Department of Social Science,
Health & Medicine

WORKSHOP REPORT

Synthetic Biology and Biosecurity: How Scared Should We Be?

Catherine Jefferson, Filippa Lentzos & Claire Marris
Department of Social Science, Health & Medicine
King's College London

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This report and the slides from the workshop presentations
are available from the SSHM website: http://www.kcl.ac.uk/sshm

Executive Summary

This document reports on a workshop on synthetic biology and biosecurity held at King's College London on 28 February 2014.

Synthetic biology's aim to make biology easier to engineer has raised concerns that it could 'deskill' biology and increase the risk of misuse for biowarfare or bioterrorism. The workshop brought together synthetic biologists, policy experts, science journalists and social scientists to explore whether concerns about these risks are realistic or exaggerated in the light of current scientific realities.

The first part of this report summarises the discussions that occurred, replicating as accurately as possible what was said by the workshop participants, without commenting on those statements. In the second part the authors use their social science expertise to analyse those discussions and the key findings are summarised here.

The synthetic biology/engineering conundrum

The failures encountered by former bioweapons programmes were used to demonstrate that there are tangible and intangible barriers to the misuse and reproducibility of science. Tacit knowledge and socio-technical factors limit the possibility of reproducing experiments based on the informational aspects of science alone. It was argued that a more in-depth analysis of these socio-technical dimensions would lead to more refined assessments of the biosecurity threats posed by synthetic biology. It was, however, argued by some participants that because synthetic biology is an engineering discipline, these tangible and intangible barriers would in future become irrelevant. This position was challenged from two perspectives:

Firstly, there were discussions about the extent to which synthetic biology has achieved, or ever will achieve, the goal of transforming biology into an engineering discipline. The consensus was that it had not yet, but for some of the participants it was only a question of time before it did. This meant that it was important to focus on trends rather than absolutes, because even if synthetic biology does not make the engineering of biology easy, it will probably make it easier.

Secondly, there were discussions about the extent to which an engineering approach would eliminate the need for the kinds of tacit knowledge and other socio-technical factors that had impeded the development of large state-sponsored bioweapons programmes in the past. During these discussions, the more extreme depiction of synthetic biology as an engineering discipline tended to become tempered, and it was pointed out that skills and large infrastructures remained important in other (non-biological) fields of engineering.

This revealed an interesting tension. On the one hand, if tacit knowledge remains important in synthetic biology, then this implies that it will not be easily accessible to outsiders and this reduces concerns about the dual use threat. On the other hand, if synthetic biology is an engineering discipline and if this means that we overcome the barriers posed by tacit knowledge, then this implies that it could become more accessible to outsiders and this increases the dual use threat. Thus, biosecurity concerns are heightened when the more extreme depiction of synthetic biology's ability to engineer biology is emphasised. We characterise this as the 'synthetic biology/engineering conundrum'.

What do we mean by 'de-skilling'?

This conundrum arises because the 'de-skilling' of biology is often misrepresented as meaning that any layperson, working outside professional scientific institutions, is or soon will be able to design and produce organisms that behave predictably and reliably. However, a different understanding of 'de-skilling', and of the engineering approach of synthetic biology, emerged during the workshop discussions. In this understanding, dependence on the craft skills of a small number of highly trained individuals is reduced for some parts of the production process, usually by standardisation and mechanisation. This does not mean that skills become irrelevant or that all aspects of the work become easier. Specialised teams, expertise, complicated machinery, advanced technology, trouble shooting - and thus organisational factors - continue to be required when a design and engineering approach develops.

If we are to disentangle synthetic biology and biosecurity concerns, and to have a more refined assessment of biosecurity threats (how scared should we be?) we believe that it is necessary to have more nuanced discussions about the extent to which synthetic biology is, or ever will be, an engineering discipline; and whether, in practice, this would reduce the importance of tacit knowledge, specialist expertise of different kinds, collective work, large infrastructures, and organisational factors. Such discussions would need to identify those aspects of the work that would become easier – in the sense that they can, for example, be automated and reliably performed by a robot - and those which are likely to remain difficult, in the sense that they still require craft skills to be successfully achieved. This would need to take into account not only the material and informational aspects of the field, but also other important socio-technical dimensions that will shape the development of the field.

Blaming the media

Some synthetic biologists and some policy makers argued strongly that the way in which the media reported science was a major obstacle for rational debate. However, for good or ill, the primary role of the media is not to communicate science calmly and rationally. It is an industry that, just like any other, seeks to make money and in many cases this is best achieved by entertaining their audiences. In addition, it is entirely legitimate for debates among scientists about the purposes and findings of research to be represented, so that citizens are more able to understand and participate in such debates and to have their say about future directions. It is also interesting to note that scientists often perceive dramatic scare stories about science as damaging, but that dramatic – and often equally overstated - stories of scientific breakthroughs, which are the mirror image of such scares, are usually welcomed as generating support for science. Scientists also often assume that lay members of the public are easily swayed by negative accounts of science, and that the tenor of media reports will determine whether 'the public' will be 'for' or 'against' a particular technology. This set of beliefs about science and the media, and about public understanding of science is, however, challenged by social science research that demonstrates that members of the public are not passive recipients of media messages and that they can hold nuanced views on scientific and technological developments.

'Hype' as a double-edged sword

Discussions at the workshop demonstrated how different communities stress particular issues in particular contexts, and how this plays an important role to construct and maintain resources and support for each of these communities. Thus, scientists who promote synthetic biology need to portray an optimistic vision of the potential of the engineering approach to biology as part of their endeavours to develop support for a new field of research which they believe has great significance and potential. Some of those in the security field, including some policy makers, social scientists and natural scientists often exaggerate the 'dual use threat' in order to attract resources to their own work. Researchers who conduct social studies of science and technology often seek to emphasise the complexity of real world situations, and the importance of social dimensions of science, in order to justify the need for their expertise. Unfortunately, this can sometimes have unintended consequences that are detrimental to their own interests and/or to the nature of public debate. We argue that a better understanding and acknowledgement of these dynamics would help towards developing more productive discussions in which the different communities involved could move beyond simply defending their own positions.

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Introduction

This document reports on a workshop titled 'Synthetic Biology and Biosecurity' held at King's College London on 28 February 2014, and organised by Catherine Jefferson, Filippa Lentzos and Claire Marris of the Department of Social Science, Health and Medicine.

The aim of the workshop was to explore the extent to which concerns about the misuse of synthetic biology for biological warfare or bioterrorism are realistic or exaggerated in the light of the realities of scientific research in this area. The workshop brought together a group of synthetic biologists, policy experts, science journalists and social scientists with specialist expertise in these areas. A Scoping Report was prepared and circulated to all participants in advance of the workshop in order to frame the discussions. This document (reproduced in Appendix 1) identified five recurring 'myths' about the dual use threat of synthetic biology that dominate discussions in policy arenas and the media, and highlighted some key challenges to this narrative.

The meeting was held under the Chatham House Rule in order to facilitate open and productive discussion:

When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

The speakers at the workshop have given their consent for their names to be used in the summary of their talks and related citations.

The workshop was organised around four sessions that focused on different aspects of synthetic biology and biosecurity, each introduced by two short presentations with ample time allocated for interactive discussion among all the participants:

Session 1: How have concerns about biological weapons and bioterrorism emerged and evolved over time?

Session 2: How have 'dual use' concerns about synthetic biology been framed in the media and in policy discourse?

Session 3: What are the tangible and intangible barriers to state and non-state production of biological weapons?

Session 4: What scientific developments within synthetic biology might be relevant to misuse concerns, now or in future?

The first part of this report summarises presentations made by eight experts in the field and the discussions that occurred, replicating as accurately as possible what was said by the workshop participants, without commenting on those statements, and without endorsing (or not) any of the views expressed. Arguments are reported even when they were only expressed by one or a few participants. The aim is to represent the diversity of views expressed, and we do not seek to assign particular weight to any of the arguments reported. The aim was not to reach consensus or to develop any recommendations. In the second part of the document, we take a step back and use our social science expertise to identify key themes that emerged from the discussions, and to reflect on the dynamics of those discussions. We tease out some of the key arguments that participants made throughout the day and how they related to each other and to social science scholarship in these areas.

The slides used for the presentations are available from the SSHM website: http://www.kcl.ac.uk/sshm.

A Twitter hashtag (#synbiosec) was created for this workshop. You can view comments made by participants and others there, and we encourage readers to use this hashtag to post further comments about this report.

Summary of Discussions

Session 1: How have concerns about biological weapons and bioterrorism emerged and evolved over time?

'The world's most deadly weapons': The politics of bioterrorism

Presentation by Filippa Lentzos
SSHM, King's College London

This presentation explored the question of how concerns about bioterrorism have emerged and evolved. It provided a brief background to the history of biological weapons and the multilateral treaties banning their use, development, production and stockpiling. It noted that in the last years of the Cold War, US security analysts began to project a new set of threats posed by rising third-world states and terrorists supported by those states. As the Cold War faded, terrorists with weapons of mass destruction began to replace the Soviet threat and this became the driving force behind US preparedness and biodefense programmes in the 1990s.

The talk highlighted how early political debates contained different assessments of the importance, urgency and scale of the bioterrorism threat. 'Alarmists' emphasised the vulnerability of civilian populations and the possibility of apocalyptic attacks with natural or genetically engineered pathogens; 'sceptics' emphasised the identities of 'bioterrorists' and their historical lack of interests in and capacities to pursue such attacks. Ultimately, alarmism triumphed and federal funds poured into major new civilian biodefense programmes in the late 1990s.

Following 9/11 and the 'anthrax letters' attacks, the focus on bioterrorism became central to national security concerns in the US. It was argued that 'Amerithrax' powerfully illustrated how biology could be used to terrorise and kill, and highlighted the lack of means available to detect and mitigate, much less prevent, such an attack. It noted that while political debates in the 1990s were vague about who the potential bioweapons users might be, the Bush administration post-9/11 was very explicit about its 'enemy': Osama bin Laden and Al Qaeda, Iraq, North Korea, Iran, Libya, Syria and Sudan.

The presentation went on to explore how this perception of threat drastically expanded the biodefense infrastructure, multiplying the number of laboratories, projects and people working on dangerous pathogens. One estimate is that more than $70 billion have been spent on civilian biodefense since 2001.

It was argued that the initial framing of bioterrorism, conceived and pushed by Washington as high consequence ‘superterrorism’, was spread in the first decade of the century to international security forums and back to capitals around the world. Within a decade, many states had not only commonly accepted the threat, but obligations under UN Security Council Resolution 1540 and the Biological Weapons Convention ensured that the threat of bioterror as a security concern became codified in national legislation and that states committed themselves to implementing measures to counter it.

> *“The initial framing of bioterrorism, conceived and pushed by Washington as high consequence ‘superterrorism’, was spread in the first decade of the 21st Century to international security forums and back to capitals around the world.”*

The presentation concluded by arguing that more recently, however, security concerns about bioterrorism have become increasingly linked with health concerns. Bioterrorism, or the deliberate spread of disease, is no longer thought of as a stand-alone threat, but has instead come to be understood as one element of a spectrum of disease outbreak threats that also encompass natural outbreaks, unintended consequences, accidental releases, negligence, and sabotage. This ‘spectrum approach’ where bioterrorism is framed as a ‘catastrophic health event’ is starting to manifest itself in national policies, and is opening up alternate responses and intervention strategies to keep us secure from the threat of disease.

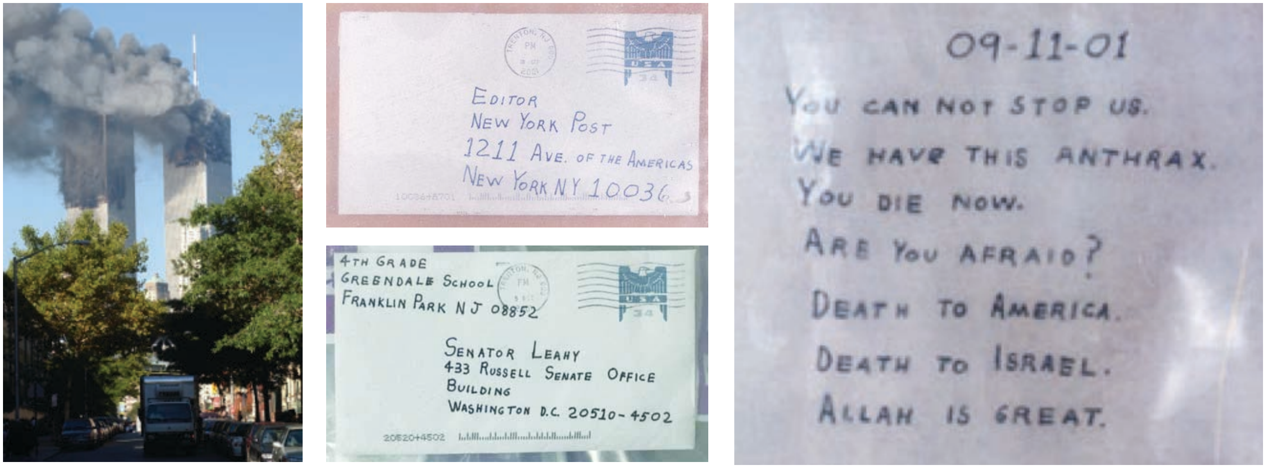


Figure 1: Following 9/11 and the 'anthrax letters' attaks, the focus on bioterrorism became central to national security concerns in the US - and this was also when synthetic biology first emerged.

