Special report Bioterror

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FRIEND OR FOE?

Efforts to combat killer pathogens with new vaccines and drugs could be inadvertently writing a handbook for biowarfare. The US, home to many such "dual-use" projects, faces a tough dilemma

"At what point, if any, does working on how pathogens evade immunity become a threat to national security?"

PETER ALDHOUS

TWEAKING the anthrax toxin to render experimental drugs ineffective. Turning a harmless rodent virus into a deadly pathogen. Enhancing the potency of botulinum toxins – already the most lethal poisons known. Transferring genes that help viruses evade the human immune system from one pathogen to another.

These projects may sound like the clandestine activities of a hostile bioweapons programme. But in fact, all are in progress or being planned in US academic labs. They were identified by *New Scientist* in a database that documents research funded by the US Department of Health and Human Services (DHHS). And while each project may sound alarming to the uninitiated, most won the qualified support of the biosecurity specialists we asked to consider their risks and benefits. Only one of those mentioned above – the anthrax project – generated serious objections from some of our experts.

This survey illustrates the difficulties facing the National Science Advisory Board for Biosecurity (NSABB), which the US government has asked to draw up a system for regulating "dual-use" biology – research intended to combat disease, but which could also be misused by bioterrorists or enemy states. The problem is that it is difficult to pursue such work without potentially helping others design bioweapons. "This is the very nature of infectious disease and toxin research," says Michael Stebbins, director of biology policy with the Federation of American Scientists in Washington DC. NSABB will have to tread very carefully if it is to avoid tying up in red tape scientists' ability to respond to emerging diseases.

Dual-use biology hit the headlines in 2001, when *New Scientist* revealed that researchers in Australia had created a strain of mousepox that killed even animals that had been vaccinated (13 January 2001, p 4). The scientists, hoping to control plagues of mice, engineered a mousepox virus ■

to act as a contraceptive vaccine. Instead, they ended up producing deadly vaccine-resistant viruses, raising concerns that the technique could be used to do the same to the related human killer, smallpox.

Since then, the dual-use debate has reached the public consciousness on just a few occasions, notably in 2002 when Eckard Wimmer and his colleagues at Stony Brook University in New York state synthesised polioviruses from scratch, and in 2005 when a collaboration led by the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, used similar techniques to resurrect the 1918 influenza virus that killed some 50 million people. Efforts to investigate the likelihood of a new flu pandemic by combining genes from common human flu viruses and the deadly avian virus H5N1 have also generated unease (see "Mix-and-match flu", opposite).

Cause for concern

These projects are just a small fraction of those that could meet NSABB's definition of "experiments of concern" – dual-use projects that may require additional oversight (see Table, below right). *New Scientist* searched for examples in the CRISP database, a service that details projects funded by the National Institutes of Health (NIH), the CDC, and other branches of the DHHS. We followed up any interesting grants by searching the Medline database of published research for papers written by the grant holders.

It took just a week or so to identify a handful of projects that provided ample grist for debate among biosecurity experts. "You clearly found experiments of concern that are going on," says Stebbins. "I would expect that, in future, you'll find more." Indeed, the anthrax mail attacks that terrorised the US five years ago prompted a multibillion-dollar investment in biodefence that is luring ever more biologists into the dual-use arena.

Of obvious concern are experiments involving the "select agents" identified by the US government as potential bioweapons. Researchers led by Scott Weaver of the University of Texas Medical Branch in Galveston, for instance, are investigating outbreaks of Venezuelan encephalitis. The virus responsible normally circulates in a harmless "enzootic" form among South American rodents, but every decade or two, virulent forms emerge that can kill horses and people. These strains are on the select agents list, and Weaver revealed in March how to create them. His team first predicted the genetic change involved, and then proved the point by engineering it into an enzootic rodent strain and showing that the resulting virus made horses sick (*Proceedings of the National Academy of Sciences*, vol 103, p 4994).

