the Center for Bioethics at the University of Pennsylvania.

But how long that restriction can last is uncertain. Eventually researchers will want to create embryos from their patients' tissue, because cells transplanted from these embryos will not risk rejection by the patients' immune system. The scientific report approved by the British government already goes in this direction. It not only would allow extraction of stem cells from embryos but also opens the door to cloning human embryos via nuclear transfer—but for purposes of disease therapy only, rather than for reproduction.

Calls for the creation of human embryos to use in research would certainly raise hackles, even among those who are well-disposed to using surplus embryos. In addition, the opponents now have an increasingly powerful argument against it: a recent string of successes with stem cells taken from adults. Stem cell transplants from mouse pancreas, for example, have reportedly reversed diabetes in mice. Bone marrow transplants have mitigated the condition of people suffering from lupus and may lead to therapies for other immune system diseases. In fact, although there was some excitement about stem cell research in US financial markets after the guidelines were announced, most of it focused on companies planning to work with adult cells.

Opponents have a powerful argument against embryonic stem cells: successes with stem cells taken from adults

Whether US taxpayers will bestow stem cell research money on anybody, however, probably depends entirely on the results of the upcoming national elections. The guidelines govern current policy, but they can be overturned in a trice by congressional action or a presidential executive order. Congress is polarized on the issue, and so are the presidential candidates. Republican George W. Bush has declared himself opposed to federal funding for stem cell research that involves destroying a living human embryo. Democrat Al Gore, the sitting vice president, supports stem cell research, and so does the party's official platform. The present Republican-led Congress is following a firm policy of doing as little as possible between now and Election Day, although it will probably try to interfere with funding if the House remains under Republican control. But since all 435 members of the House of Representatives are up for re-election, and so is one-third of the Senate, majority sentiment might well be completely different after the election in November.

NIH recognizes these political realities. The agency's timetable for handing out grants for research on human embryonic stem cells is nothing if not deliberate. Potential stem cell grantees must run two gauntlets before their proposals even make it into the agency's usual pipeline for consideration. First, they will be vetted by the Human Pluripotent Stem Cell Review Group, a special NIH committee of scientists and ethicists that will make sure the research design observes the guidelines. A second committee of scientists will subsequently take a look at protocols and judge scientific merit. Only after passing muster with both committees will a proposal be considered for funding.

One NIH official has said that work might be funded as soon as early next year, but it seems far more likely that successful proposals will not get money until the next fiscal year, at the end of 2001. As further evidence that NIH is keeping its usual prudent eye on the results of the November 7 election, it has set the grant proposal deadline for November 15, and scheduled the first meeting of the Pluripotent Group for December.

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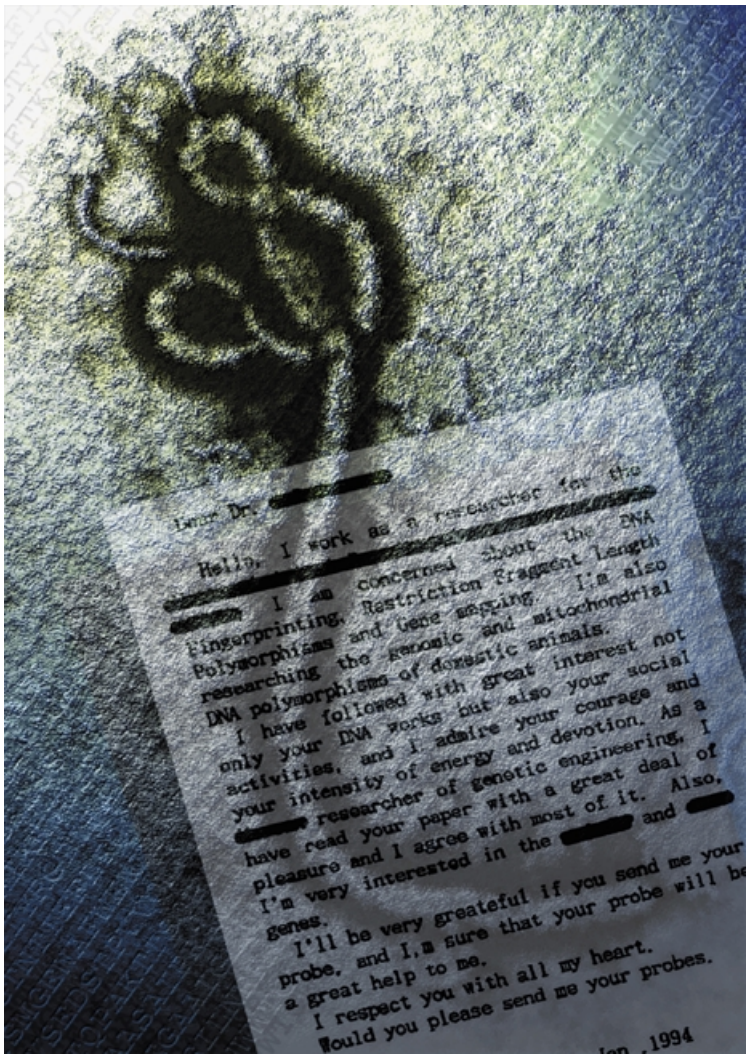
Toxins for terrorists

Do scientists act illegally when sending out potentially dangerous material?