Credit: istockphoto (left image) and the FBI, Famous Cases & Criminals, Amerithrax Case
http://www.fbi.gov/about-us/history/famous-cases/anthrax-amerithrax/the-envelopes

The Transmissible H5N1 Saga: Where do we go from here?

Presentation by Debora MacKenzie Reporter, *New Scientist*

This presentation went through the different arguments that arose during the dispute about whether or not the research conducted by Ron Fouchier on the bird flu virus H5N1 should be published. It was noted that in scientific journalism, stories are rarely eyewitness accounts so journalists must rely on sources. This means that, while they try to report what is true, in fact they can only report what people tell them is true.

H5N1 does not spread easily from human to human, but it kills more than fifty per cent of people infected. The Fouchier experiment sought to investigate whether H5N1 could become readily transmissible between mammals and still remain highly virulent. A virus as contagious as ordinary flu, that would kill half its cases, is a terrifying thought. Some virologists had been concerned that this could happen and were worried that governments were not taking the threat seriously enough. The Fouchier experiment passed H5N1 among ferrets as an animal model and discovered that a mutated H5N1 virus that was air transmissible could emerge. Moreover, Fouchier initially stated that the virus had not lost any of its pathogenicity.

The researchers were taken by surprise when it was suggested that their findings should perhaps not be published. At first the discussion focused on finding ways to limit access to people who need that knowledge, while restricting access to those who might misuse it. But a WHO meeting in 2012 concluded that there was no easy way to achieve this. Scientists, however, argued that the known threat of a potential pandemic should override an unknown biosecurity threat, and that conducting and publishing scientific research was the only way to defend against it. Moreover, because the WHO brought non-Americans to the table, this allowed different sensitivities to emerge. In particular, Indonesians were unhappy that they might not be given access to research results based on experiments that had used a virus obtained in their country.

Public debates focused on biosecurity: it was feared that publication of the research would provide a recipe that putative terrorists could use to make a highly dangerous virus. In private, however, biosafety concerns were the real worry: the fear was that the mutated virus might escape from the lab. Concerns were not expressed specifically about Fouchier's lab, which is presumed to adhere to high biosafety standards, but about other researchers who might try to

The presentation argued that, in order to improve biosafety, we need to establish internationally-agreed mechanisms to regulate 'gain of function' (GOF) research. This would involve three things. Firstly, there should be a wider conversation about how limiting publication can sometimes make GOF research safer. For example, it was noted that in the case of the recent discovery of a new type of botulinum toxin, restrictions on the publication of the genetic sequence until an antidote was developed made sense. Secondly, there is a need to revise the vetting procedures for laboratory biosafety that were set after Asilomar in 1974. Thirdly, consultation to decide which GOF experiments are worth conducting should take place before the research is done, based on a thorough risk-benefit analysis; the publication stage is too late. Wider scrutiny of this kind could create peer pressure and a new norm for occasionally limiting scientific freedom in the interest of safety. Unfortunately, the way in which the dispute around the publication of the Fouchier experiment unfolded has made that kind of consultation and openness less likely.

The presentation concluded by suggesting that the H5N1 saga was characterised by an unprecedented amount of spin from the scientists involved. The scientists initially portrayed the virus as very dangerous, and this was therefore how journalists reported the story. Fouchier initially said that all the ferrets had died, and that the virus was as transmissible as seasonal flu. But when the scientists realised that they might not be allowed to publish their work, the story changed and they suggested that the virus was not terribly lethal or contagious, and that the whole thing had been invented by sensationalist journalists. They key issue here is not that scientists spin, but that the scientists felt that they had to do this in order to keep doing work that they truly believed was needed to protect public health. This tends to lead to pre-emptive self-justification on the part of scientists rather than opening up genuine discussion about substantive concerns. This is not helpful and does not encourage the transparency we need to keep GOF work safe.

"A virus as contagious as ordinary flu, that would kill half its cases, is a terrifying thought. Some virologists were worried that governments were not taking the threat seriously enough."

Discussion in Session 1

Discussion in this session focused predominantly on communication of science and the role of the media.

Some participants argued that it is not scientists who 'spin', but the media who sensationalise; and that a rational discussion that focuses on the science is required, based on published scientific literature. These participants bemoaned the fact that journalists used attention-grabbing headlines with adjectives such a 'killer flu' or 'deadly virus' that will tend to scare people.

However, it was noted that in the H5N1 example, some virologists, and notably Fouchier, did initially emphasise the alarming aspects of the research, precisely in order to raise concern, because they were genuinely scared about the threat and worried that nobody was doing anything to develop vaccines or to eradicate the virus from the poultry population. Thus, journalists were simply quoting what the scientists had said.

Some felt this demonstrated that some individual scientists - just like members of society in general - behaved in irresponsible ways, but that this did not represent the majority of the community: there is a spectrum and most scientists seek to communicate their research in responsible ways. In response, it was noted that, understandably, scientists talk differently in different contexts and/or to different audiences, for example when seeking research funds or speaking to journalists compared to when speaking with their post-docs in the lab, giving talks at scientific conferences or writing in the scientific literature. Thus, it is not always just a case of dividing scientists into those who act responsibly and those who do not.

Discussion evolved into the larger theme of the need for scientists to take responsibility for the way they speak about their research, and it was argued that scientists need to learn to communicate their research carefully where it touches on the question of risk. For example, instead of simply emphasising the danger of a particular experiment they could have given more attention to the biosafety precautions they had taken and the difficulties they faced in conducting the research.

It was noted that the synthetic biology community has a high level of awareness of safety and security issues. The voluntary screening of orders by gene synthesis companies was given as an example of responsibility, although the effectiveness of this voluntary mechanism was contested.

Questions were raised about how the H5N1 controversy had affected the scientists involved, and how more openness and discussion could be encouraged in future. It was suggested that, unfortunately, the experience had made the scientists less likely to open up to broader consultation about their work. Regulations and guidelines set out since Asilomar focus on the biosafety risks associated with laboratory research and possible unintended releases of genetically modified organisms, but do not enable deliberation about the broader risks and benefits involved. Reticence to this wider kind of accountability could in part be explained by the fact that the scientists involved genuinely believe that they are doing important work that contributes to public health.

The need for international agreement on containment measures for biosafety was re-emphasised; and it was pointed out that even in the UK there have been cases where reputable universities have been prosecuted by the Health and Safety Executive for failure to comply with safety measures established by the Government's Advisory Committee on Genetic Modification.

A number of participants pointed out that it is important to emphasise the potential benefits of synthetic biology, as well as possible misuses. For example, it was noted that synthetic biologists are working to develop methods for rapid vaccine development to respond to new strains of flu, as well as biosensors that could aid in the detection of pathogens.

Questions were also raised about differences between the UK and US in the way that perceptions of the bioterrorism threat have emerged and evolved. 9/11 and the anthrax letters had an impact on security thinking in both the US and the UK. In the US, bioterrorism became a specific focus of concern, with dedicated measures put into place to detect and avert potential attacks and significant funding being directed to such measures. However, in the UK, bioterrorism has not been singled out in the same way, and any potential threats have been addressed as part of a broader resilience framework to chemical, biological, radiological and nuclear threats.

> *"Consultation to decide which GOF experiments are worth conducting should take place before the work is done, based on a thorough risk-benefit analysis; the publication stage is too late."*
>
> *Debora MacKenzie*

Session 2: How have ‘dual use’ concerns about synthetic biology been framed in the media and in policy discourse?

Synthetic Biology and Biosecurity in the Media

Presentation by Catherine Jefferson
SSHM, King’s College London

This presentation focused on the way in which mass media discusses the dual use issue in its coverage of synthetic biology, and how prevalent that narrative is. It began by identifying a number of ‘news values’ that characterise a ‘good’ news story and suggested that threshold, relevance, co-option and negativity were particularly notable in examples of coverage of synthetic biology. It was noted that accounts of synthetic biology as a radical and revolutionary new field with huge potential (threshold) often coexisted with fears about its negative impacts and potential for misuse (negativity).

The presentation went on to explore the prevalence of dual use concerns in media reports of synthetic biology. A LexisNexis search for articles on synthetic biology in all major English language newspapers found 465 articles about synthetic biology, of which 116 (25%) included the terms ‘bioweapon’ or ‘terror’, indicating that they mentioned dual use concerns. A smaller sample of UK broadsheet newspapers was also analysed and the prevalence of dual use concerns there was found to be around 16%. Within this sample, a number of key ‘alarmist anchors’ were identified – the 2002 polio synthesis experiment, the 2005 reconstruction of Spanish flu experiment, and Craig Venter’s statements about creating synthetic life – which served to provide symbolic visions of risk. It was argued that these alarmist anchors amplify the threat narrative of synthetic biology.

The presentation went on to suggest that the threat narrative in media accounts of synthetic biology and biosecurity is underpinned by a number of assumptions about science and technology in general, and synthetic biology in particular. It was suggested that there is a strong element of technological determinism in media narratives of synthetic biology, which presumes that, once set in motion, synthetic biology will head down an inevitable one-way path in which biology will be ‘de-skilled’ and that this means that it will become accessible to anyone. However, it was argued that this fails to take into account the challenges and contingencies involved in trying to make biology easier to engineer, and overlooks the continued importance of infrastructural and socio-technical factors, such as tacit knowledge, that limit the extent to become accessible to anyone. It was also suggested that by focusing so much on the technology, any analysis of the real-world adversaries who might actually want to use this technology gets side-lined.

It was suggested that one of the reasons why uncertainties and contingencies disappear in media stories about science, is because there is a focus on future promise. It was argued that media reporting of science is compelled to include future visions, and scientists, especially synthetic biologists, are also increasingly under pressure to 'big up' the impact of their work. It was noted that if we start from the premise that synthetic biology will deliver on future promises of making biology easier to engineer, then the question becomes: what are the perils? Thus, the more hype there is around the future promise, the more hype there also is around perils.

It was noted that this 'promise and perils' way of framing synthetic biology dominates media and policy discourse. The presentation concluded by suggesting that the circulation of these alarmist anchors in the media serves to reinforce the same threat narratives in policy discourse.

"Out of 465 newspaper articles about synthetic biology in the English language, 116 (25%) mentioned the words 'terror' or 'bioweapons'."

"The Promises and Perils of Synthetic Biology"
Tucker et al., *The New Atlantis*, 2006

"[Synthetic biology] promises great things in medicine, energy and the environment, but what are the perils?"
The Times, 2009

"Biology's Brave New World: the Promises and Perils of the Synbio Revolution"
Garret, *Foreign Affairs*, 2014

"Synthetic Biology - life 2.0: The new science of synthetic biology is poised between hype and hope"
The Economist, 2006

"Master the new loom before life's tapestry unravels at our hands"
Savulescu, *Times Higher Education*, 2012

Figure 2: Media headlines often frame the debate in terms of 'promises' versus 'perils'.

Synthetic Biology and Dual Use Concerns in Policy Discourse

Presentation by James Revill Harvard Sussex Program, University of Sussex

This presentation examined the way in which synthetic biology and dual use concerns have been addressed in the policy area, with a particular emphasis on States Parties to the BWC. It was noted that while there has been some hype around synthetic biology, there have also been a number of more nuanced statements in the context of the BWC, such as a statement by the Australian delegation which noted the theoretical possibilities but current technical challenges of misuse of synthetic biology. However, there have been other statements, such as the Chinese delegation in 2011 (cited in Appendix 1), that are bolder and hype the dual use threat of synthetic biology.

The presentation went on to explore the context of the dual use threat framing. It was noted that in the immediate aftermath of 9/11 and 'Amerithrax', advances in biotechnology and potential misuse began to be perceived as a broader challenge. The emergence of synthetic biology and perceived increases in the capacity, global nature and accessibility of the life sciences further fuelled concerns.

