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Developments in science & technology with relevance to the Australia Group

An executive summary commissioned by the Ministry of Defence

DISCLAIMER: *The advances identified in this paper are indicative of developments since 2011 and are not exhaustive. The advances discussed provide an overview of the speed and direction of research and can be used to identify relevant trends. Given the number of sciences and disciplines of possible relevance, the geographic distribution of scientists, the number of languages in which they publish and the increasing pace of research, there are other specific advances which could have been captured in this report.*

Biosecure has conducted a review of relevant developments in the life sciences and biotechnology since 2011 and of potential relevance to the Australia Group (AG). The developments identified included advances in technology with direct contemporary relevance, such as the advent of the first desktop gene printer. They also include mature scientific developments whose applications are currently under development, such as the advent of CRISPR/CAS9-mediated gene drives, whose implications will be felt in the coming years. There have also been relevant applications of technologies of relevance to the work of the AG, such as the demonstration by two IT researchers that synthesis and rebooting of a virus by non-specialists is feasible.

A. Lists of agents

A number of new agents of potential interest to the AG have been identified, including MERS-CoV, H7N9 influenza, the mammalian Orthoreovirus connected to porcine diarrhoea outbreaks, and a novel form of the botulinum toxin. There have also been notable developments in enabling technologies that aid in the identification and characterization of previously unknown or unidentified pathogens and toxins.

Agents of concern and their constituent parts are increasingly available from commercial sources; in particular the commercial production of peptides and toxins has become commonplace. An expanded range of service providers has begun to appear, such as cloud-based laboratories that enable the outsourcing of relevant activities. There have also been numerous examples of online services, in particular on the dark web, being used to acquire controlled agents.

The recent demonstration that non-specialists can compile and reboot a virus has profound implications for the AG. It established that tacit knowledge is not a barrier to synthesizing viruses. The release of the first desktop gene printer could further complicate non-proliferation efforts by decentralising a core production activity. More sophisticated efforts have enabled the synthesis of an expanded range of viral pathogens. The production of a chimeric influenza virus with increased pathogencitiy over any of its progenitors was of particular note. Relevant sequence data for bacterial pathogens has continued to be added to public databases, including for pathogens not available from nature (for example the strain of *Y. pestis* responsible for historical outbreaks including the black death). Progress has also continued in sequencing and characterising the metabolic processes responsible for the production of toxins and biologically active peptides.

There has been considerable progress towards designing and developing custom-made controlled agent, including microbes, toxins, or biological active peptides or genetic materials. Of particular note was the use of viral vectors to deliver genome editing tools enabling modulation of disease states. Relevant advances have covered: genome editing and engineering; systems biology; synthetic biology; increasingly sophisticated understanding of pathogenicity, infectivity, transmissibility, antimicrobial resistance, and environmental stability (including gain-of-function dual-

use research of concern); the synthesis of genetic material; computational methods, software tools and programming languages; nanotechnology; neuroscience, neuropharmacology and optogenetics; vaccinology; as well as the convergence of scientific disciplines.

B. Production technologies

There have been notable change in the footprint or signature of production activities. Pre-industrialisation strain optimisation has reduced some of the challenges involved in scaling-up laboratory processes for commercial production. Certain scale-up activities have been simplified and the need to undertake complex steps involving materials from a limited range of suppliers have been removed. Increasing automation and miniaturization of these processes have increased the speed, throughput and optimisation of scale-up activities but have increased costs. Improvements in downstream purification have resulted in much greater levels of quality assurance in large-scale production efforts but have also led to increased costs.

Outsourced procurement and production have increased the choices open to those seeking to acquire biological weapons. Proof of principle experiments on the routine synthesis of vaccine candidates is industrialising this production approach. Multipurpose, industrial-scale fermentation production plants are now a reality and have been used to produce products from engineered microbes on a commercial scale. Platforms for the commercial production of peptides have also become more common. The advent of virtual biotechnology companies demonstrates the potential to combine outsourcing approaches so as to completely remove the need for a dedicated physical infrastructure for a biotechnology-based commercial enterprise.

The increasing use, scale sophistication, modularization and standardisation of disposable production equipment makes it much easier and faster to switch between biological production processes, offering previously unavailable capabilities for a potential break-out capacity. The trend towards multiplexed batch production increases this potential and provides large-scale production capacity using equipment that may fall below volume thresholds traditionally considered for export controls.

Additional procurement options for relevant production equipment are challenging traditional controls. A recent study of the applications of existing control measures to purchases of relevant production equipment through online retailers identified worrying shortcomings. Developments in 3D printing also potentially provide access to production-related equipment currently on control lists.

