

It has been stated many times before that science and technology are advancing at an ever-increasing pace, shortening the time from scientific discovery to application in society and often outpacing steps in policy, regulations and law to regulate their impact. Yet again, Spiez CONVERGENCE 2021 confirmed this observation. Perhaps most noticeable were two aspects: the expansion of the chemical space which is providing access to new and vast domains of unknown molecules with unknown functionalities, combined with a further shift from conducting experiments using wet chemistry and living organisms to employing algorithms, modelling and computation.

The conclusion of the first Spiez CONVERGENCE conference in 2014 that "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" may still hold true today. But the combination of these advances, of ever improving algorithms, growing computational power, expanding data libraries, automation and distributed cloud services, and technologies that allow to ever more precisely deliver physiologically active molecules to an intended target –are already changing some of the fundamentals in the life sciences. Key bottlenecks of the past have been overcome, the predictive power of models has increased significantly and experimentation as well as manufacturing is becoming easier and cheaper.

That does not mean that old technologies should be excluded from the assessment of risks and benefits. This became evident again by the use of chemical weapons in the Syrian conflict and by recent assassination attacks using nerve agents including VX and agents of the Novichok type. Furthermore, many of the technologies discussed in this report are still maturing, and whilst some of their promised application may not materialise, others will emerge that at this stage cannot be evaluated for their societal impact.

The life sciences and related enabling technologies are not driven by chemical and biological weapons objectives. The broad universal adherence to and support for the two arms control treaties, as well as political and public responses to cases when the norm against these weapons has been broken, is testimony to this end.

The advances in the life sciences can be deployed for good or bad – there is no single-use life science technology as such. Scientific advances can bring enormous benefits to humankind, but they could also be deployed to open up more advanced paths to known as well as yet unknown chemical or biological warfare agents and concepts; they could enable the development, testing, manufacturing and use of chemical and biological weapons with smaller and/or different signatures that could defeat detection, verification and forensic investigation; they could compromise existing countermeasures.

Yet, the life sciences and related enabling technologies are not driven by chemical and biological weapons objectives. The broad universal adherence to and support for the two arms control treaties in the field, as well as political and public responses to cases when the norm against these weapons has been broken, is testimony to this end. The primary drivers today emanate from the science and technology enterprise itself as well as from societal demands and expectations, and from the needs to manage the consequences of global warming, pandemics and other threats. This defines a context for risk mitigation strategies that goes beyond arms control and security: arms control measures must not obstruct scientific and technological progress but help to steer its application towards beneficial purposes.

As at previous conferences, Spiez CONVERGENCE 2021 recognised that the response to these challenges will have to come from a variety of actors – governments, international organisations, industry, the science community, educators, different user communities (including DIY biologists, AI/ML enthusiasts, and hobby chemists). It will have to rely on an array of interconnected governance measures, from awareness raising and education including ethics training to self-regulation and oversight, the adaptation of national regulations or the creation of new laws, to the adaptation of the implementation practices of the international Conventions.

When discussing who should take on the evaluation of the risks emanating from the advances in the life sciences and related technologies, the attention focussed on the importance of intent. Science and technology advances manifest themselves in capabilities, but how these capabilities are deployed will be directed by intent. The goals and ethical standards followed by the different stakeholder communities therefore are important. Whilst laws and international conventions frame the regulatory context and articulate the long-term values, norms and aspirations, there was a recognition that the pace of the scientific enterprise was such that these instruments may not be able to adapt their implementation tools as quickly as is necessary. This, then, calls for complementary measures by other communities and actors.

There are other questions to ask when considering policy responses to the advances in the life sciences. There is an increased dependence on open-source data and software, on cloud services, and on the internet as a means of access to materials, equipment and services. This poses questions such as who actually owns these data or can access them? Equally, how can one recognise objectives if activities and transactions are compartmentalised within a complex programme structure to obscure the intent of the final product? And what does this all mean for cybersecurity?

Arms control measures must not obstruct scientific and technological progress but help in steering its application towards beneficial purposes

It has been argued that it was the subject matter experts who are best placed to recognise and understand the implications of their work – risks, benefits, as well as measures needed to make their work safe and secure. In practice, however, it has become apparent that humans have a tendency of underestimating the risks associated with their own work, overestimating its benefits as well as overestimating the risks posed by the work of others. Hence, a two-way communication is needed between the policy community (best placed to express concerns about how existing norms could be undermined) and the scientists (best placed to explain whether a given technology could enable that).