It was argued that concerns over the perceived game-changing capacity of synthetic biology need to be understood in the context of a changing physical and human geography of synthetic biology. In addition to the wide global distribution of those engaged in synthetic biology research, synthetic biology also represents a range of disciplines beyond biology that includes engineering, computing, mathematics, etc. Furthermore, the existence of non-professionals such as DIY biologists who operate outside of traditional institutional settings is also feeding into the concern that synthetic biology is new and novel and perhaps less stringently regulated and therefore could be seen as potentially more dangerous.

The presentation went on to argue that organisational frames serve as a lens for a particular way of looking at things. A common organisational frame is to view scientific advances as leading to rapid changes in biotechnology, its applications and its potential threats. However, it was noted that this framing overlooks the complexity and socially embedded nature of bioscience research. It was suggested that a fixation on worse case scenarios and minimising possible blame in the intelligence community, particularly following 9/11, had compounded this framing. It was suggested that if these changes in the capacity, global nature and accessibility of the life sciences are accepted and viewed through this organisational frame, then the focus shifts to risk. This focus on risk is compounded by synthetic biology's capacity to elicit 'dread risks' which, according to eminent social psychologist Paul Slovic, are those that are characterised by being unfamiliar, not well understood, difficult to control and perceived as a harbinger of future and possibly catastrophic mishaps. Accidents in systems that are familiar and well understood will cause far less social disturbance, even if many lives are lost, than accidents associated with these ‘dread’ characteristics.

“Just because it is hyped it does not mean it should be ignored.”

The use of toxicity and infection as weapons has been treated with particular obloquy and it was noted that there exists a ‘taboo’ against biological weapons due to their invisible, intangible, insipid and ‘ungodly’ characteristics. It was suggested that synthetic biology could be viewed as a ‘taboo on steroids’ due to similar characteristics and a limited understanding of what an attack would look like.

It was argued that failure to react – and to be seen to be reacting – to known risks, particularly dread risks, would be politically unacceptable. It was also suggested that while caution is needed when faced with the hyperbole of synthetic biology, developments in the field should not be discounted: just because it is hyped it does not mean it should be ignored.

Discussion in Session 2

Discussion in this session began by returning to complaints about media reporting of scientific issues. It was argued that dual use is not a new problem, but the context in which the debate arises has changed, and the way the mass media covers the issues is now part of the problem. The media was criticised for seeking controversy; focusing on shock and horror; maliciously, deliberately or inadvertently distorting the facts; oversimplifying subtle and complex issues; trivialising them by picking sound bites and grabbing headlines; a lack of proportionality; and episodic coverage, meaning that there is no consistent measured coverage of an issue. Instead, half-truths and myths such as those described in the Scoping Report for this workshop get recycled and get a life of their own and become the established wisdom. Overall, media coverage was considered to be unscientific. Moreover, recent trends in the media mean that news bulletins have to be filled every half hour and journalists do not have the time to consider long-term issues.

> *In a policy context, misuse scenarios and speculative hypotheses can be used to pose questions for the existing regulatory system in order to address issues before they emerge.*

It was pointed out that similar things could be said about diplomats and politicians. When security experts have to explain an issue to senior civil servants or ministers, the information has to be very short and condensed. Thus, although scientific experts from the UK Government produce in depth well researched reports of high quality, diplomats who attend the BWC meetings usually do not have the time to read them.

Some participants pointed out, however, that not all media coverage of synthetic biology was negative and that the field had, in fact, managed to distance itself - so far - from debates about genetically modified organisms.

Participants from the security community explained that misuse scenarios and speculative hypotheses can serve a variety of functions. For example, in policy contexts they can be used to pose questions for the existing regulatory system in order to address issues before they emerge. This does not necessarily involve a misrepresentation of the science, but encourages discussion of potential long-term security challenges. In this sense, it was argued that it can be useful to think of the myths in terms of future trends rather than as absolutes. For example, it may be more accurate and helpful to speak of synthetic biology making the engineering of biology easier, rather than easy.

Scientists from Imperial College London explained that, through their conceptual work with artists from the Interactive Design Department at the Royal College of Arts, an idea had emerged about how synthetic biology could be misused that they felt had serious security implications. Because the potential issues relate to civil liberties and forensic sciences, rather than terrorism or defence, they had reported this to the London Metropolitan Police. However, despite some initial discussions during which these contacts expressed their concern, the scientists had received little to no feedback. The example was used to demonstrate the frustration that can be experienced by scientists: they feel under a lot of pressure to demonstrate that they are acting responsibly and to consider all the societal aspects related to their research, but when an issue arose that they felt was serious, the agencies they contacted had not responded effectively.

This case study also usefully demonstrated how the way in which security issues are generally framed by organisations, in terms of defence and bioterrorism, can limit what is seen as a relevant concern, so that when a civil liberties issue is raised, it mismatches all the existing organisational frames and can make it difficult to know which organisations might be responsible. In the event, the workshop served to open up new channels of communications, since representatives from the Defence Science and Technology Laboratory and from the Foreign and Commonwealth Office were present and offered to look into this case.

Several participants noted that there are agencies that scientists could contact with security concerns but that these networks are not evident. It was noted that in the US, engagement between the security and synthetic biology communities through the Federal Bureau of Investigation (FBI) outreach activity is much more proactive and much better resourced. As a result, scientists voluntarily report concerns to the FBI, and do not see their involvement as an affront to the independence of scientific research. It was argued that knowledge of the BWC among UK university researchers was low, that it was crucial to raise awareness of dual use issues among scientists, and that this could help foster the kind of transparency that Debora MacKenzie had argued for in her talk. It was reported that the UK is trying to establish something akin to the FBI outreach programme in order to address the issue of engagement and awareness, and that there may be opportunities for sharing best practice with other countries, many of which have even fewer resources devoted to biosecurity than the UK.

Engagement between the security and synthetic biology communities is much more proactive and much better resourced in the US than in the UK.

Session 3: What are the tangible and intangible barriers to state and non-state production of biological weapons?

Weaponization Challenges

Presentation by Sonia Ben Ouagrham-Gormley
Department of Public and International Affairs, George Mason University

This presentation examined the challenges to weaponisation, drawing on data from interviews with former members of the bioweapons programmes in the US and the USSR. The findings from that research demonstrated that it is very difficult to develop biological weapons. These programmes had lasted many years and had been very well funded, however, they had not been successful in achieving their goals. The Soviet programme ran for 60 years, with over $20 billion investment and approximately 15,000 personnel directly involved. The US programme ran over 27 years, with about $700 million investment and 4500 personnel involved at the height of the programme. Other state programmes, for example in Iraq and South Africa, and the well-resourced Aum Shinrikyo cult had also failed to produce a working weapon.

The Soviet programme was successful in its early stages, where they developed bombs and spray tanks working with classical agents; but their work on developing weapons based on new pathogens that didn't exist in nature only reached the research and development stage. In addition, they did not succeed in producing bioweapons-specific ballistic or cruise missiles. The US programme was also able to weaponise classical agents and produce a few bombs and spray tanks, but none of the weapons developed met military requirements. One explanation for these failures is that unlike nuclear and chemical weapons, which use materials that are quite stable and have predictable behaviour, biological weapons rely on microorganisms that are living, can mutate, and are sensitive to their environment and to the way in which they are handled. This makes their use as a weapon more challenging.

Another key challenge has been the ability to ensure the successful passage from one stage of the development life cycle to the next: from research, to development, to small-scale production, large-scale production, testing and weaponisation. This is not a linear process and scale-up is particularly challenging, because at each stage the whole process needs to be modified and tested before you can move on to larger-scale production. In addition, each stage is performed by different people, in different teams, and with continuity of the work. Moreover, experience from the US and Soviet programmes demonstrated that civilian expertise in a specific agent (such as anthrax or smallpox) is not sufficient to weaponise the biological agent, and that bioweapons-specific expertise can take more than a decade to develop.

The presentation identified endogenous and exogenous factors that have affected bioweapons programmes. Endogenous factors refer to organisational and managerial models. In a successful model, there is careful coordination and integration of teams and stages. This might involve functional overlap, whereby upstream and downstream teams work collaboratively. The main virtue of functional overlap is to allow individuals working at different stages to be aware of their respective technical constraints, and therefore to make decisions that take these constraints under consideration. In an unsuccessful model, there is fragmentation and compartmentalisation of teams and stages. This prevents the transfer of expertise and the identification of problems until it is too late or the problems become too difficult to resolve. Compartmentalisation and fragmentation - an organisational model used by most covert programmes thus far - are useful to evade detection, but they impede the scientific process and the successful transfer of knowledge from one stage to the next.

> *“Experience from the Soviet programme demonstrates how political, economic and organisational factors had a severe adverse effect on bioweapons development, despite a high level of expertise, political support and funds.”*
>
> *Sonia Ben Ouagrham-Gormley*

Exogenous factors refer to issues such as political priority (either lack of priority or excessive political intervention), economic circumstances, foreign technical assistance and geographical location, which can all impact on the success or failure of a bioweapons programme. It was pointed out that political priority is usually perceived to be positive, because it leads to funding for necessary resources, but too much involvement of political leaders can also create disruptions. In both the Soviet and Aum Shinrikyo programmes, political leaders became too closely involved in scientific decisions, preventing the establishment of a continuous and stable work environment required to make progress. In conclusion, experience from the Soviet programme demonstrates how political, economic and organisational factors had a severe adverse effect on bioweapons developments, despite a high level of expertise, political support and funds. In other state and terrorist programmes - such as Iraq's, South Africa's and Aum Shinrikyo's - these factors prevented the development of working bioweapons altogether.

What is the role of tacit knowledge in what malevolent actors could achieve?

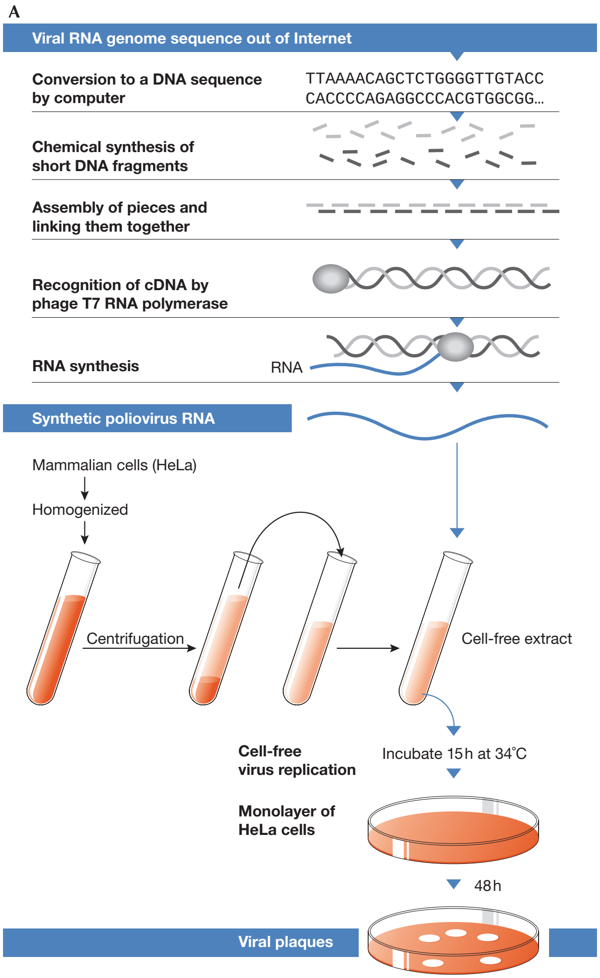
Presentation by Kathleen Vogel
Department of Science and Technology Studies, Cornell University

This presentation started by noting that many analyses of the threat posed by synthetic biology emphasise that research is becoming cheaper and easier and does not require the kinds of specialised skills and expertise that were needed for other kinds of biological research. The emphasis in these accounts tends to be on the material, informational aspects of synthetic biology: the fact that it is now possible to purchase synthesised DNA from commercial companies, and DNA synthesisers through the internet, and that many scientific journals now provide open access to articles that provide details on how to perform synthetic biology experiments. Focusing on these aspects leads to statements such as this one published in a recent article by Laurie Garrett in Foreign Affairs, suggesting that '[a]ll key barriers to the artificial synthesis of viruses and bacteria have been overcome, at least on proof-of-principle'. It was argued, however, that these analyses fail to address key questions such as: what is actually required to make these synthetic biology approaches work in practical terms? By different people? In different laboratories and contexts? And in particular: what is required for replication?

