# Too Radical for NIH? Try DARPA

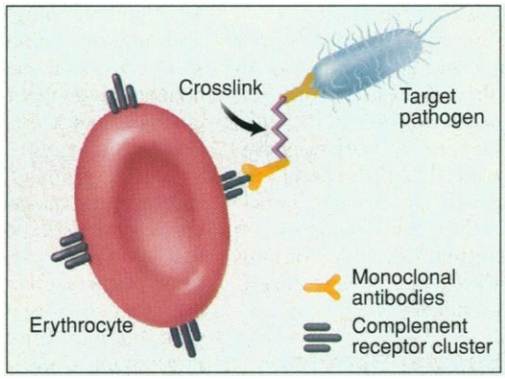
Alarmed by evidence that terrorists may exploit biological weapons, the Internet's sponsor is moving into a brand-new field with some serious money

You have a radically new idea for fighting pathogens that your colleagues are dubious about—a scheme, say, to program blood cells to remove viruses from the bloodstream in minutes. Where would you go for funding? To the National Institutes of Health (NIH), the big bank of biomedical research? Perhaps. But NIH would ask a committee of peers to evaluate your idea, and peers can be brutal about radical concepts. For the same reason, you would not expect much enthusiasm from private charities or from public health agencies like the Centers for Disease Control and Prevention. But there is one federal outfit that says it loves revolutionary ideas, and it has just begun spending millions of dollars on pathogen research: the Pentagon's wunderkind, the Defense Advanced Research Projects Agency (DARPA)—best known as the originator of the Internet.

For 3 decades, DARPA has been bankrolling far-out engineering and electronics projects, and about 2 years ago, its leaders got interested in biology. Now, they are talking about spending serious money on basic and applied science projects to protect the military—and maybe civilians—from biohazards. According to Jane Alexander, deputy director of DARPA's basic sciences division and an electronics expert, the agency aims to fund about $40 million to $50 million worth of biodefense research this year. By 1999, DARPA may be spending $100 million, and after that, she says, "we may aim at a $200-million-a-year effort."

That would be a good chunk of DARPA's budget, now $2 billion a year. The commitment reflects the concern of DARPA's new director, Larry Lynn, about the risk of biological attack by "rogue governments" or terrorist groups (see sidebar). Lynn, who majored in physics as an undergraduate and has spent his career managing defense projects for the military and industry, was appointed by President Clinton to take over DARPA in 1995. He set out to reorganize the place quickly, and in 1996, DARPA emerged a smaller, more focused agency, with newly defined objectives. And there was something entirely new on the list: basic biology, a field DARPA had never funded before. Lynn told Congress last year that "biological warfare defense" is fourth of the top nine military problems DARPA wants to tackle and that "biological systems" are among the top nine technologies the agency has targeted for development.

Congress approved, making biodefense research a line item in DARPA's budget last year, and the agency moved eagerly to take up the assignment. Outsiders have also been swept up: "I feel the enthusiasm," says Stanford University biologist Stanley Falkow, current president of the American Society of Microbiology, who has served as one of DARPA's advisers from academia. "I think we'd be mistaken if we didn't address" the threat of assault by biological weapons, he says, both as a military issue and a public health risk. But Falkow, who says he is doing "a little work" himself with DARPA support, is hedging his bets on the likelihood of success. The ideas DARPA is funding, he says, "sound wonderful," but no one knows how well they're going to work.




K. SUTLIFF

**Blood sweeper.** DARPA is investing heavily in this idea for removing pathogens from the bloodstream.

Outside researchers add that agency wizards—accustomed to quick-turnaround engineering projects—may be unrealistic about what can be done in biology on a short schedule. DARPA is "quite serious for the moment," says one scientific adviser, but he worries about what will happen if the excitement passes. In engineering and computers, says Michael Donnenberg—a microbiologist at the University of Maryland, Baltimore, who advises DARPA—the agency tends to support an experiment at one lab for a couple of years, then move the experiment to another place. In contrast, says Donnenberg, NIH-funded researchers "are used to 5-year cycles ... and then getting refunded." DARPA's hands-on management style may also ruffle biologists, he says.