There have also been notable shifts towards the use of bio-based production processes for a range of products and compounds traditionally produced using alternative means. Both processes where a biological agent is used to produce a product, and those where it is the product have become more commonplace. There has been particular progress in the use of engineered animals and crops to produce biologically active compounds. As a result, the knowledge and capacity to develop and implement such processes has spread. There has also been a trend towards the decoupling of design, development and manufacturing processes leading to increasingly distributed industries.

C. Stockpiling and delivery technologies

Traditional approaches to stockpiling of agents, such as freeze-drying, have continued to spread to a wider audience. For example, detailed video instructions, as well as advice on the optimal approach for different agents are now freely available online.

There has been notable progress in developing agents that negate the need for specialised storage provisions, such as a cold chain. For example, work using silk protein matrices has extended the shelf life of vaccines from days to months in adverse temperature conditions. There has also been progress in increasing the half-life of agents in the environment post-release. For example, developments in biocontrol efforts have led to new formulations which allow agents to remain active for months at a time.

Advances in the design and production of nanoparticles have the potential for a particular impact on the storage and delivery of biological agents. There has been notable progress in the development of design principles, tools and self-assembly approaches. Recent developments of note include: the creation of communication between nanoparticles for enhanced targeting; optimised tuning for tissue-specific cellular entry; bio- and environmentally responsive nanoparticles able to release their payload on demand; manipulation of nanoparticles to confer additional characteristics to a payload, such as improved activity, increased duration, resistance to being metabolised, etc.; nanoparticles optimised for transdermal delivery; nanoparticles optimised for aerosol delivery; as well as nanoparticles designed to cross the blood-brain barrier enabling the delivery of biologically active compounds directly to the brain.

There have also been a number of other developments pertinent to the transdermal delivery of biological agents, including advances in chemical permiablisation agents as well as low-frequency sonophoresis, microneedles, electroporation and iontophoresis. Pathogen-based infection and cellular entry mechanisms have also been repurposed for the delivery of therapeutic compounds.

Developments in aerobiology and modelling of releases could also help optimise prohibited activities. Notable work has been undertaken on investigating and optimising the use of unmanned aerial vehicles for the aerosol delivery of agents, such as for crop spraying. New tools will help model how an agent might spread in the atmosphere or inside buildings or in transport hubs. Other tools enable much more accurate tracking of simulants and agents in field trials, increasing the value of undertaking such efforts.

D. Intangible technology

There have been a large number of developments in software, computational tools and public databases enabling the above activities. Examples identified cover: protein design; the identification of pathogenicity islands; drug effects and interactions; enzyme design and inhibition; data mining, including from text; network modelling; nanoparticle design and optimisation; metabolic pathway engineering; and structural design of genetic material.

E. Findings & recommendations

Digitization of the life sciences & biotechnology

Biological function and digital data is increasingly interchangeable. As the science becomes more data-driven so must too the security provisions. There is a need to develop more data-driven tools and approaches for the implementation of AG aims and objectives.

Recommendation 1: The AG should convert the current agent lists into a searchable database that could be used for screening by commercial gene synthesis companies and other providers of outsourced support services.

The synthesis of a functional virus by non-specialists demonstrates that the physical control of pathogens will become increasingly marginalised. There may be value in retaining such barriers until a tipping point is reached where it is easier to synthesise an agent than obtain it from nature. In the meantime it is important that a more data-driven approach is developed.

Recommendation 2: Explore possibilities for function-based rather than taxonomy-based classification of biological risk.

Decoupling of design, development & manufacturing

Growing financial importance of bio-based production, the data-driven nature of the science and technology, combined with the outsourced nature of many key services increases drivers for and capacities to provide illicit markets for products and services. Efforts to control goods and services

may compound efforts to circumvent them. As biotechnology becomes more democratised, security may be better served by increasing transparency and with it our capacity for situational awareness.

Recommendation 3: A conceptual re-examination of underlying security considerations of digital, distributed, democratised biotechnology.

There has been a significant change in the footprint or signature of efforts to produce biological weapons and differentiating between permitted and prohibited activities is increasingly complicated. We may need to look for different indicators of a biological weapon programme. The decoupling of design, development and manufacturing is resulting in more decentralised, distributed capacities relevant to the work of the AG. That will continue to stress technology controls through increased international movement of goods and services. A contemporary biological weapons programme may look nothing like those of the past.

Recommendation 4: Revision of signatures of footprints of prohibited activities in light of advances in production approaches and technologies.

Industrialization of the life sciences & biotechnology

The uptake of biological-based production processes by an increasingly diverse range of industries is distributing relevant technology to a wider range of more dispersed sectors. Relevant capacity is increasingly generated and used by such actors and to improve technological awareness and implementation of the aims and objectives of the AG greater transparency and accessibility for non-governmental actors is necessary.

Recommendation 5: Proactive engagement with non-governmental experts in relevant science and technology.