So how can the policy community more effectively engage with the wide spectrum of actors within the scientific community (chemists, biologists, engineers, physicists, specialists in AI and machine learning, and more) as well as the many other communities concerned? What needs to be undertaken to broaden awareness for the relevance and need of considering arms control and security issues in the context of their work? What can be done to embed such considerations within the professional self-image of these communities?

A first consideration relates to funding of ethics training. Working out good funding streams to implement ethics outreach is important. Implanting ethics training into the work of companies and scientific institutions is often met with resistance, as it may be seen as a sign that something has gone wrong, or that it takes time and effort away from mainstream activities. Furthermore, the life sciences industry is not limited to large companies. There are many small groups and companies which are often more difficult to engage with. More can be done for example, to invite them to events such as Spiez CONVERGENCE, to get the message about responsible conduct in the context of chemical and biological security and arms control across to forums such as meetings and conventions of scientific association, and to use decentralised tools and channels including social media to provide training and share best practices. Perhaps similar to how the DIYbio movement has taken up safety and security issues.

Science and technology advances manifest themselves in capabilities, but how these capabilities are deployed will be directed by intent.

A second consideration is the balance between the focus on the individual and on institutions. Education and training target the individual, but self-governance is more than good behaviour of individuals. It includes institutional objectives and policies; institutions influence incentives through recognition, empowerment and rewards.

Thirdly, Codes of Conduct remain a useful tool. The Hague Ethical Guidelines and the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists are good examples for how to devise such codes, but how to get them out to practitioners still remains a challenge. It is important to recognise that there are many other ongoing conversations about ethics in the science and technology world. There is a risk of fragmentation that needs to be overcome if the overall goal is to build considerations of how to mitigate risks of science misuse into the self-image of the professions concerned.

A fourth consideration is how to frame ethics discussions and training so that they match the needs and attitudes of the next generations of scientists and other members of the life science community. Positive messaging is important: not based on fear of what might go wrong or could be used with nefarious intent, but led by values and aspirations for responsible conduct. In fact, it was argued that the very terminology of “ethics training” may be unhelpful, and that conversations about risks and benefits of scientific advances should be framed in terms of taking responsibility for the outcomes and consequences of this work.

This fourth Spiez CONVERGENCE conference has again demonstrated how important it is to engage policy experts and experts from the worlds of science, technology and industry in conversations about how advances in the life sciences and associated technologies affect the norms and measures of chemical and biological weapons arms control.

The very terminology of "ethics training" may be unhelpful, and conversations about risks and benefits of scientific advances should be framed in terms of taking responsibility for the outcomes and consequences

Take-home points

- Science and technology can challenge the scope of prohibitions, change the implementation environment, offer new implementation and verification tools, provide new defences against biological and chemical weapons or affect perceptions and incentives regarding their utility.
- The expansion of the chemical space provides access to unknown molecules with unknown functionalities; it is combined with a further shift from wet chemistry experiments and living organisms to algorithms, modelling and computation.
- Models have increased significantly in predictive power, and experimentation as well as manufacturing is becoming easier and cheaper.
- The dependence on open-source data and software, cloud services, and the internet to access materials, equipment and services poses questions regarding the ownership of data, the recognition of objectives of activities as well as cybersecurity.
- Advances in the life sciences open-up alternative paths to known or unknown chemical or biological warfare agents and concepts; enable their development, testing, manufacturing and use; reduce and/or alter their signatures potentially defeating detection, verification and forensic investigation; or compromise existing countermeasures.
- The use of chemical weapons in the Syrian conflict and in recent assassination attacks demonstrate the need to include old technologies in the assessment of risks and benefits.
- As the implementation of laws and international Conventions is not as dynamic as the sciences, complementary measures such as ethical standards are important.
- Ethics outreach requires a variety of actors and sufficient funding; it is important to overcome resistance and to implement outreach activities in a broader range of companies and scientific institutions.
- Education and training target individuals, but self-governance includes institutional objectives and policies; incentives through recognition, empowerment and rewards.
- Positive messaging is important to frame conversations about risks and benefits of scientific advances: value-based, and in terms of taking responsibility for the outcomes and consequences thereof.