The concern is that someone could download all the necessary information and quite easily replicate experiments conducted by professional scientists. However (as discussed in a recent article in the New York Times), although replication is the gold standard of science, it is actually difficult to accomplish in practice. For many scientific experiments, replication can only be accomplished in particular circumstances and using highly specialised techniques and skill sets. The challenges involved in replication are familiar to scholars from Science and Technology Studies (STS), but get very little attention when the threat of bioweapons is discussed in the media or among security communities. It was argued that paying insufficient attention to the crucial issue of replication leads to erroneous assessments of the threat posed by these technologies; and that a new analytic framework (and kind of science journalism) is needed that takes tacit knowledge seriously in security assessments of synthetic biology. This would involve more in-depth analysis of what is shaping the development, diffusion and adoption of synthetic biology by different actors (including possibly malevolent ones).

The importance of tacit knowledge was illustrated by the example of the 2002 polio synthesis experiment (see Box 1 in Appendix 1) which is often used to demonstrate the security threats posed by synthetic genomics and triggered a lot of concern in the US policy community and in the media when it was published. Concerns were based on the fact that the published scientific article contained explicit detail of the materials and methods used, and that terrorists would be able to purchase the necessary DNA sequences in order to replicate the experiment, and may even be able to modify the protocol to create other kinds of deadly pathogens. Closer analysis of the experiment, based on interviews and site visits with the research team involved and other polio virologists, had, however, revealed that there was an entire part of the experiment that was not talked about in the media and policy discussions, and yet was crucial to its success. Discussions focused on the 'top part' of the experiment, but not the 'bottom part', which involved putting the synthesised RNA into HeLa cell extracts (see Figure 3). Being able to produce good quality HeLa cell extracts turns out to be a critical factor to successfully conduct this experiment: if you cannot do this you will not be able to produce any virus using this published protocol, regardless of how many DNA sequences you purchase or how closely you follow the protocol described in the article. And making good HeLa cell extracts is not easy, even though it is not a cutting edge technology and has been around for more than 20 years. It remains a craft-like technique that requires specialised and localised know-how that is very difficult to transfer between laboratories. Thus, even 12 years after publication of the article, replication of this experiment remains non-trivial. This demonstrates that some biological techniques are not necessarily becoming easier. It was argued that mapping out what exactly is getting easier, and what might remain difficult, would enable a more refined assessment of the biosecurity threats posed by synthetic biology, from both state and non-state actors, in order to better inform policy-making and the public about these threats.

The presentation concluded by arguing that STS research could usefully provide in-depth analyses of laboratory practices in different settings (university, commercial, iGEM, DIY), in order to elucidate the social and technical dimensions involved in synthetic biology that contribute to shaping (and limiting) biosecurity threats but tend to get glossed over in enthusiastic accounts of the field.



"If you cannot produce the high quality HeLa cell extract that is needed to perform the bottom part of this experiment, you will not be able to make any virus using this published protocol, regardless of how many DNA sequences you purchase."

Kathleen Vogel

Figure 3: Synthesis of poliovirus in the absence of natural template. From Wimmer, E. (2006). "The test-tube synthesis of a chemical called poliovirus", *EMBO reports* 7:S3-S9.

Credit: Image reproduced with the kind permission of *EMBO Reports*

Discussion in Session 3

This session began by raising questions over what is meant by a ‘weapon’ in these discussions. It was noted that it is important to distinguish between weapons of mass destruction (WMD), and those that aim to have less catastrophic impacts in terms of casualties, but can still cause terror. Some participants argued that for low-impact attacks, low-tech options were available for which tacit knowledge was not such an important barrier, but others argued that even for low-tech attacks, a terrorist would need to know how to handle the agent, so specialist expertise and tacit knowledge would remain significant. This view was supported by the fact that the key suspect in the relatively low-tech anthrax letters attack in 2001 (Bruce Ivins) was a senior biodefense researcher with specialist expertise in anthrax.

What do we mean by weapons? It is important to distinguish between weapons of mass destruction and those that have less catastrophic impacts.

It was also noted that, in addition to barriers to weaponisation, from the perspective of state-sponsored bioweapons programmes, militarisation would also be crucial i.e., the process needed to enable military use: training, handling, storage and assimilation into military doctrine.

Discussion then moved on to a more conceptual argument about what synthetic biology is and how it might undermine the necessity of socio-technical factors such as tacit knowledge. It was argued by some synthetic biologists present that synthetic biology is different from molecular biology: it is the engineering of biology. These synthetic biologists recognised the description of the challenges created by tacit knowledge and other socio-technical dimensions described in the two presentations, and suggested that they applied equally well to their own labs as to the Soviet bioweapons programme. However, they argued these problems would be removed by the engineering approach of synthetic biology. The abstraction hierarchy, and the engineering tenets of modularity, characterisation and standardisation would enable design to occur at different levels while still being integrated. Engineers are already developing protocols for experimental work that are so reliable they can be described as ‘bullet-proof’ (e.g. for the production of competent cells), which will overcome the challenges of reproducibility described by Kathleen Vogel.

Some participants suggested that this discussion illustrated an interesting tension. On the one hand, if tacit knowledge remains important in synthetic biology, then this implies that it will not be easily accessible to outsiders and this reduces concerns about the dual use threat. On the other hand, if synthetic biology is an engineering discipline and <u>if this</u> means that we overcome the barriers posed by tacit knowledge, then this implies that it could become more accessible to outsiders and this increases the dual use threat.

Other participants pointed out that synthetic biology was nowhere near that level of characterisation and standardisation yet. For example, there are problems with the reliability of biological parts from the registry populated by students competing in iGEM. In response, it was argued that this registry does not represent the full potential of synthetic biology. For example, researchers at Imperial College London are developing standardised protocols and procedures and robotic high-throughput systems to enable part characterisation at a professional level; and as the field develops it will seek to build biological systems that are more predictable, reliable and robust.

More care needs to be taken in the interpretation of statements about how synthetic biology will 'make biology easier to engineer.'

It was suggested that it would be useful to conduct fine-grained analyses to examine the extent to which the engineering of biology is something that is achievable, in order to inform assessment of the associated security threat. Moreover, historical studies of engineering practice (in non-biological sectors) demonstrate that troubleshooting, skills and socio-organisational factors remain necessary for engineered systems to function; and protocols are not always fully reliable.

An analogy to aeronautical engineering was used to illustrate that de-skilling does not necessarily mean that teamwork and large infrastructures are no longer necessary. Planes are built from a large number of well-characterised parts in a systematic way, but this does not mean that any member of the general public can build a plane, make it fly, and use it for commercial transportation. This suggests that it is too simplistic to suggest that if synthetic biology becomes an engineering discipline it will necessarily become easier for anybody to engineer a biological application, including dangerous ones. Thus, more care needs to be taken in the interpretation of statements about how synthetic biology will lead to 'de-skilling' and 'make biology easier to engineer.'

Planes are built from a large number of well-characterised parts in a systematic way, but this does not mean that any member of the general public can build a plane, make it fly, and use it for commercial transportation.

It was noted that ideas about synthetic biology leading to the democratisation of biology and enabling non-professionals to work with biological materials and develop their own biotechnologies had arisen from the discourse used by DIY biology communities, and that in some ways they had been almost too successful in promoting their vision and enthusiasm for the field, because this had also raised concerns.

The session ended with the suggestion that an iGEM team could be run that was entirely outsourced, to demonstrate the power of platform technologies. It was argued that this was already entirely feasible, because there are companies that offer services for design, DNA synthesis and cloning.

It was also pointed out that some iGEM teams (e.g. the 2012 Edinburgh team) have argued that failure is an integral part of research and have been open about sharing their negative results, on the basis that this can help develop the field (FAIL= 'Future Awesomeness Is Likely'). The suggestion here was that sharing negative results with the scientific community could perhaps help overcome some of the challenges posed by tacit knowledge.

Synthetic biology is different from molecular biology: it is the engineering of biology.

Session 4: What scientific developments within synthetic biology might be relevant to misuse concerns, now or in future?

From whence the evidence?

Presentation by Piers Millet Biological Weapons Convention Implementation Support Unit

The presentation began by suggesting that interest in synthetic biology in the context of the BWC started with a 2006 article in the Economist ('Synthetic Biology - Life 2.0: The new science of synthetic biology is poised between hype and hope'). There had been some prior technical discussion but publication of this article brought synthetic biology to a broader audience of Geneva diplomats. This prompted the BWC Implementation Support Unit (ISU) to seek ways to create a more balanced picture and efforts were initiated to build bridges between the synthetic biology and BWC communities.

States, scientists and the BWC ISU all play a role in identifying developments relevant to the BWC. The ISU has developed a close relationship with the synthetic biology community and has presented at major international synthetic biology conferences (SB4.0, SB5.0 and SB6.0) and a range of other technical meetings. Members of the ISU act as judges for the iGEM policy & practices track and participate in the safety & security committee. The ISU has also worked to provide venues for interactions between the synthetic biology community and diplomats at the BWC, in order to explore the range of potential benefits, to showcase efforts to consider societal implications, and to enable a discussion of security implications. Each year, the ISU publishes a background document on possible advances relevant to the BWC and since 2008 this has regularly included elements on synthetic biology. The role of the ISU is not to tell States what is relevant, but rather to highlight new areas of science that they should perhaps consider. Evidence is gathered based on research discussed at synthetic biology meetings, publications in scientific journals, and work brought to the attention of the ISU by experts within the BWC and synthetic biology communities.

There is general agreement among States Parties of the BWC that developments in science and technology, including synthetic biology, can be used to our benefit, for example helping to combat diseases, as well as for prohibited purposes - and they can also be used to help strengthen compliance with the BWC. However, it was argued that it is difficult to anticipate which implications a specific advance might have. It was noted that determining this is beyond the mandate of the ISU and that national technical experts have the most influence in this respect. However, it was noted that agreement among national technical experts is not the end of the story. Common understandings need to be written down in the BWC Meeting of States Parties report and this presents challenges because written outputs become a

> *"States Parties of the BWC agree that synthetic biology can be used to our benefit, as well as for prohibited purposes."*

process of negotiation between diplomats. This process can become one of trading sentence for sentence, leading to a disconnect between the text produced and the underlying technical assessments. This has meant, for example, that paragraphs outlining areas of concern have had to be preceded by paragraphs listing all the potential benefits; and that the final text will usually emphasise that nothing should be done to restrict the peaceful use of biology.

The presentation went on to examine where evidence comes from in other processes. The Organisation for the Prohibition of Chemical Weapons Scientific Advisory Board Temporary Working Group on Chemical and Biological Convergence, for example, looked at using biology to synthesise chemicals. There was considerable discussion of synthetic biology and the working group had regular briefings from practicing synthetic biologists, representatives from synthetic biology companies and a DIYbio group. The WHO expert consultation on Dual Use Research of Concern also included a panel on synthetic biology which included practicing synthetic biologists, representatives from a gene synthesis company and the iGEM safety committee founder. The panel proved to be so useful that they were invited to reconvene at the start of the next day. Global science bodies have also convened a series of events to look at implications of science and technology developments for the BWC and the Chemical Weapons Convention. These meetings included practicing scientists, representatives from companies, national technical experts, experts from international organisations and experts from the BWC and the Chemical Weapons Convention communities.

The presentation concluded by suggesting that national processes are considerably more opaque since those involved in it generally cannot talk about it. One of the few good sources of information about these is a paper by Kathleen Vogel.

Figure 4: iGEM has been an important venue for engagement between the synthetic biology and the security communities.

Credit: Image reproduced with kind permission of the BWC Implementation Support Unit

The Realities of the Research

Presentation by Jim Ajioka
Department of Pathology, University of Cambridge

The presentation began by stressing that synthetic biology is the engineering of biology, and that the design-build-test engineering cycle is central to that endeavour. The design principles needed to implement this cycle are essentially composed of scientific knowledge. A range of different types and sources of scientific knowledge can be used, including scientific literature, patents and laboratory notebooks. Knowledge about negative results - things that did not work - can save time but unfortunately there is almost no dissemination about such failures. The necessary design tools and materials - databases, analytical tools, and repositories - are largely publicly available, although some resources are more open than others.

The presentation went on to explore the 2001 experiment by Jackson et al. in which researchers inserted the gene for interleukin 4 (IL-4) into the mousepox virus (see Box 1 in Appendix 1). The aim of this research was to produce a virus that would induce infertility in mice, but the virus created was unexpectedly found to be lethal to mice. The significant aspect of this study was that the altered virus even killed mice that had previously been immunised against mousepox. This experiment had raised concerns and is often cited as an example to demonstrate that 'gain of function' is possible to engineer. The presentation proceeded to examine whether it would be possible to develop a lethal vaccination-resistant smallpox virus, using synthetic biology's design-build-test cycle. It was noted that accounts of this experiment in non-scientific arenas do not pay sufficient attention to related scientific literature that provides important context for assessing the threat caused by its publication.