Weaver says he considered the project's risks before going ahead. A terrorist could use the information he generated to make a bioweapon, but Weaver argues that it would be easier to obtain a virulent virus by infiltrating a lab working on epidemic strains of the pathogen – of which there are several in Latin America. In contrast, it would require a sophisticated virology lab to isolate a harmless strain from the field and then reproduce the genetic engineering described in Weaver's paper.

Given such arguments, and that Weaver's goal was to improve the monitoring of the natural emergence of dangerous strains, biosecurity specialists consulted by *New Scientist* agreed with the decision to let the project to go ahead. "You want to learn how outbreaks happen," says Gigi Kwik Grönvall of the Center for Biosecurity at the University of Pittsburgh Medical Center in Pennsylvania.

The Venezuelan encephalitis virus is hardly the most dangerous pathogen on the select agents list. Other projects we uncovered concern so-called category A agents, identified as the most significant threats. Botulinum toxins, produced by the bacterium *Clostridium botulinum*, occasionally cause deadly food-poisoning outbreaks, but could kill thousands if mass-produced and introduced into the food or water supply.

SAM DIEPHUISZEN/CORBIS

Restrictions don't stop people reading the published work

To counter this threat, researchers led by Kim Janda of the Scripps Research Institute in La Jolla, California, have won NIH funding to screen a library of chemicals for any that inhibit botulinum toxins and might be deployed to treat people exposed in a bioterrorist attack. In April, Janda revealed that the project has also thrown up a few compounds that enhance the activity of botulinum toxin A up to sevenfold (*Journal of the American Chemical Society*, vol 128, p 4176).

Publishing a paper that describes how to increase the potency of one of the most lethal poisons known may sound like madness, but botulinum toxins are also used in minute doses to treat conditions such as cerebral palsy and to iron out facial wrinkles,

WHAT IS AN EXPERIMENT OF CONCERN?

The criteria listed by the US National Science Advisory Board for Biosecurity

- Enhances the harmful consequences of a biological agent or toxin
- Disrupts immunity or the effectiveness of an immunization without a clinical and/or agricultural justification
- Confers on a biological agent or toxin resistance to clinically and/or agriculturally useful prophylactics or therapeutics, or facilitates the ability to evade detection methods
- Increases the stability, transmissibility or ease of dissemination of a biological agent or toxin
- Alters the host range of a biological agent or toxin, or alters the cells and tissues that it affects
- Enhances the susceptibility of a host population
- Generates a novel pathogenic agent or toxin, or reconstitutes an eradicated or extinct biological agent

thanks to their muscle-relaxing effects. Janda's discovery should allow doctors to use even smaller doses, minimising the risk of dangerous immune reactions. Given this benefit, the experts we asked defended Janda's decision to publish his findings. They also pointed out that botulinum toxins are so poisonous anyway that bioterrorists would have little need to enhance their toxicity.

The other category A project in our sample split the experts right down the middle. Also in La Jolla, John Young of the Salk Institute for Biological Studies is leading a project to investigate how the toxin released by the anthrax bacterium *Bacillus anthracis* enters human cells. Young and his colleagues are developing soluble molecules that mimic the cell-surface receptors that the toxin binds to, as an anti-toxin treatment for anthrax infection. But their NIH grant summary also states that they will try to produce altered toxins that target other receptors, to "pre-empt the actions of bioterrorists". The idea is to understand how bioterrorists might engineer altered toxins, which would allow researchers to keep one step ahead.

To John Steinbruner, a security specialist at the University of Maryland at College Park, this is a dangerous trend. "You're creating the threat you're concerned about with no reason to believe that anyone is doing that," he claims.

Young says that attempts to tweak the anthrax toxin to use alternative receptors are "on a back-burner" for now, but he defends the logic behind the proposed experiments. "The people who think our project is dangerous have got their heads in the sand," Young claims. "I think it's much better to be prepared for the next generation of threats."

Other biosecurity specialists agree. "I don't think it's a good idea to create a therapy that is easily subverted," says Grönvall, who also praises Young for bringing the dual-use aspects of his proposal to the attention of the grant committee: "He could have just done it and not told anyone."