DARPA officials acknowledge that they are taking a big gamble. But one staffer says, with a touch of hubris, that this is exactly why DARPA is betting on "only the best" advisers and ideas.

### Star Wars of biology

Lynn set DARPA on this new course, he says, because biological threats are becoming "more acceptable" as weapons of terror. "Probably they are next to nuclear weapons in the magnitude" of damage they might cause, while being "much easier to build and dispense, with relatively rudimentary training," he adds. While the Department of Defense is already spending "a fair amount of money" to cope with "near-term" issues—developing better protective gear and refining vaccines—this work tends to be agent-specific and limited to immediate worries, Lynn says. DARPA likes bigger challenges.

"We are concerned with a much broader range of agents than you would think of today," says Lynn. DARPA is especially concerned about genetic engineering, and it has set an extremely ambitious goal—reminiscent of the Star Wars antimissile program. Lynn says the aim quite simply is to "eliminate biological weapons as a serious threat to military activities." Along the way, DARPA may inspire researchers to develop products useful to the civilian economy, like new antibiotics.

DARPA prides itself on moving fast, and it has already blitzed into pathogen studies and immune-system research. It has recruited a blue-ribbon panel of academic advisers that includes eight members of the National Academy of Sciences and is chaired by the president emeritus of Rockefeller University, Joshua Lederberg. Lynn himself has been visiting biotech companies—"a wild lot," he says, adding that "when you mix them with a funding organization that's willing to play wild, a lot of excitement gets generated." DARPA last year issued two invitations to scientists to submit proposals for research contracts totaling $50 million. It received more than 250 responses, and is now signing contracts with the winners, which include both biotech ventures and nonprofits.

Although a full list of awardees wasn't available at press time, DARPA staffers mentioned some of the early winners and outlined for *Science* a few of the concepts they are exploring. One award, worth "millions," according to a consultant, has been

signed with Molecular Geodesics Inc. of Cambridge, Massachusetts. The aim: to design synthetic "bioskins," filters, and other protective gear based on principles of cellular structure elucidated by Donald Ingber of Harvard Medical School. Another contract will go to Isis Pharmaceuticals Inc. of Carlsbad, California, to create "novel, broad-spectrum antimicrobial agents." And a third will go to The Scripps Research Institute in La Jolla, California, to create a library of "invasive intracellular antibodies" for use in the development of exotic new therapeutic agents.

As an example of the kind of high-risk, potentially high-payoff, basic science experiment the agency wants to fund, Alexander and Commander Shaun Jones, program director for unconventional pathogen countermeasures, described a project involving blood research DARPA began funding last year. Jones says he was "laughed out of conference rooms" when he first talked to biologists about this project—an idea developed by physical chemist Ronald Taylor of the University of Virginia, Charlottesville. But now, it's being taken more seriously.

Taylor says he had established by 1991 that previous studies had overlooked the importance of a pathway in primates for clearing foreign bodies from the bloodstream. He concluded that a receptor called CR1 on the surface of red blood cells plays a key role in removing material tagged as alien by the immune-system proteins known as complement. Once bound to the receptor, the material is quickly flushed out of the body by the liver. (A report on his initial work was published in 1991 in the *Proceedings of the National Academy of Sciences*.) Taylor looked for a way to improve upon CR1's ability to clean up the blood. Borrowing an idea developed in the 1980s at Dartmouth, he created a "bispecific" polymer that hooked at one end to CR1 and, at the other, to almost any protein one might want to target.