The whole DNA sequence of the variola virus genome is available in publicly accessible databases. There are (or soon will be) publicly accessible tools and protocols necessary for the design and build stages. But it would still be necessary to obtain the viral material, and variola is not easily available from strain repositories. An alternative would be to engineer vaccinia instead, which is available and is closely related. One of the challenges for this kind of work is that virus culture requires a sterile environment, and this is not a simple matter. It also requires expensive equipment and reagents; and making a recombinant virus is not a routine procedure. This means that it would be hard to do in a DIY lab, but would be possible in a well-equipped and well-funded laboratory, operated by trained scientists.

The testing stage of the engineering cycle would be particularly problematic. Testing in mice is of limited value because humans do not necessarily react in the same way;

and it would not be possible to find a human population willing to voluntarily participate in such testing. This means that it is not possible to go through the design-build-test cycle when developing a bioweapon.

It was noted that an experiment testing IL-4 gene expression in vaccinia had been performed prior to the mousepox experiment. Insertion of the IL-4 gene exacerbated the infection but did not confer massive lethality, as in the Jackson et al. experiment with mousepox. This demonstrates that it is not possible to extrapolate from one experiment to another, even when the viruses are closely related and even in the same host (in this case, mouse).

It was argued that we have to be careful when talking about 'gain of function', because losing a gene can in some cases lead to gaining a phenotypic function. For example one virus homologue of the IL-1 receptor, called B15D15R, is mutated in variola and does not work. Since IL-1 promotes fever, this means that when this gene is lost, host IL-1 is not 'soaked up' by B15D15R, so the virus gains a function (to induce fever).

In conclusion, it was argued that going through this example of the IL-4 experiment and how it could be used to develop a bioweapon illustrates the unpredictability of biological responses. Although there have been tremendous advances in the development of tools and protocols to drive the engineering design-build-test cycle, the bottom line is that we do not, at present, have enough information to know the design rules that would enable us to construct a lethal pox virus using synthetic biology.

Looking forward, both scientists and non-scientists need to take a more balanced and dispassionate view of the potential to engineer bioweapons because the potential to engineer bioweapons will change over time and each case is bespoke, thus requiring independent, periodic review.

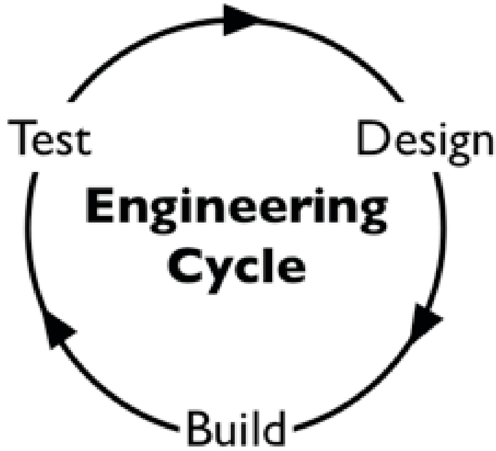


Figure 5: Some workshop participants stressed synthetic biology is an engineering discipline that aims to implement the design-build-test engineering cycle.

Credit: Image reproduced with kind permission of Jim Ajioka.

Discussion in Session 4

Discussion in this session began with a question about the timescales involved in the design-build-test cycle. It was noted that this is difficult to anticipate and is dependent on the type of project being conducted. Drawing on the example of the Artemisinin developed by the company Amyris, it was argued that while the original work required a decade and an enormous amount of funds and person hours, this work was then used to develop an industrial approach and the company was able to produce their next product - biodiesel - with far fewer funds and researchers. The whole point of the engineering approach to industrialisation is to make each iteration of the design-test-build cycle quicker and easier; and to enable work to be transferred from one purpose to another.

Discussion then returned again to the question of the extent to which the engineering of biology is achievable. Synthetic biology aims to exercise control in the design, characterisation and construction of biological parts, devices and systems, in order to produce more predictable biological systems. However, some participants felt it would be important to consider that there might be limits to the level of control and predictability that the engineering approach could achieve over the complexity and contingency of biology. Scale-up was identified as a key challenge in this respect, in particular for viral systems. Producing larger quantities of virus requires serial passage in cell culture, and viruses will necessarily incur mutations during that process. Moreover, these mutations will tend to lead to a loss of virulence (the viruses will be attenuated), which is problematic if the aim is to develop a bioweapon. Selection - be it natural or artificial - is a driving force that has to be contended with.

Questions were raised about how much knowledge synthetic biologists need to have about biological systems in order to be able to engineer them; and it was suggested that synthetic biology was at a similar stage to the Wright brothers with respect to the development of planes, in the sense that they did not know whether or not a flying plane could exist. In response, it was pointed out that even today, world experts in aeronautical engineering do not fully understand wing turbulence, but this has not prevented the development of

We do not need to know everything about biology before being able to do synthetic biology: even today, world experts in aeronautical engineering do not fully understand wing turbulence, but this has not prevented the development of commercial aviation.

commercial aviation. Basic research and commercial development in aeronautics continue in parallel: we do not need to know everything about wing turbulence to fly a plane across the world. Similarly, we do we do not need to know everything about biology before being able to do synthetic biology; and it was suggested that biology and synthetic biology should be considered to be different but complementary, just like chemistry and chemical engineering.

Some participants felt it would be important to consider that there might be limits to the level of control and predictability that the engineering approach could achieve over the complexity and contingency of biology.

The historical example of the Wright brothers was also used to raise the issue of timespan. Drawing on an example developed in the book by Rob Carlson, it was pointed out that there was a long interval of (approximately 90 years) between the first flight by the Wright brothers and the Boeing 777, which was the first airplane designed on computers, tested on computers, and built predominantly without wind tunnel testing.

This led to a discussion about the extent to which synthetic biology was, or not, distinct from previous forms of 'genetic engineering'. It was suggested that there was absolutely no engineering practice in previous forms of 'genetic engineering' - that were simply the bespoke manipulation of genetic material - and that the term had been coined in order to suggest that the researchers involved knew what they were doing. Synthetic biologists expressed frustration about the fact that many people do not understand that synthetic biology is, in contrast, 'proper engineering'. In response, it was pointed out that when scientists talked about 'genetic engineering' in the 1970s, they also stressed that what they were doing was much more systematic and rational than previous forms of genetic manipulation, such as animal and plant breeding. This can help to explain why some people are sceptical of the 'engineering' claims made today for synthetic biology.

It was pointed out that most synthetic biology research is conducted with E. coli, which is an academic tool with some industrial applications; but that the Synthetic Yeast 2.0 project was an example of how the field was developing work with more industrially relevant organisms. It was also suggested that the choice of microorganism used could affect public discussions, because members of the general public often express more disgust at the idea of using E. coli than yeast. Members of the public associate E. coli with health threats and faeces - which is accurate, but not for the strains used in laboratories - whereas there is a better reception to the idea of genetically manipulating yeast, because it is used to make familiar products such as beer, bread, champagne, and even chocolate. Some synthetic biology projects for the production of biofuels and biobutanol are now using clostridia. This has relatives that produce botulism but is also used in Botox, which has medical and cosmetic applications. If synthetic biology wants to expand the range of organisms used in the future, concerns about misuse may emerge from a lack of understanding of microbes and of biology among lay people.

The session ended with a discussion of why synthetic biology was being tangled up with concerns about bioterrorism. It was argued that if synthetic biology could lead to a situation where there was such good confidence in the engineering cycle that you could produce a weapon that would function in a predictable way without any need for trials and prototyping, that could have serious security implications; because testing is the stage that is most difficult to conduct in secret. Thus, in terms of threat assessment, the prospect of a reliable trials-free biological engineering is worrying. For some participants, this meant that the promises made about the prospects for synthetic biology to help meet global challenges, (for example, to produce biofuels and new pharmaceuticals) is directly linked with concerns about biosecurity. Others, however, argued that the technology needs to be disentangled from the human beings who might want to use it for bioterrorism, and refuted the idea that there is necessarily a correlation between advances in synthetic biology and the rise of the biosecurity threat.

It was noted that in the context of the BWC, there are now annual reviews of developments in science and technology that could have the potential for misuse, and that the focus is on identifying possibilities, not probabilities. It was also noted that the treaty, while primarily focused on the prohibition of biological weapons, also emphasises prevention of bioweapons development and the responsible development of science.

It was argued that from a security perspective, it is important to understand how developments in a technology could change the equation and to be aware of what threats could emerge in the short, medium and long term. A fully synthetic microbe is probably a long term issue. But in the shorter term,

The BWC was created in an age where weapons development necessitated the movement of bacterial specimens and equipment. If - as is often stated - biology is now becoming an information science, this would raise difficult questions.

one could, for example, envisage engineering the metabolic pathway to produce a toxin such as saxitoxin, which is currently only available in very small quantities, by extraction from shellfish. Potential long-term threats also need to be considered so that they can be addressed before they occur.

It was pointed out that the BWC was created in an age where weapons development necessitated the movement of bacterial specimens and equipment. If - as is often stated - biology is now becoming an information science, this would raise difficult questions and the security community would need the help of practising synthetic biologists to help to address them.

Session 5: General discussion

The general discussion began with feedback on the Scoping Report that had been prepared for the meeting. This document identified five recurring 'myths' about the dual use threat of synthetic biology that dominate discussions in policy arenas and the media, and highlighted some key challenges to this narrative (see Appendix 1). Feedback was generally positive, but concerns were raised about the use of the term 'myths' as it can imply a polarisation between 'myths' and realities, as if everything in the dominant narrative is untrue and all the challenges identified in the Scoping Report are 'realities'. But there are elements of truth and falsity in both ways of framing the issue. It was also noted that myths serve to mobilise support and resources and that further discussion of the purposes the myths are serving would be valuable.

A number of themes from the day's discussion were returned to, in particular the role of media, the question of the extent to which synthetic biology would make biology 'easier to engineer', and interpretations of the concept of 'de-skilling' biology. It was noted that the role of the media is not just to communicate or teach science, but also to entertain and make money, and that there are many 'news values' that characterise a 'good' news story. With respect to de-skilling, caution was urged in the way this concept is interpreted. Drawing a parallel to the Industrial Revolution, it was suggested that synthetic biology is moving towards a more systematic process, but this does not necessarily mean skills become irrelevant.

Drawing a further parallel to furniture making from Chippendale in the 18th century to IKEA in the 21st, it was pointed out that de-skilling a process does not imply that anyone can do it, but involves moving from a system that relies on a small number of highly skilled craftsmen towards a more systematic process. Technological and other developments reduce the amount of specialised craft knowledge that is required to complete a process successfully. This makes the process less dependent on individual skill, and more systematic and reliable, but often requires more complicated machinery. Thus, even if the de-skilling of synthetic biology makes the engineering of biology easier, this does not mean that synthetic biology will become accessible to any layperson.

Caution was urged in the way in which 'de-skilling' is interpreted: even if the de-skilling of synthetic biology makes the engineering of biology easier, this does not mean that synthetic biology will become accessible to any layperson.

One example of such a development in synthetic biology is Gibson Assembly, which has reduced the number of hours of mindless lab work that was previously necessary to put DNA fragments together. The experimental protocol does not always work and there is still a degree of tacit knowledge involved: laboratory researchers have to learn how to make it work through personal experience, and from their peers - but in the context of a professional lab, stitching DNA fragments together is definitely becoming easier that it was before.

Questions were raised about the way in which the bioterrorism threat is understood, in particular who did we imagine were the actors who would try to use synthetic biology for malevolent uses? It was noted that would-be terrorists have other low-tech options at their disposal, and that even unsophisticated threats or attacks that cause few (or even no) casualties can cause terror. It was suggested that the WDM bioterrorism scenario is much less likely, although that is the type of mass impact scenario typically envisaged is discussions of synthetic biology. Thus, low-impact and high-impact scenarios are often conflated in the debate. It was noted that both high- and low-tech scenarios are examined in the context of defence and security, and that synthetic biology could be an enabling technology for both categories. It was pointed out that terrorists have many means at their disposal that do not require the use of bioweapons, but that some groups were fanatical about using the latest science and technology.

These discussions have been taken into account to produce a revised version of the Scoping Report, to be published in a forthcoming article in *Frontiers for Public Health*.