In 1999, Tommy Nilsson, Rainer Pepperkok and Brian Storrie published results about protein export in cells they obtained by using shiga toxin. One month later, Nilsson (a group leader at the European Molecular Biology Laboratory in Heidelberg, Germany) received a request for the plasmids that his laboratory used to produce non-toxic fragments of the toxin. As a scientist, Nilsson shares his published knowledge and material with every colleague who asks for it. But one aspect of the request for the toxin constructs made him hesitate. The letter came from North Korea. After considering the request and discussing the matter with other colleagues, Nilsson decided not to send these plasmids to a country labelled as a 'rogue' state. 'You have to think about what consequences might arise from this,' he explained, 'because the material might fall into the hands of people working on biological weapons.' Indeed, he did not make his decision easily. 'I felt pretty bad about not sending it,' he said, 'because you are obliged to send out material after you have published it—that's the norm. And you must pay particular attention to requests from third world countries where any material, be it an antibody or a plasmid, may be of great help.'

Nilsson made his decision because he was uncertain about legal aspects and the

possibility of abuse. And without knowing about these details, he was right, as Germany is one of the countries that have passed laws to control the export of material that could be used for the development of weapons of mass destruction. But many scientists, when sending strains or genetic elements to a colleague, do not give a second thought to such consequences. They are simply not aware of those laws or the fact that some strains or genetic material could be turned into a weapon. And given that preparing a terrorist attack using bioweapons would be relatively easy, scientists should be made aware of the potential abuses of their knowledge and materials.



'Black biology', the research on bacteria, viruses and toxins for the purpose of creating weapons of mass destruction, is the nightmare of security experts in western countries and is also beginning to capture the attention of scientists and politicians. Although the possibility of a biological attack wiping out Washington, London or Paris is rather small, bioweapons have become the 'poor man's nuke' for states and terrorist groups that do not have the means to build nuclear weapons. Among the countries that are suspected of developing biological weapons are those that have tried to build or acquire nuclear weapons, including North Korea, Libya and Iraq. Indeed, for a terrorist group to extinguish a metropolis like New York City, an atomic bomb would certainly not be the weapon of choice. The huge facilities required to produce bomb-grade plutonium or uranium cannot be hidden and are easy targets for a preventive attack. Furthermore, a nuclear warhead is too bulky to fit into a plane's storage bin, and it does not have enough power to annihilate all of New York's five boroughs. A well-designed bacterial or virus strain, in contrast, can be produced in a garage hidden from spy satellites, transported in a thermos flask, and, theoretically, has the potential to wipe out whole cities.

But the main advantage of biological weapons is the fact that they are easy to manufacture. The know-how to produce a toxin, increase the virulence of a bacterial strain or design a deadly virus is only a few mouse clicks away on the World Wide Web. The raw material—plasmids, bacteria and viruses—can be obtained by simply asking the scientists who work with them. Indeed, this is common practice among scientists, as most journals even require them to provide material on request after publishing their results.

But this practice, when it concerns materials that could be turned into a biological weapon, runs counter to international treaties designed to ban weapons of mass destruction. These treaties are based on the 'United Nations Convention on the prohibition of the development, production and stockpiling of bacteriological and toxin weapons and on their destruction', which came into force on 26 March 1975 (http://www.state.gov/www/global/arms/treaties/bwc1.html). Those countries that signed and ratified the convention committed themselves to opposing the production of biological weapons. Particularly important for scientists is article III of the convention, which obliges the countries 'not to transfer to any recipient whatsoever, directly or indirectly, and not in any way to assist, encourage, or induce any State, group of States or international organisations to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or means of delivery […]'.

