

## Moving Beyond Dual Use Research of Concern Regulation to an Integrated Responsible Research Environment

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### **Introduction**

The potential for nefarious use of findings derived from well-intentioned research has been appreciated for many years, well before the modern era of post-WWII science. The problem is particularly acute in the life sciences, where the pace of research advances is rapid, the work is usually published in the open literature, there is a strong profit motive driving research, and there are many researchers and labs around the world engaged in the effort. Naturally, many research findings can be said to be of dual use, e.g. a virus that performs better as a gene therapy vector to ameliorate genetic diseases could also be used to deliver a harmful payload. It is very difficult to distinguish molecular biology work meant to be beneficial from that designed to do harm, and this realization has driven much effort within the US Intelligence Community, tasked with understanding the capabilities, intent and actions of US adversaries, to identify indicators of nefarious activity.

The remarkably rapid rise of molecular biology at the end of the 20<sup>th</sup> century, in particular the increased facility with which viral and bacterial genomes could be manipulated, led to concerns that pathogens with increased virulence or other harmful properties could be constructed. The anthrax letters attack of 2001 and the subsequent Amerithrax investigation reinforced this concern and demonstrated that a bioterrorism attack, even of relatively small scale, could have major economic and societal impacts (Schmitt and Zacchia, 2012).

Although the strain of *Bacillus anthracis* used in the anthrax letters was derived from a US government lab at Fort Detrick, and had not been subject to molecular genetic manipulations (FBI, 2010), it was understood that relatively simple manipulations, say, to incorporate antibiotic resistance into *B. anthracis*, could have yielded a much worse outcome.

Among the US government responses to this attack, and to increased concern about terrorism in general, was to create the Select Agent Program, which regulates the possession, use and transfer of organisms and toxins on the HHS and USDA Select Agent lists. The organisms on these lists are bacteria and viruses that are of concern because of their potential to cause large-scale economic and social disruption, and, potentially, a large loss of human life in an attack. Although an exclusive focus on a small set of pathogens has flaws as a strategy to prevent attack, it was a logical extension of this strategy to state that any research on organisms and toxins on a defined list (currently there are 15) should be evaluated as being *dual use research of concern* (DURC). DURC is defined as “Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products or technology that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel or national security”.

Much of the governmental oversight of what is now called DURC is under the National Science Advisory Board for Biosecurity (NSABB), established in 2004 by the Secretary of HHS, and managed by the NIH. The need for such a body was highlighted in a NRC report titled "Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma." As originally conceived, the NSABB would:

1. Advise on strategies for local and federal biosecurity oversight for all federally funded or supported life sciences research.

2. Advise on the development of guidelines for biosecurity oversight of life sciences research and provide ongoing evaluation and modification of these guidelines as needed.
3. Advise on strategies to work with journal editors and other stakeholders to ensure the development of guidelines for the publication, public presentation, and public communication of potentially sensitive life sciences research.
4. Advise on the development of guidelines for mandatory programs for education and training in biosecurity issues for all life scientists and laboratory workers at federally-funded institutions.
5. Provide guidance on the development of a code of conduct for life scientists and laboratory workers that can be adopted by federal agencies as well as professional organizations and institutions engaged in the performance of life sciences research domestically and internationally.

This is a remarkably broad set of goals, particularly given the general aversion of scientists in the life sciences to regulation, and the lack of interest in sweeping international measures. It is worth noting that the current charter (2016) for the NSABB lists a description of duties that is substantially less grand, although focused on similar key points:

1. Provide recommendations on the development of programs for outreach, education and training in dual use research issues for scientists, laboratory workers, students, and trainees in relevant disciplines.
2. Advise on policies governing publication, public communication, and dissemination of dual use research methodologies and results.
3. Recommend strategies for fostering international engagement on dual use biological research issues.
4. Advise on the development, utilization and promotion of codes of conduct to interdisciplinary life scientists, and relevant professional groups.
5. Advise on policies regarding the conduct, communication, and oversight of dual use research and research results, as requested.
6. Advise on the Federal Select Agent Program, as requested.

7. Address any other issues as directed by the Secretary of HHS.

The move towards a defined regulatory structure for DURC was precipitated by several examples of research that raised genuine concerns. These have been reviewed in many previous treatments of this topic, so I only briefly consider the highlights here.

- In 2001, Jackson, et al. (Jackson et al., 2001) found that adding the host gene for the immune modulator interleukin-4 to the mousepox virus genome made the virus more virulent, killing even mice that had been vaccinated against the virus. Would this work in smallpox to make an already potent virus even worse for humans?

- In 2002, Wimmer and colleagues (Cello, 2002) synthesized the polio virus genome from oligonucleotides and showed that this, not surprisingly, functioned the same as the natural virus. Could this be used to make more complex viruses and to modify them at will? The poliovirus experiments caught the eye of Congress, with Representative Dave Weldon (R-FL) characterizing the paper as a "blueprint that could conceivably enable terrorists to inexpensively create human pathogens." (<http://www.sciencemag.org/news/2002/07/polio-paper-sparks-criticism-congressional-representatives>).