The idea didn't fare well in peer review: After several rejections, Taylor finally received support from NIH in late 1995 to carry out a narrowed-down experiment focused on proteins in autoimmune disorders. In mid-1996, however, DARPA picked up Taylor's big idea and now regards it as one of its great finds. With DARPA's funding, Taylor and his colleagues have already shown in rhesus and cynomolgus monkeys that the polymer-CR1 system can be used to move huge quantities of a model virus ($\phi$X174) in 90 minutes from the blood to the liver. Neither the blood nor liver appears to be adversely affected.

Jones says he's "very excited" about these results and about the potential payoffs of a more recent, unpublished study. Jones says this work suggests it may be possible to "decorate red blood cells in a variety of ways" that will enable the cells—the "platform," in DARPA parlance—to process $10^{13}$ or more pathogens per minute.

These blood-based studies fit into one major category of projects DARPA is funding, called pathogen countermeasures. The program also includes an even more visionary scheme that would engineer mesenchymal stem cells—the source of muscle, fat, bone, and cartilage—that can sense and respond to biological threats. According to Jones, the program director, cells bearing a "cassette" of transplanted genes would populate the recipient's tissues and, in theory, recognize certain pathogens and turn on genes to produce an appropriate response.

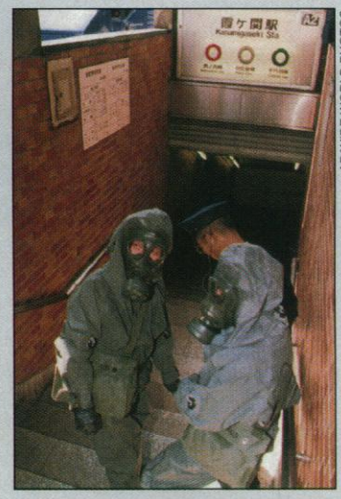
In a variation on this idea, Jones says, the program is interested in developing cells that would "autovaccinate" the body against biological threats, avoiding the need for repeated injections and all the problems they create. It sounds far-out, but DARPA has already paid an animation company in Iowa to create a three-dimensional (3D) movie illustrating how such exotic battles might be fought within the human body. Members of the academic advisory board said they donned special 3D glasses to watch the cartoon at a meeting sponsored by DARPA last December in Santa Fe, New Mexico.

On a less fantastic level, DARPA is studying a concept from basic biology—the idea that pathogens may share some common, fundamental vulnerabilities that remain undiscovered. Both Falkow and microbiologist John

## Bracing for a Biological Nightmare

Leaders of the Defense Advanced Research Projects Agency's (DARPA's) new biology program say that several recent biological-weapons threats goaded them into action to develop countermeasures. Close to home, a man associated with survivalist groups was arrested in 1995 for trying to smuggle 130 grams of ricin—a plant toxin that can cause death within minutes of contact—into the United States from Canada. And in separate incidents, others were arrested or convicted in 1995 on charges of illicit use of ricin or bubonic plague. While police work avoided tragedy in these cases, DARPA officials warn that next time, it may not.

The most shocking case in point occurred on 20 March 1995, when the Aum Shinrikyo religious group attacked passengers on Tokyo's subway trains with nerve gas, killing 12. This cult—more than 60,000 strong by one estimate—used a global network of offices and a technically skilled membership to buy hardware and manufacture weapons in secret. After the Tokyo attack, investigators discovered that Aum members had built crude biological weapons, including a bomb containing anthrax, whose bacterial spores enter the lungs and—unless treated quickly—lead to inevitable death. They may have set off one anthrax device in Tokyo, but it didn't work. (One U.S. pathogen expert warns: "I could make one that works; but don't tell [the Aum cult]—they might kidnap me.") Other evidence suggests that Aum members were trying to collect the deadly Ebola virus and manufacture botulinum toxin. Police also found that Aum members in New York and Japan had purchased sophisticated molecular-design software and bacterial growth media, an indication, according to the U.S. Senate Permanent Subcommittee on Investigations, that the cult was trying to engineer deadly new bacteria.