Key Themes

The workshop provided a fairly unique forum for actors from different disciplines and professions to interact together in an environment that facilitated a fruitful debate and raised some issues that are not often aired in discussions about synthetic biology. The first part of this report has summarised those discussions, replicating as accurately as possible what was said by the workshop participants, without commenting on those statements, and without endorsing (or not) any of the views expressed. In this section, we, the authors, take a step back and use our social science expertise to analyse the dynamics of those discussions. We tease out the key arguments that participants made throughout the day, and how they relate to each other and to social science scholarship in these areas. We believe that this analysis reveals a set of topics that need to be addressed further in order to foster a more productive debate about synthetic biology and biosecurity.

Beyond 'myths' versus 'realities'

The use of the term 'myths' can imply a polarisation between 'myths' and 'realities', as if everything identified as a 'myth' is imaginary and all the challenges to those myths are real, but there are elements of truth and falsity in both. What is needed is a more refined assessment of biosecurity threats related to synthetic biology that takes into account not only the material and informational aspects of the field, but also other important socio-technical dimensions that will shape the development of the field; and that also adopts a more nuanced view of the 'de-skilling' of biology.

Just because it is hyped doesn't mean it should be ignored

Biosecurity experts present at the workshop stressed that even if the threats associated with synthetic biology are exaggerated, this does not mean that they should not be investigated. Misuse scenarios serve a variety of functions, some of which are to represent possible, though not necessarily probable, future scientific developments in order to explore potential long-term security challenges. In this policy context, speculative thinking can be helpful to identify worst-case scenarios and potential responses to these, and should not be discounted as mythmaking. However, problems arise when these scenarios are portrayed as scientific reality in the present, or as inevitable in the future, which tends to occur in the media, in political and diplomatic forums, and in some bioethical analyses. This diverts political and policy discourse and initiatives in unhelpful ways.

The need to distinguish different categories of terrorists, attacks, and weapons

There are different assessments of the nature, importance, urgency and scale of the bioterrorism threat, and these have varied over time and across countries. There are different kinds of ‘users’ of bioweapons, and they can have very different motivations and objectives. It is often assumed that terrorists would seek to generate mass casualties, but historical examples demonstrate that some terrorist attacks aim to cause few casualties and still cause massive disruption and terror. Assessments of biosecurity threats often conflate these different kinds of attacks, and it would be helpful if they distinguished more clearly between high-impact and low-impact scenarios, and between high-tech and low-tech weapons.

Engagement between synthetic biology and security communities is crucial

It was suggested that more engagement is needed in the UK between the security community and the synthetic biology community, in order to ensure that scientists know which authorities to contact if they have concerns, and to facilitate the security community’s role in identifying relevant developments. In the US, the engagement by the security community is much more proactive and well resourced, via the FBI outreach programme.

There are tangible and intangible barriers to the misuse and reproducibility of science

Drawing on failures encountered by former state and terrorist-sponsored bioweapons programmes, it was argued that the development of bioweapons is difficult: biological organisms are unpredictable, scale-up is particularly challenging, there are many stages in the process, each stage requires different expertise performed by different teams, and these teams need to coordinate effectively. Drawing on the example of the 2002 polio synthesis experiment, it was argued that while some aspects of biological research have become easier, some techniques remain craft-like and require specialist, tacit knowledge which is difficult to learn and transfer between different laboratories. This means it is essentially impossible to reproduce a scientific experiment using only the information contained in a published scientific article. It was argued that analyses of dual use threats tend to focus on the material, informational aspects of science and technology rather than a more in-depth analysis of these kinds of socio-technical factors; and that taking into account these dimensions would lead to more refined assessments of the biosecurity threats posed by synthetic biology.

Synthetic biology is an engineering discipline, so these barriers will become irrelevant

Some of the synthetic biologists present at the workshop stressed that it is important to understand that synthetic biology is different from molecular biology; it is the engineering of biology. These synthetic biologists stressed that the engineering approach is composed of standardised protocols, tools and platform technologies, including professional registries of well-characterised biological parts, that will enable the implementation of a ‘design-built-test cycle’. Thus, synthetic biology aims to exercise control in the design, characterisation and construction of biological parts, devices and systems, in order to produce more predictable biological systems.

This argument is frequently made as a means to distinguish synthetic biology from previous forms of ‘genetic engineering’. In the context of this workshop, it was also specifically used to argue that, as the engineering process becomes more systematic, the tangible and intangible barriers described above for the development of bioweapons, and for the reproducibility of scientific experiments from one laboratory to another, would become irrelevant. According to this depiction of synthetic biology, it will essentially eliminate the need for tacit knowledge and specialist skills, and will be able to control the contingency and complexity of living organisms; with some participants suggesting, for example, that engineers can produce experimental protocols that are so reliable they can be described as ‘bullet-proof’, and that all the daily grind of laboratory work can already be outsourced to service companies.

This position was challenged in two ways. Firstly, there were discussions about the extent to which synthetic biology has achieved, or ever will achieve, the goal of transforming biology into an engineering discipline. The consensus was that it had not yet, but for some participants it was only a question of time before it did. For example, although there are limits to the work conducted by iGEM teams and the registry of biological parts created through that competition, these will be overcome as the field becomes more professionalised.

Secondly, there were discussions about the extent to which an engineering approach would eliminate the need for the kinds of tacit knowledge and other socio-technical factors that had impeded the development of large state-sponsored bioweapons programmes in the past. During these discussions, the more extreme depiction of synthetic biology as an engineering discipline tended to become tempered, and some participants pointed out that skills and large infrastructures remained important in other (non-biological) fields of engineering.

The ‘synthetic biology/engineering conundrum’

An interesting tension emerged during the workshop. On the one hand, if tacit knowledge remains important in synthetic biology, then this implies that it will not be easily accessible to outsiders and this reduces concerns about the dual use threat. On the other hand, if synthetic biology is an engineering discipline and if this means that we overcome the barriers posed by tacit knowledge, then this implies that it could become more accessible to outsiders and this increases the dual use threat. Thus, biosecurity concerns are heightened when the more extreme depiction of synthetic biology’s ability to engineer biology is emphasised. We characterise this as the ‘synthetic biology/engineering conundrum’.

What do we mean by ‘de-skilling’?

This conundrum arises because the ‘de-skilling’ of biology is often misrepresented as meaning that any layperson, working outside professional scientific institutions, is or soon will be able to design and produce organisms that behave predictably and reliably. However, a different understanding of ‘de-skilling’, and of the engineering approach of synthetic biology, emerged during the workshop discussions, in which dependence on the craft skills of a small number of highly trained individuals is reduced for some parts of the production process, usually by standardisation and mechanisation. This does not mean that skills become irrelevant or that all aspects of the work become easier. This was illustrated during workshop discussions by an analogy with the shift from Chippendale to IKEA furniture. An analogy with aeronautical engineering was also used, to illustrate that specialised teams, considerable expertise, complicated machinery, advanced technology, trouble shooting - and thus organisational factors - continue to be required when a design and engineering approach develops. From this perspective biology can become industrialised and subject to an engineering approach without necessarily becoming accessible to laypeople working outside institutions, including those with hostile intentions.

If we are to disentangle synthetic biology and biosecurity concerns, and to have more nuanced discussions about the realities of the threat (how scared should we be?) we believe that it is necessary to have realistic and evidence based discussions about the extent to which synthetic biology is, or ever will be, an engineering discipline; and whether, in practice, this would reduce the importance of tacit knowledge, specialist expertise of different kinds, collective work, large infrastructures, and organisational factors. Such discussions would need to identify those aspects of the work that would become easier – in the sense that they can, for example, be automated and reliably performed by a robot - and those which are likely to remain difficult, in the sense that they still require craft skills to be successfully achieved. It would also be more accurate and helpful to speak of synthetic biology making the engineering of biology easier, rather than easy.

Blaming the media

Another theme that permeated discussions throughout the day was coverage of science in the media. Some synthetic biologists and some policy makers argued that the way in which the media reported science was a major obstacle for rational debate. They argued that the media 'sensationalises' stories; likes controversy and horror stories; oversimplifies complex scientific research; gives too much weight to individual maverick scientists who behave irresponsibly rather than the consensus from the more responsible scientific community; and trivialises issues by latching onto key words and seeking catchy headlines. These participants felt that the media should be more scientific, reporting facts based on scientific literature rather than the views of individuals.

However, for good or ill, the primary role of the media is not to communicate science calmly and rationally. It is an industry that, just like any other, seeks to make money, which means that increasing sales and advertising revenues are key objectives, and in many cases this is best achieved by entertaining their audiences. In addition, it is entirely legitimate, and perhaps important, for debates among scientists about the purposes and findings of research to be represented, so that citizens are more able to understand and participate in such debates and to have their say about future directions. Blaming the media for generating scare stories is also inaccurate in the sense that journalists are often not the original source. For example the potential for misuse of the H5N1 research conducted by Fouchier was first raised as an important problem by the biosecurity experts at the US National Science Advisory Board for Biosecurity (NSABB), not by journalists. It is also interesting to note that scientists often perceive dramatic scare stories about science as damaging, but that dramatic – and often equally overstated - stories of scientific breakthroughs, which are the mirror image of such scares, are usually welcomed as generating support for science.

Moreover, although this was not explicitly stated during the workshop, an underlying assumption was that lay members of the public are easily swayed by negative accounts of science, and that the tenor of media reports will determine whether 'the public' will be 'for' or 'against' a particular technology. There is also a presumption that laypeople are unaware that media stories are sensationalised. This set of beliefs about science and the media, and about public understanding of science is, however, challenged by social science research. Research demonstrates, for example, that members of the public are not passive recipients of media messages. On the contrary, they are exposed to - and select from - multiple sources of information, and are aware of the ways in which media stories are constructed. They create their own understandings on the basis of many sources, and do not merely naively accept this or that scare story.[1] Research from the field of social studies of science also undermines simplistic accounts of 'the public' and demonstrates that lay people can hold nuanced views on scientific and technological developments, which takes into account the social, economic and cultural settings of scientific institutions.[2]

[1] See for example: Bucchi, M. (1998). Science and the Media. Routledge; and Kitzinger, J. (2004). "Audience and Readership Research" in The SAGE Handbook of Media Studies, Sage.

[2] For a review, see Wynne, B. (1995). "Public Understanding of Science" in S. Jasanoff et al. (Eds) Handbook of Science and Technology Studies, Sage.

‘Hype’ as a double-edged sword

Discussions about the extent to which synthetic biology differs, or not, from previous forms of genetic engineering, and about the extent to which the ‘engineering vision’ of synthetic biology is achievable, often recur in policy discussions about synthetic biology. In this report, it is not our role to arbitrate between the different views expressed on this topic. Rather, we are interested in how these arguments played out during the workshop, and the implications they have for the entanglement between synthetic biology and biosecurity. Thus, what was especially striking was that, for some participants, the argument that synthetic biology is (or soon will be) an engineering discipline was directly associated with heightened concerns about the potential biosecurity threat of synthetic biology: the greater the stress on this promise, the greater the estimation of the perils. But for other participants, notably some of the synthetic biologists, this link between optimistic promises and heightened concerns - the ‘synthetic biology/engineering conundrum’ - was not obvious.

It is important to reflect on the role that these dynamics play in popular representations of synthetic biology. Discussions at the workshop illustrated how different communities stress – and perhaps overstress - particular issues in particular contexts, and how this plays an important role to construct and maintain resources and support for each of these communities. Thus, scientists who promote synthetic biology need to portray an optimistic vision of the potential of the engineering approach to biology as part of their endeavours to develop support for a new field of research which they believe has great significance and potential. Conversely, scientists in adjacent fields of biology often seek to emphasise the messiness and contingency of biology in order to maintain support for their areas of research. Actors who work in or contribute to the security field, including some policy makers, social scientists and natural scientists often exaggerate the ‘dual use threat’ in order to attract resources to their own work. Researchers who conduct social studies of science and technology often seek to emphasise the complexity of real world situations, and the importance of social dimensions of science, in order to justify the need for their expertise. What is needed, we would argue, is for each of these groups of actors to recognise the ‘performativity’ of their own discourses - that is to say, the ways in which they have consequences. Some of these consequences are intended, but there can also be unintended consequences that are detrimental to their own interests and/or to the nature of public debate. We argue that a better understanding and acknowledgement of these dynamics would help towards developing more productive discussions in which the different communities involved could move beyond simply defending their own positions. This was in part the aim of this workshop and we feel that we made a step in that direction.