- In 2005, Tumpey, et al. (Tumpey et al., 2005) used reverse genetics to reconstruct the flu virus from the 1918 pandemic that killed more than 20 million people worldwide. The reconstructed virus had the properties of a much more virulent virus than the contemporary H1N1 flu virus. If released from the lab, accidentally or intentionally, could this cause a new pandemic?

Once in place, the NSABB and the DURC regulations have been tested several times by research on increasing the virulence of H5N1 "bird flu" virus (Russell et al., 2012), by potentially dangerous strain mix-ups at CDC, and, most recently, by other experiments explicitly designed to provide "gain-of-function" to pathogens. In each of these cases, the regulatory apparatus has seemed to lag well behind the science.

### **Limitations of the current approach**

It is reasonable, more than ten years after establishing the NSABB framework for DURC, to examine its effect, and consider whether it is serving our needs going into the future. I will focus here on what I consider to be three main failings of the approach, which will need to be addressed for it to continue to be effective in its current limited form, and for it to grow into something that is a more integral part of the research enterprise.

1) Lack of engagement of the scientific community:

My experience comes from my involvement in two very different areas of research and technology. The first is as a professor in a large basic science department at a leading research university. This department, the Department of Biology at Stanford University, covers most of modern biology, from structural biology to global ecosystems. From interactions with my colleagues, I believe that very few of the more than 50 faculty in the department are aware of the NSABB and efforts to manage DURC, other than incidental knowledge from news stories in the science journals. Thus, it is possible to function at a very high level in the research community with essentially no engagement with this issue. When questioned about this, colleagues have said that they feel that those regulations are for researchers working on explicitly "concerning" problems, such as human pathogens or select agents, and that their research has no such concerning elements. There is also often a tendency to view the government as a welcome source of research funding, but an unwelcome source of burdensome regulations. There is often a strong preference for "flying under the radar" with respect to regulation - self- or imposed, and thus no desire to engage.

Another element of this lack of engagement with respect to biology research and its uses is that there is little knowledge among researchers about the history of the development of biological warfare agents. The US and USSR had substantial biological weapons programs during the Cold War, and the Soviet program continued after the signing of the Biological Weapons Convention (BWC) in the early 1970's. Faculty, postdoctoral fellows, and graduate students are largely ignorant of this history. This contrasts with the physics community, in which the development of the fission and fusion bombs in WWII and after is part of the lore

of the discipline, and also led to the involvement of prominent physicists in nuclear disarmament and nuclear non-proliferation.

2) Failure to capture other research of potential concern under the DURC heading:

My second role is as a member of JASON, an advisory group to the executive branch on matters of science and technology, as they relate to national security. JASON began in the 1960's, with a strong representation of some of the leading physicists in the US, and much, but not all, of its work was classified. I was asked to join JASON 15 years ago, as the organization broadened its expertise, reflecting the increasingly diverse problems the government sought advice about. JASON does its work in summer studies, on topics brought to it by government sponsors. The sponsors of biology-related studies have been government agencies tasked with assessing and understanding the biological threat, and the topics of these studies over the years reflect the concerns of the time. A sample of these studies over the last 20 years includes the following:

JASON Report	Title	Topic	Year	Classification
JSR-97-105	Biological Threats Enabled by Molecular Biology	Genetically engineered BW possibilities	1997	Unclassified
JSR-05-130	BioEngineering	Construction of novel BW threats	2005	Unclassified
JSR-05-502 JSR-05-503	Emerging Viruses	Emerging viral threats	2005	Classified
JSR-07-508	Synthetic Viruses	Synthetic viral constructs	2008	Classified
JSR-16-010	Genome Editing	CRISPR/Cas9, genome	2016	Unclassified

		editing, gene drive		Class appendix
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It is important to note that many of the issues most often mentioned as being of concern in the research community now, such as manipulating pathogens to alter virulence, or to reconstruct previous versions of viruses, were discussed in some detail in studies in 1997 and 2005, and the Intelligence Community already has those on their radar. However, the very rapid adoption of CRISPR/Cas9 as a genome editing tool, and the associated possibilities it enables, was unanticipated, and has been the subject of government-wide discussion, with little agreement on whether it poses a threat, and if so, in what way and how serious.

CRISPR/Cas9 was discovered in the course of basic research into bacterial immune systems, and like many of the previous advances in molecular biology, the specifics of the biology, pace of adoption, and applications were not predictable in advance. However, it was predictable that researchers would develop increasingly effective means of altering genomes, since that has been a driving force in research for many decades. *This research, and other basic research like it, would not have been considered to be DURC by the standard definition.* Similarly, research in gene therapy is typically not considered to be in the DURC category, but the manipulations of gene therapy, and their benevolent goal, are much the same as what one would do to achieve a malevolent goal, perhaps only with a different cargo carried by the vector.