The divergent views of Young's project underline the difficulties facing NSABB in devising a system to weigh the pros and cons of dual-use research. Even more problematic than the anthrax research are efforts to examine how certain pathogens interact with the immune system. Such knowledge may be crucial to making better drugs and vaccines, and could help gauge the threat posed by emerging diseases. Yet some projects in this area are revealing potential strategies to make pathogens more dangerous.

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At the Mount Sinai School of Medicine in New York, influenza researchers who helped reconstruct the 1918 virus are trying to work out how flu viruses evade the human immune system. They have transferred the gene for an influenza protein called NS1 to a weakened strain of the Newcastle disease virus, which infects chickens. In July, they showed that the new virus suppresses key components of the human immune response, much like flu (*Journal of Virology*, vol 80, p 6295).

No one suggests that the engineered virus itself represents a significant threat. "On a scale of 1 to 100, with smallpox being 100, we are dealing with a virus that is a 5, and making a 7 of it," argues Peter Palese, one of the Mount Sinai researchers. However, genes that can suppress the human immune response when transferred into other viruses are bound to be of interest to anyone hoping to create "enhanced" bioweapons. "With the knowledge we acquire, people could expend effort to make viruses more deadly," agrees Adolfo García-Sastre, another member of the team.

The Mount Sinai team's work with NS1 illustrates the fine line that NSABB needs to walk. At what point, if any, does working on how pathogens evade immunity become a threat to national security? "It's very difficult to project experiments into the future," observes Jens Kuhn, a virologist at the New England Primate Research Center in Southborough, Massachusetts.

NSABB chair Dennis Kasper, a microbiologist at Harvard Medical School, declined to comment on the projects identified by *New Scientist*, but the board plans in January to unveil a report on its progress in developing a framework for overseeing such work. The report is likely to focus in large part on the institutions in which the research is conducted. One option is to expand the remit of local biosafety committees, which currently decide whether projects pose a risk to lab staff or the public, to include consideration of the bioterror implications. "Another equally viable option is separate committees," says Kasper.

NSABB may also advise that the riskiest projects be considered by higher-level panels. Steinbruner and colleagues at the Center for International and Security Studies at Maryland, meanwhile, have proposed a scheme that would subject some projects to scrutiny by national and even international bodies. According to Kuhn, who surveyed papers published from 2000 to 2005, this scheme would have affected 310 US research facilities and 2574 scientists if it had operated over this period, with most of these projects requiring only local review.

That represents about 1 per cent of the research on bacteria, viruses and toxins in the US, according to Kuhn. Nevertheless, biologists whose projects may receive such scrutiny are concerned that additional bureaucracy will slow efforts to combat the biggest threat by far. "Nature is still the most effective terrorist," says Palese. "If you stifle the research, I think it's much more dangerous." ●

Additional reporting by Michael Reilly

Mix-and-match flu

In July, the threat of a flu pandemic receded just a little: the US Centers for Disease Control and Prevention (CDC) revealed that viruses combining the external protein "coat" of deadly H5N1 avian flu with the internal proteins of a common human strain, H3N2, are not likely to transmit readily between people.

Given that such "reassortant" viruses may arise by natural genetic recombination, the CDC argued that it was important to investigate this danger. But when the project got started, some researchers questioned the wisdom of creating potentially pandemic viruses in the lab (*New Scientist*, 28 February 2004, p 6).

Wendy Barclay, a virologist at the University of Reading, UK, always doubted that a simple reassortant would be dangerous, but notes that the CDC also deliberately passed one virus five times from ferret to ferret, to see if this would adapt it for transmission between mammals. She argues that this possibility could be investigated more safely by tweaking the genes for receptors that allow H5N1 to enter host cells, and then placing the genes into harmless viruses, to see if doing so enhances their ability to infect human cells.

The CDC's experiments are not the last word on the dangers posed by reassortant flu viruses. *New Scientist*'s grant survey showed that at least two other US groups – one led by Daniel Perez of the University of Maryland, the other by Yoshihiro Kawaoka at the University of Wisconsin-Madison – are embarking on similar experiments.