Feedback Received

Feedback from the workshop participants was overwhelmingly positive. The extended discussion periods, broad range of expertise, and the 'genuine sense of sharing perspectives' were repeatedly mentioned in the feedback forms as the best aspects of the workshop.

Most of the participants (15 of the 17 who completed the questionnaire) said the workshop would have an impact on their future work. Policy experts noted they would 'continue to highlight the value of the genuine engagement by the synthetic biology community with the societal impact of their work', 'take on board the possible need for guidance to the scientific community on how to deal with issues of concern and who to contact', and 'think about a national regulatory framework, e.g. an Advisory Committee for Synthetic Biology'. Synthetic biologists noted that they would 'think more carefully about responsibilities of publishing research that may have dual use', 'think more about biosecurity in design', and 'better frame what synthetic biology enables'. Social scientists noted the discussions 'have stimulated new ideas', 'will feed directly into on-going research', and 'will inform thinking and teaching'.

One participant commented: 'The workshop was extremely valuable in promoting cross-national perspectives on synthetic biology. It stimulated discussions about the technical complexities and challenges in synbio that would not have occurred in the United States.' Reflecting these complexities and challenges, another participant said one of the key issues to emerge from the discussions was 'that there is still some way to go to create a common narrative of the security implications of synthetic biology.'

Workshop Programme

10:00-10:10	**Welcome** Richard Kitney Claire Marris
10:10-11:20	**Session 1: How have concerns about biological weapons and bioterrorism emerged and evolved over time?** Filippa Lentzos: 'The world's most deadly weapons': The politics of bioterrorism Debora MacKenzie: A case study of the 2011 H5N1 avian influenza transmission studies DISCUSSION (40 minutes)
11:20-12:30	**Session 2: How have 'dual use' concerns about synthetic biology been framed in the media and in policy discourse?** Catherine Jefferson: Synthetic biology and biosecurity in the media James Revill: Synthetic biology and 'dual use' concerns in policy discourse DISCUSSION (40 minutes)
12:30-13:30	**LUNCH**
13:30-14:40	**Session 3: What are the tangible and intangible barriers to state and non-state production of biological weapons?** Sonia Ben Ouagrham-Gormley: What are the barriers to weaponisation? Kathleen Vogel: What is the role of tacit knowledge in determining what malevolent actors could achieve? DISCUSSION (40 minutes)
14:40-15:50	**Session 4: What scientific developments within synthetic biology might be relevant to misuse concerns, now or in future?** Piers Millett: What evidence and expertise are drawn on in assessments of misuse risks? Jim Ajioka: What are the realities of scientific research in this area? DISCUSSION (40 minutes)
15:50-16:15	**BREAK**
16:15-16:55	**General discussion**
16:55-17:00	**Closing Remarks** Paul Freemont

List of Participants

Jim Ajioka, Department of Pathology, University of Cambridge

Brian Balmer, Department of Science and Technology Studies, University College London

Sonia Ben Ouagrham-Gormley, Department of Public and International Affairs, George Mason University

Sophie Brice, Home Office

Jane Calvert, Science Technology and Innovation Studies, University of Edinburgh

Brett Edwards, Department of Politics, Languages & International Studies, University of Bath

Steve Eley, Defence Science and Technology Laboratory

Tom Ellis, Centre for Synthetic Biology and Innovation, Imperial College London

James Field, Centre for Synthetic Biology and Innovation, Imperial College London

Paul Freemont, Centre for Synthetic Biology and Innovation, Imperial College London

Alex Hamilton, Department of Sociology, London School of Economics

Catherine Jefferson, Department of Social Science, Health & Medicine, King's College London

Richard Kelwick, Centre for Synthetic Biology and Innovation, Imperial College London

Richard Kitney, Centre for Synthetic Biology and Innovation, Imperial College London

Filippa Lentzos, Department of Social Science, Health & Medicine, King's College London

Debora MacKenzie, *New Scientist*

Claire Marris, Department of Social Science, Health & Medicine, King's College London

Lorna Miller, Defence Science and Technology Laboratory

Piers Millet, Biological Weapons Convention Implementation Support Unit

James Revill, Harvard Sussex Program, University of Sussex

Guy-Bart Stan, Centre for Synthetic Biology and Innovation, Imperial College London

Kathleen Vogel, Department of Science and Technology Studies, Cornell University

John Walker, Foreign and Commonwealth Office

Institutional affiliations are provided for purposes of identification only. The views expressed by participants during the discussions were their own and do not necessarily represent those of their institutions.

List of Abbreviations

BWC	Biological Weapons Convention
CSynBI	Centre for Synthetic Biology and Innovation
DIY biology/DIYbio	Do-it-yourself biology
EPSRC	Engineering and Physical Sciences Research Council
ESRC	Economic and Social Research Council
FBI	The Federal Bureau of Investigation, US Department of Justice
GOF	Gain of function
iGEM	International Genetically Engineered Machine Competition
IL-4	Interleukin 4
ISU	Implementation Support Unit (of the BWC)
NSABB	National Science Advisory Board for Biosecurity, US
SSHM	Department of Social Science, Health & Medicine, King's College London
STS	Science and Technology Studies
WHO	World Health Organisation
WMD	Weapons of Mass Destruction

Appendix 1: Synthetic Biology and Biosecurity: Challenging the 'Myths'

Scoping Report for the Workshop on 'Synthetic Biology and Biosecurity' held at King's College London on 28th February 2014. Prepared by Catherine Jefferson, Filippa Lentzos and Claire Marris, Department of Social Science, Health and Medicine, King's College London and distributed to all participants in advance of the workshop. Please note that a revised version of this document will be published in the Journal Frontiers in Health *and wherever possible that article should be cited in preference to this version.*

Introduction

A common narrative has emerged in the media and in policy arenas, in which advances in biosciences are seen to make biology easier and more accessible, and this is presumed to increase the 'dual use' threat, i.e. the potential for legitimate peaceful research to be misused for the production of biological weapons. Developments in synthetic biology, a field that emerged at the start of the 21st century with the stated aim of 'making biology easier to engineer', have further fuelled these concerns. One school of synthetic biology aims to build a set of standard biological parts whose functions have been well characterised and which can be assembled in a modular fashion into devices to produce living organisms that predictably perform human-designed functions. Concerns have been expressed that this, combined with open online access to DNA sequences of living organisms (including viruses and other pathogens) and the reduction in price for DNA synthesis, could make biology increasingly accessible to non-biologists and amateurs. The emergence of 'do-it-yourself' (DIY) biology communities have come to epitomise this supposed trend towards greater ease of access and the associated potential threat from rogue actors.

However, these dual use concerns are largely based on promissory constructions of synthetic biology and speculative assumptions about the field's ability to produce well-characterised biological parts that function predictably in living organisms; assumptions that may not accurately reflect current scientific realities. Furthermore, there remain a number of tangible and intangible barriers to the production of biological weapons using synthetic biology. There are considerable challenges involved in successfully creating a viable biological threat agent, and further challenges to turn these into weapons. Amateurs lack the necessary specialist 'tacit' knowledge and institutional support to overcome these challenges; and rogue actors have other means at their disposal that are less onerous. In discussions about biosecurity, it is also important to distinguish between weapons designed to generate terror from weapons designed to cause mass destruction: terror weapons do not need to cause extensive physical harm and thus do not require sophisticated weaponisation.

This Scoping Report identifies five recurring 'myths' about the dual use threat of synthetic biology that dominate discussions in policy arenas and the media. It highlights some key challenges to this narrative and suggests that the biosecurity threat may be exaggerated. This is not to argue that there is no threat, but rather to draw out some of the subtleties that frequently disappear from these discussions. Moreover, it is important to note that these 'myths' have power and perform real functions by mobilising support, resources and action. Emphasising the potential biosecurity threats of synthetic biology serves to bolster the speculative promises of the field. These myths also serve to attribute roles and influence to particular actors: they define who is legitimate to speak on these topics, what they can say, and where. They influence who gets funded, for what. Contrasting the 'promises and perils' of a field such as synthetic biology also aligns particularly well with the way in which science and technology is typically framed in mass media, and this serves to further fuel these myths.

The aim of the Flowers Consortium Workshop on 'Synthetic Biology and Biosecurity' is to examine the assumptions that underlie these 'myths' and to explore the implications for policy.

2001 Mousepox Experiment
Australian researchers used genetic engineering techniques to insert the gene for interleukin-4 into the mousepox virus. They aimed to produce an altered virus that would induce infertility in mice and serve as an infectious contraceptive for pest control. However, the altered virus was found to be lethal to both mice that were naturally resistant to mousepox and mice that had been recently immunised against ordinary mousepox. The publication of these findings led to concerns that this could provide instructions to terrorists to produce novel biological weapons.

Jackson, RJ, Ramsay, AJ, et al. (2001) Expression of mouse interleukin-4 a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox, *Journal of Virology*, 75(3): 1205-10.

2002 Poliovirus Experiment
Researchers at the State University of New York at Stony Brook synthesised the poliovirus without using any natural virus or viral components. They obtained published poliovirus RNA genome sequence information and converted this into DNA sequence data, which they then ordered from a commercial DNA synthesis company and assembled into a viral genome. Enzymes were used to convert the DNA back into RNA and to translate the RNA into a functional virus. Publication of the research article raised concerns that terrorists could synthesise viruses ‘from scratch’.

Cello, J, Paul, AV & Wimmer PE (2002) Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template, *Science*, 297 (1016): 1016-18.

2005 Spanish Influenza Virus Experiment
Researchers at the US Centers for Disease Control and Prevention reconstructed the Spanish flu virus, which is thought to have killed around 50 million people during the 1918 pandemic, using a recently recovered genomic RNA. Concerns were expressed that publication of the full genome sequence could give bioterrorists the information necessary to make their own version of the virus.

Tumpey, TM, Basler, CF, et al. (2005) Characterisation of the reconstructed 1918 Spanish influenza pandemic virus, Science, 310: 77-80.

2011 H5N1 Virus Experiment
Researchers in the Netherlands and the USA developed a novel, contagious strain of the H5N1 ‘bird flu’ virus. They infected ferrets with genetically modified H5N1 and found that the modified H5N1 acquired small mutations during passage in ferrets, ultimately becoming airborne transmissible. When two papers relating to the research were submitted for publication to *Science* and *Nature*, concerns were raised about the dual use risk and the US National Science Advisory Board for Biosecurity (NSABB) recommended against full publication of the study. After additional consultations at the World Health Organisation, the NSABB reversed its position and recommended publication of revised versions of the papers.

Herfst, S, Schrauwen, EJA, et al. (2012) Airbourne transmission of influenza A/H5N1 virus between ferrets, *Science*, 336(6088): 1534-41.c

Box 1: Examples of dual use experiments

Myth 1: DNA synthesis has become faster and cheaper and this will make it easier for terrorists to create biological threat agents.

DNA synthesis is one of the key enabling technologies of synthetic biology and the increasing speed and reduced costs of DNA synthesis have raised concerns that this technology could make it easier for bioterrorists to recreate dangerous viruses from scratch, especially when complete DNA or RNA sequences for viruses and other pathogenic agents are increasingly freely available online. Reconstruction of poliovirus (2002) and Spanish influenza virus (2005) have come to epitomise this threat narrative (see Box 1).

> ‘With the spread of synthetic biology, some small scale research groups and even some individuals are now able to make the deadly Ebola and smallpox viruses and even some viruses against which all drugs are ineffective, thus making it much harder to counter bioterrorism.’ (China 2011)

> ‘in the near future... the risk of nefarious use will rise because of the increasing speed and capacity [of synthetic genomics].’ ... ‘ten years from now, it may be easier to synthesize almost any pathogenic virus than to obtain it through other means.’(Garfinkel, Endy et al. 2007, pp. 12-13)

> ‘Synthetic biologists have already shown how terrorists could obtain life forms that now exist only in carefully guarded facilities, such as polio and 1918 influenza samples.’ (Maurer and Zoloth 2007, p. 16)

> ‘One potential misuse of synthetic biology would be to recreate known pathogens (such as the Ebola virus) in the laboratory as a means of circumventing the legal and physical controls on access to ‘select agents’ that pose a bioterrorism risk. Indeed, the feasibility of assembling an entire, infectious viral genome from a set of synthetic oligonucleotides has already been demonstrated for poliovirus and the Spanish influenza virus.’ (Tucker and Zilinskas 2006, p. 37)

Challenges:

Although DNA synthesis has become cheaper and quicker, it is still not fully accurate and reliable.

While the technology for synthesis of large DNA fragments has advanced, assembly of these fragments into larger segments is still a technical challenge.