### 3) Inadequate articulation of the risk

In research, when we talk about risky experiments, we usual mean experiments whose feasibility is not clear from the preliminary data, or that are sufficiently complicated to challenge the existing technology (or the researcher's ability). With DURC, the risk is presumed to be release of information, or organisms, that could be used by an adversary for malevolent purposes. Neither "adversary" nor "malevolent purposes" is well-defined in

most scenarios, and are taken to mean different things in different contexts, and by people with differing knowledge of the capabilities and intent of various potential adversaries.

I have had recent experience with this difficulty, in attempting to convey the results of red-team exercises as part of the JASON study on Genome Editing referred to above. Such exercises within the Intelligence Community are intended to capture attempts to think as a potential adversary might when considering the use of biological weapons. The scenarios developed in these exercises were classified because they could be considered to be a "cookbook" for someone with malevolent intent, and classification would help to prevent the spread of information. The scenarios devised differed in the extent to which genome editing was an essential element, and in the perceived intent of the perpetrator, that is, mass casualties vs. economic disruption vs. local terror. This classified appendix to the report elicited a wide range of responses within the US government, with some groups believing that JASON had greatly overstated the threat posed by genome editing, and others believing that we had greatly understated it. In some cases, the viewpoint could be interpreted as having been affected by the stake that the agency or group would have in mitigating the problem. *Clearly, there is little agreement about the threat posed by even relatively straightforward technologies, and there are relatively few practicing scientists with sufficient background to assess it, and to engage with the relevant government personnel.*

### **Recommendations**

It is clear from the above that a change of culture in the biology research community would be needed if we are to succeed in raising the profile of the dual use issue among practicing scientists. Such changes are difficult to bring about in the competitive setting of biomedical research in which individual effort is highly valued and the profit motive is strong. Two historically effective tools are 1) training of current practitioners, with compliance enforced by making the training a requirement of receiving federal funding, and 2) educating students of the discipline such that mandatory training of more senior researchers might not be necessary in the longer term, as the culture changes. I am reluctant to recommend



mandatory training, given the regulatory burden already faced by researchers receiving federal funding, so will consider only the second of these approaches.

The solution to the education problem will require more than a NAS committee report, and this committee might not view it as part of their mandate. However, there is strong precedent for calls to action in science education to have real impact. I give as an example a National Academies report from 2003 titled "Bio 2010 Transforming Undergraduate Education for Future Research Biologists" (National Research Council Committee on Undergraduate Biology and Education, 2003). This document guided many universities in the revision of their biology curriculum, and, in considering education itself as something to be assessed quantitatively, engaged many professors in thinking more deeply about education.

What might such an education program look like? University research departments or programs that have federal graduate training grants are familiar with the research ethics training requirement. There is rather little direction from the NIH in terms of what students should be taught in such training, and universities had adopted a variety of means of satisfying the requirement. At Stanford University, as at many similar institutions, the trainees must take a course titled "Responsible Conduct of Research." This course is focused on research ethics, consistent with the NIH mandate, but I would propose that the issue of the broader aspects of research, as considered in the DURC discussion, should be part of such courses. In addition to the ethical concerns already covered (ownership of data, authorship, collaborations, research integrity), such a course might seek to educate trainees in graduate programs in the history of bioweapons programs, of bioterrorism events (fortunately, few in number) and in the interesting examples of the published work, such as listed above, that have prompted much of this discussion. These topics are amenable to being covered in the case study discussion format that such courses often use, indeed, the rich history is likely to make such a course more engaging, and be perceived less as a burdensome requirement that must be satisfied.

Graduate education seems to be a natural focus for such training, but I believe that a course on this topic could be successful at the undergraduate level as well. The historical parts of the story are accessible to any level of student, and a course could bring together elements of science, technology, diplomacy and international cooperation, and openness of scientific communication. This might be particularly appealing to undergraduates at technology-oriented universities who often cite the desire to make the world a better place as the rationale for their choice of major and of careers after graduation.

What of people who don't pass through the standard college or university training? I think that the number of people who are capable and came upon that capability independent of such training is relatively small. However, it is likely growing as part of the growth of the "maker" community. There are many opportunities to interact with this and related communities, and there are some excellent examples of individual efforts in the government can have a large effect. Ed You has been with the FBI since 2005, and is the point person there for bio community outreach (Regalado, 2016). The FBI is now a sponsor of the iGEM ([www.igem.org](http://www.igem.org)) competition in synthetic biology, and, largely through Ed You's work, has made a serious attempt to interact with these "homebrew" communities.

Lastly, I believe that we need to develop a better understanding the effectiveness of the measures already taken to educate about dual use issues, and that might be taken in the future. We are scientists, and yet there is very little data about what scientists, broadly considered, and the public, really understand in this domain, and how they think about some of important issues. The people who are usually involved in discussions about such topics are the same limited set of scientists who, for a variety of reasons, have become interested in the topic, familiar with the background, and knowledgeable of the points of contact with the government. In education, it is no longer acceptable to make claims about efficacy without assessment. That should be true with the effort to change the culture of biologists with respect to dual use research of concern as well.

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