Since then, nearly all countries, including Iraq, Iran and Libya, have signed and ratified the convention. Interestingly, North Korea is one of the few countries that has not even signed it. Many of the signatories have passed additional export control laws in order to regulate the export of material or equipment that could be used to create biological weapons. Based on the UN convention, these countries compiled lists of strains and toxins for which export regulations apply (see sidebar, p. 300). Most countries have even expanded the UN convention by introducing the 'dual use' definition: goods that have the potential for both military and civil uses. Consequently, export control laws also regulate the export of genetically modified organisms and genetic elements 'that contain nucleic acid sequences associated with pathogenicity' or 'coding for any of the toxins' specified in their lists [UK Export of Goods (Control) Order, No. 3092, 1992]. Under these laws, it would be illegal for a scientist to send a colleague in Iraq or Libya a plasmid containing a gene for a surface protein from whitepox virus, for instance. Frank Bonaldo, a spokesperson for the German Federal Ministry of Economics and Technology, confirmed that scientists who wish to send such material to designated states

must seek approval from the relevant German authorities. 'If one works in such a sensitive area,' he said, 'one has to be aware that there are regulations'. But most scientists have never heard of these laws. 'I had no idea about these international laws and treaties,' Nilsson said, 'I had never come across this issue before'. His decision not to send shiga toxin constructs to North Korea was based mainly on his concerns about the legality and possible abuse, he explained.

For many scientists, it is common practice to share knowledge and material once it is published

Many scientists think that these laws will not stop the development of bioweapons at all. 'I have very little confidence that regulations will work', Hidde Ploegh, a pathologist at Harvard Medical School, said. 'My experience tells me that if things are feasible they will be done,' he said. 'The system is too leaky.' Ploegh also sees no sense in regulations that include only a small number of organisms and toxins without regulating the export of other technologies that could be equally dangerous. 'Should we equip the North Korean military with all the sophisticated biochemistry without giving them the toxins?' He questioned the 'dual use' definition. Furthermore, prohibiting the export to certain countries would also be a form of scientific discrimination. A scientist cannot know whether a Libyan colleague will use his or her plasmid containing the gene for a whitepox virus surface protein to design a bioweapon or to develop a vaccine against the virus.

Prohibiting the export of biological material to certain countries would be a form of scientific discrimination

Export control laws might even be useless, as the knowledge is already available to everybody. For instance, the last stocks of smallpox—at least the ones the public knows of—are stored in Atlanta and Moscow, but the full sequence of variola is public knowledge. So, Internet access, a gene assembler and recombinant technology are sufficient to create a bioweapon based on the variola sequence. Some scientists therefore argue that certain research should not be carried out if the potential dangers that would come with abuse are too large. 'In fact, the problem is that as soon as someone has got the information, it will be available,' Antoine Danchin, a bacterial geneticist at the Pasteur Centre of Hong Kong University, said. 'So I think there is knowledge that should not be obtained.' Consequently, he considers the sequencing of variola and publishing the sequence to be an error. 'Now the sequence is available on the World Wide Web and nobody knows who's using it,' he said. 'I think it's stupidity.' To prevent the construction of bioweapons based on public information, Danchin would like scientists to refrain from some areas of research that are considered to be dangerous.

The know-how to produce a biological weapon is only a few mouse clicks away on the World Wide Web

Ploegh, who was a member of the committee on the assessment of future needs for smallpox virus and came out in favour of not destroying the remaining stocks, disagrees. Scientific knowledge *per se* should not be suppressed or destroyed, he argued, as nobody is capable of making a realistic assessment of its dangerous or useful potential. 'Today we might see the destruction of smallpox as desirable but we might look at it differently 20 years hence,' he said, citing the development of new antivirals as an argument in favour of preserving and studying the virus. Furthermore, Ploegh thinks that nobody should be able to make decisions to suppress basic research or the dissemination of knowledge. 'These things are very difficult to regulate, even by scientists,' he said.

In the end, the decision not to send biological material comes down to the moral values of an individual scientist, as in Tommy Nilsson's case. 'I wholeheartedly agree with Nilsson,' Ploegh said. 'It's a personal issue and people should decide according to the standards they can set for themselves.' But to make such a decision, a scientist must know about the possibility of abuse as well as about existing laws designed to prevent it. 'As scientists, we are not always aware of or care about the potential implications,' Nilsson explained. He, therefore, would like to see governments educate biologists

Some bacterial and virus strains and toxins whose export is regulated in various countries. This incomplete list is based on the UK Export of Goods (Control) Order.

Bacteria
Bacillus anthracis
Clostridium botulinum
Francisella tularensis
Vibrio cholerae
Yersinia pestis
Chlamydia psittaci
Brucella abortus
Brucella melitensis
Brucella suis
Pseudomonas mallei
Pseudomonas pseudomallei
Salmonella typhi
Shigella dysenteriae

Viruses
Variola
Ebola, Marburg
Dengue
Hantaan
Lassa fever
Rift Valley fever
Whitepox
Yellow fever
Junin
Lymphocytic choriomeningitis
Machupo
Chikungunya
Equine encephalitis viruses

Toxins
Clostridium botulinum toxins
Clostridium perfringens toxins
Conotoxin
Ricin
Saxitoxin
Shiga toxin
Staphylococcus aureus toxins
Tetrodotoxin
Verotoxin
Microcystins

about the legal situation, probably as part of their education. Danchin thinks that biologists should be educated in ethics to 'push the considerations of the human sciences into natural science'. But more important than passing laws or educating scientists would be a public discussion of the potential dangers of abusing scientific research. Such a debate would be a good way of showing scientists the dark side of science rather than regulating their work. 'I'm interested in a debate about these issues,' Nilsson said, 'to answer the question: "Where do you draw the line between scientific freedom and responsibility?"'