Constructing a genome size DNA fragment is not the same as creating a functional genome. In particular, ensuring the desired expression of viral proteins is a complex challenge.

There are logistically easier and technologically less demanding sources of biological threat agents in nature (eg, soil-borne bacterial pathogens such as *Bacillus anthracis* and *Clostridium botulinum*).

Synthesis of a biological threat agent is not equal to weaponisation. Considerable knowledge and resources would be necessary for the processes of scaling up, storage and developing a suitable dissemination method. It is however important to distinguish between weapons designed to generate terror from weapons designed to cause mass destruction: terror weapons do not need to cause extensive physical harm and thus do not require sophisticated weaponisation (see challenges to Myth 5).

Genome synthesis companies have taken steps to screen sequence and consumer orders (though these measures are currently voluntary and only apply to double stranded DNA).

Myth 2: Synthetic biology could be used to design radically new pathogens

In addition to recreating dangerous viruses, concerns have also been expressed that synthetic biology could be used to enhance the virulence or modify the transmissibility of known pathogens; or to create novel threat agents. The mousepox experiment (2001) and the H5N1virus experiments (2011) have come to epitomise this threat narrative (see Box 1).

> 'Synthetic biology's efforts to reprogram life have raised concerns in some quarters that the technology could one day be used to make radically new weapons, such as pathogens that could be narrowly targeted towards populations with known genetic susceptibilities.' (Maurer and Zoloth 2007, p. 16)

> 'The possibility of designing a new virus or bacterium *a la carte* could be used by bioterrorists to create new resistant pathogenic strains or organisms, perhaps even engineered to attack genetically specific sub-populations.' (European Commission 2005, p. 18)

> 'While nature has provided would-be terrorists an ample supply and selection of quite virulent viruses, there is concern that genetic technologies will be used to modify these already pathogenic agents and create 'super-pathogens', viruses that are more lethal and disruptive than naturally occurring pathogens, and that are designed to evade vaccines or to be resistant to drugs.' (Collett 2006, p. 95)

> 'Living synthetic cells will likely be made in the next decade; synthetic pathogens more effective than wild or genetically engineered natural pathogens will be possible sometime thereafter...' (Wheelis 2004)

> 'Our concern is that publishing these experiments in detail would provide information to some person, organization, or government that would help them to develop similar mammal-adapted influenza A/H5N1 viruses for harmful purposes.' (Members of the NSABB 2012, p. 661)

Challenges:

There are significant technical and logistical challenges involved in creating a new human pathogen, or a more lethal or transmissible variant of a known pathogen. For example, the former Soviet biological weapons programme experienced difficulties with pleiotropy, where changing one gene to, say, make an agent more transmissible caused other traits such as pathogenicity to diminish.

There are logistically easier and technologically less demanding sources of biological threat agents in nature.

Synthesis of a biological threat agent is not equal to weaponisation (see challenges to Myth 5).

Myth 3: Synthetic biology is de-skilling biology and making it easier for terrorists to exploit advances in the biosciences

The key goal of synthetic biology is to 'make biology easier to engineer' by building a set of standard biological parts whose functions have been well characterised and which can be assembled into functional devices and systems that reliably perform human-designed desired functions in live organisms. Concerns have been expressed that this 'de-skilling' agenda could make it easier for non-specialists to exploit this technology to do harm. iGEM and the DIYbio community have come to epitomise this de-skilling narrative.

> 'Synthetic biology strives to make the engineering of biology easier and more predictable.' (The Royal Academy of Engineering 2009, p. 6)

> 'Synthetic biology includes, as a principal part of its agenda, a sustained, well-funded assault on the necessity of tacit knowledge in bioengineering and thus on one of the most important current barriers to the production of biological weapons.' (Mukunda, Oye et al. 2009, p. 14)

> 'The reagents and tools used in synthetic biology will eventually be converted into commercial kits, making it easier for biohackers to acquire them. Moreover, as synthetic biology training becomes increasingly available to students at the college and possibly high-school levels, a 'hacker culture' may emerge, increasing the risk of reckless or malevolent experimentation.' (Tucker and Zilinskas 2006, p. 42)

> 'Ethical issues arise particularly from dangers of using synthetic lethal and virulent pathogens for terrorist attacks, bio-war, or maleficent uses ('garage terrorism', 'bio-hacking'), particularly if knowledge and skills on how to produce such pathogens are freely available.' (European Commission 2009, p. 43)

> 'Imagining a world where practically anybody with an average IQ would have the ability to create novel organisms in their home garage...' (Schmidt 2008, p. 2)

Challenges:

This framing of the dual use threat is based on the assumption that synthetic biology already has made, or shortly will make, 'biology easier to engineer', by providing open-access online registries of well-characterised parts that can be easily assembled, by people with no specialist training, into devices and systems that predictably perform desired functions in live organisms. This does not necessarily reflect current realities in professional science laboratories.

Experiences of iGEM teams and DIYbio community labs tend to demonstrate the considerable challenges of successfully performing synthetic biology experiments outside of professional settings, including the need for guided instruction, and for collective work.

Synthetic biology has not yet created weaponisable parts or devices.

There remain significant tangible and intangible barriers to adapting a technology for weaponisation (see challenges to Myth 5).

Myth 4: Synthetic biology has led to the growth of a DIYbio community, which could offer dual use tools and equipment for bioterrorists seeking to do harm

Developments in synthetic biology are seen to be closely associated with the growth of the DIYbio community, and concerns are expressed that this could offer the knowledge, tools and equipment to bioterrorists seeking to do harm.

> ‘I worry about the garage scientist, about the do-your-own scientist, about the person who just wants to try and see if they can do it.’ (NSABB member in Zimmer 2012)
>
> ‘Although advocates emphasize the educational value and economic potential of DIY biology, some security analysts worry about the prospect of possible abuse for nefarious purposes... it has the potential both to benefit society and to cause much harm – if the people using DIY biology do so for malicious purposes, including criminal activities and terrorism.’ (Wolinsky 2009, pp. 684-5)
>
> ‘We have to be aware and not be naive about the potential for misuse of this technology, particularly if it’s going to be democratized in the way that the DIY visionaries would like.’ (Tucker cf. Wolinsky 2009, p. 685)
>
> ‘As synthetic biology techniques become easier and less expensive and the applications become more widely relevant, the range of practitioners expands to include scientists from a variety of disciplines; students at all levels, including high school; and amateur scientists and hobbyists who may lack any formal affiliations with universities or research institutions. The diversity of practitioners will also include individuals of different ages and varied social and educational backgrounds who may not have been sensitized to the ethical social and legal norms of the traditional life science research communities.’ (NSABB 2010, p. 11)

Challenges:

The link between synthetic biology and DIYbio, and the level of sophistication of the experiments typically being performed in DIYbio community labs, is overstated (Wilson Center 2013, p. 10).

Members of DIY communities who are involved in more sophisticated experiments tend to be trained biologists, not amateurs.

The experiences of iGEM students and amateur members of the DIYbio community demonstrate the importance of tacit knowledge in successfully conducting even rudimentary biological experiments.

Members of DIYbio community labs are cognisant of safety and security concerns and are proactive in addressing and engaging on these issues.

Myth 5: The bioterrorism myth? Terrorists want to pursue biological weapons for high consequence, mass causality attacks

Bioterrorism has been portrayed in some media and policy circles as an imminent threat, and emphasis is placed on the use of biological weapons for high consequence, mass causality attacks.

> “The national, state, and local governments in the United States are preparing for what is now called ‘not if, but when and how extensive’ biological terrorism.” (Franz and Zajtchuk 2002, p. 493)
>
> “The age of engineered biological weapons is here. It is now.” (Tara O'Toole in Drogin 2005)
>
> “A few technicians of middling skill using a few thousand dollars worth of readily available equipment in a small and apparently innocuous setting [could] mount a first-order biological attack.” (Senator Bill Frist 2005)
>
> “Given the goal of some terrorist groups to use weapons that can be employed surreptitiously and generate dramatic impact, we expect to see terrorist use of some readily available biological and chemical weapons.” (US National Intelligence Council 2004, p. 100)
>
> “Al-Qaida and other terrorist groups remain interested in acquiring Chemical, Biological, Radiological, and Nuclear (CBRN) weapons.” (Vice Admiral Lowell E. Jacoby 2004, p. 3)

Challenges:

Bioterrorists are portrayed as pursuing capabilities on the scale of twentieth century state biological weapons research and development programs, i.e., attempting to produce mass causality weapons. However, past bioterrorism attacks have typically been small-scale, low casualty events which have been perpetrated to cause panic and disruption rather than high impact. (For example, the 2001 anthrax letter attacks and 2013 ricin letter attacks, or the Rajneeshee cult use of salmonella in Oregon salad bars in 1984 in an attempt to sicken the electorate and influence the voting outcome.)

There are considerable barriers to acquiring a suitable biological agent. (For example, the Japanese Aum Shinrikyo group, which had considerable financial resources, spent 3 to 4 years attempting to isolate Botulinum toxin and failed.) A terrorist would need to obtain the appropriate strain of the disease pathogen, handle the organism correctly, grow it in a way that will produce the appropriate characteristics, and know how to store the culture and scale-up production properly.

There are also considerable barriers to weaponizing an agent, i.e., finding a suitable means of dissemination that will not destroy the agent’s virulence or infectivity. Even well-resourced state biological weapons programmes of the past faced critical challenges in overcoming problems of aerosolisation and delivery of biological agents.

Other technologies, such as homemade explosives and small arms, are more accessible to terrorists than a sophisticated biological weapons capability.

References

China (2011). New scientific and technological developments relevant to the Convention. Submissions from States Parties, Seventh Review Conference of the State Parties to the Convention of the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction.

Collett, M. S. (2006). "Impact of Synthetic Genomics on the Threat of Bioterrorism with Viral Agents." Working Papers for Synthetic Genomics: Risks and Benefits for Science and Society, pp. 83-103. M. S. Garfinkel, D. Endy, G. L. Epstein and R. M. Friedman (Eds.).

Drogin, B. (2005). Smallpox Exercise Poses Big Question: Is Anyone Ready? Los Angeles Times.

European Commission (2005). Synthetic Biology: Applying Engineering to Biology, Report of a NEST High-Level Expert Group. Brussels.

European Commission (2009). Ethics of Synthetic Biology. European Group on Ethics in Science and New Technologies to the European Commission. Brussels.

Franz, D. and R. Zajtchuk (2002). "Biological Terrorism: Understanding the Threat, Preparation, and Medical Response." Disease-a-month 48: 493-564.

Frist, B. (2005). A Manhattan Project for the 21st Century, prepared remarks delivered by Senator Bill Frist on June 1, 2005 at the Harvard Medical School Health Care Policy Seidman Lecture.

Garfinkel, M. S., D. Endy, G. L. Epstein and R. M. Friedman (2007). Synthetic Genomics: Options for Governance, J. Craig Venter Institute.

Jacoby, L. E. (2004). Current and Projected National Security Threats to the United States, Statement by Vice Admiral Lowell E. Jacoby for the Record, Senate Armed Services Committee: 1-23.

Maurer, S. M. and L. Zoloth (2007). "Synthesizing Biosecurity." Bulletin of the Atomic Scientists 63(6): 16-18.

Members of the NSABB (2012). "Adaptations of avian flu virus are a cause for concern." Science 335: 660-661.

Mukunda, G., K. A. Oye and S. C. Mohr (2009). "What rough beast? Synthetic biology, uncertainty, and the future of biosecurity." Politics and the Life Sciences 28(2): 2-26.

NSABB (2010). Addressing Biosecurity Concerns Related to Synthetic Biology, National Science Advisory Board for Biosecurity.

Schmidt, M. (2008). "Diffusion of synthetic biology: a challenge to biosafety." Systems and Synthetic Biology 2: 1-6.

The Royal Academy of Engineering (2009). Synthetic Biology: scope, applications and implications. Royal Academy of Engineering, London.

Tucker, J. B. and R. A. Zilinskas (2006). "The Promise and Perils of Synthetic Biology." The New Atlantis (Spring): 25-45.

US National Intelligence Council (2004). Mapping the Global Future. Report of the National Intelligence Council's 2020 Project. Pittsburgh, PA.

Wheelis, M. (2004). "Will the 'new biology' lead to new weapons?" Arms Control Today 34(6).

Wilson Center (2013). Seven Myths and Realities about Do-It-Yourself Biology. Synthetic Biology Project. Washington, DC.

Wolinsky, H. (2009). "Kitchen Biology." EMBO reports 10(7): 683-685.

Zimmer, C. (2012). Amateurs are new fear in creating mutant virus. The New York Times.

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