Holger Breithaupt

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Fight for reputation

Judah Folkman counter-sued Abbott in the legal battle over kringle 5

Patent disputes have become commonplace in the biotechnology industry, but few have taken on such a personal and bitter tone as the legal battle between Abbott Laboratories and angiogenesis pioneer Judah Folkman. The dispute concerns who discovered the anti-angiogenic potential of a plasminogen fragment and to whom the patent rightfully belongs. Abbott claims in its lawsuit of May 2000 that one of its researchers, Donald Davidson, made the discovery and seeks compensation and damages of US $10 million for 'unlawful misappropriation of and conspiracy to steal an invention.' Folkman and his collaborators at Children's Hospital in Boston, MA and Entremed Inc. in Rockville, MD, to whom the patent is assigned, maintain that this is false. Stepping up the legal battle, they counter-sued Abbott in July for fraud, conspiracy and defamation of character, demanding treble damages.

Folkman and his associates assert that Abbott's suit is an attempt to intimidate the hospital and its researchers because the drug maker wants to avoid paying royalties on kringle 5, the plasminogen fragment in question. But the stakes are higher than just money. They say that Abbott's suit represents 'an inflammatory and vicious' attempt to damage their collective reputation, and that it could have dire consequences for drug development. 'A suit such as this threatens to disrupt the long-standing practice of sharing information and techniques between physician-scientists at non-profit hospitals with scientists in private industry', Folkman said. 'We hope that Abbott's unfounded and inflammatory lawsuit will not have a chilling effect on the sharing of information among scientists,' he added. Indeed, the tone has grown increasingly bitter. Calling Abbott's lawsuit 'egregious, tasteless, and shameful', John Holaday, EntreMed's Chairman and Chief Executive Officer, commented, 'By attempting to intimidate parties in order to obtain the rights to a product it neither discovered, nor owns, Abbott has taken the lowest road […].' Abbott does not want to comment on the ongoing legal battle at this stage.

Plasminogen contains five distinct regions, each with a characteristic three-dimensional structure resembling the eponymous Danish cookie—hence the name kringle for these domains. A sixth, non-kringle domain is where the protease activity of plasminogen is located. In 1994, Folkman and Michael O'Reilly at Children's Hospital discovered that angiostatin, a fragment of plasminogen, acts as a promising anti-cancer agent in blocking the growth of blood supplies into growing tumors (O'Reilly *et al.*, 1994). A recombinant version of angiostatin is now in phase I clinical trials in the USA for the treatment of cancer. It does not contain kringle 5 and the protease domain, so the lawsuits between Abbott and Folkman do not affect angiostatin and its clinical development. At stake is the ownership of kringle 5. Folkman's team found it to be a weak angiogenesis inhibitor, but Abbott improved upon it, and the company wishes to develop it into an anti-cancer drug.

The warring parties dispute a number of key facts and events leading to the filing of Folkman's patent on kringle 5. The differences start with disputing exactly what Abbott's researcher Donald Davidson was working on, when he began collaborating with Children's Hospital in May 1994. According to Abbott's suit, he focused on tumor inhibition among other things. Davidson then began providing Yihai Cao in Folkman's lab with research quantities of kringle 1–4 for angiogenesis research. According to Folkman, however, Davidson was an expert in plasminogen and was working on thrombolytics, but had no background in angiogenesis and only learned about kringle 5's anti-angiogenic potential through Folkman and his colleagues.

> Abbott asserts that its version of kringle 5 has greater anti-angiogenic potency than Folkman's angiostatin

A letter from Davidson's supervisor, Jack Henkin, sent to Folkman in November 1995, affirms that Davidson was a novice in the field of angiogenesis. Henkin proposed a 'gentleman's agreement' for the research on angiostatin and kringles 1–4 with the understanding that 'the techniques and knowledge of his (Folkman's) lab would be readily available to them.' In return, Henkin proposed sending Davidson and another colleague to Folkman's angiogenesis lab 'to learn the methodology and art of your angiogenesis assays.' He closed the letter stating that if such an arrangement was agreeable, 'Don['s] payback will be to eat from your tree of knowledge and hopefully become our local angiogenesis maven.'