AP/WIDE WORLD PHOTOS

**Wake-up call.** Nerve gas attack in Tokyo got DARPA's attention.

Another wake-up call was the extensive bioweapons stockpile built in the late 1980s by Iraq's military under Saddam Hussein. The United Nations Special Commission (UNSCOM) on Iraq, chaired by Swedish diplomat Rolf Ekeus, reported in October 1995 that Iraqi officials admitted to running a large biological weapons program. Included in the acknowledged inventory, according to UNSCOM, were 19,000 liters of botulinum toxin (10,000 liters of which had been put in weapons); 8500 liters of anthrax (6500 liters in weapons); 2200 liters of aflatoxin, which causes liver cancer (1580 liters in weapons); and smaller quantities of hemorrhagic conjunctivitis virus, mycotoxins, and ricin. Some of these agents—including botulinum, anthrax, and aflatoxin—were loaded into 25 SCUD missile warheads. **–E.M.**

Mekalanos of Harvard University have been doing research on the genes that make pathogens virulent, and DARPA has been consulting both of them on how to exploit their work. Mekalanos is enthusiastic, but even if his work does find a new Achilles' heel of cholera, for example, he wonders how far it can be developed without support from industry: "You're going to have to bring big pharma into the equation ... because it still costs $200 million to develop one antibiotic." Jones agrees, adding that he is working hard to create an advisory group "without peer" drawn from industry and hopes that companies will be joining DARPA's effort.

**New focus.** Larry Lynn has made biology a priority.

In other project categories, DARPA is gearing up to support the development of quick sensors to detect and identify biological threats, medical and body-shielding techniques to counter an attack, and better computer systems for managing the response to an attack. One biosensor concept, according to DARPA's Alexander, consists of a single neuron stabilized in a silicon-chip array that monitors the cell's response to possible nerve agents in the environment—a fast, reliable, and portable system for detecting neurotoxins. Affymetrix Inc. of Santa Clara, California, a company that specializes in chip-based genetic analysis, and biochemist George Whitesides of Harvard University have both contributed expertise to the effort, which DARPA calls a "canary on a chip." A related project, Alexander says, aims to use color-coded fluorescent sensors linked to a variety of specific antibodies to give a quick readout on the contents of an incoming cloud from a biological weapon.

### Skeptic academics

Jones is optimistic about developing these ideas into real products. At the same time, he adds that "I understand there is skepticism" in the academic community, but suggests that it exists in part because "there has not been the equivalent of a DARPA in the biological life sciences" until now. People may not appreciate how much can be accomplished when money is applied in a focused effort.

But one of DARPA's academic advisers who asked not to be named says he was "not overwhelmed by the choice of projects" in the initial round: "More than one was chosen that wasn't favored by the advisory panel." DARPA is "looking for another Internet," he adds, and he worries that this ambition may cause it to overlook unglamorous projects that deserve backing. Another biologist-adviser, asking not to be named, was disappointed for the opposite reason: He thought initial applications were not ambitious enough. DARPA "has a lot of money, and they want you to be really imaginative." But "we got a lot of rather conventional, good-science proposals" that didn't seem likely to cause any revolution.

Some also wonder whether biologists—an independent lot—will submit to DARPA's aggressive, team-dominated supervision. Maryland's Donnenberg notes, for example, that DARPA staffers "totally manage the whole thing. ... If a proposal is good, they think nothing of saying, 'How about you drop three of your specific aims, add a fourth, and collaborate with this other person?' " He sums up the approach thus: "We'd love to give you the money, but only if you study this instead." And Richard Lerner, president of The Scripps Research Institute, another DARPA adviser, notes that the agency needs to keep in mind that "you never know what you want to discover until you discover it."

But these and other scientists who know about DARPA's new project are generally supportive. For example, John La Montagne, infectious-diseases chief of NIH's National Institute of Allergy and Infectious Diseases, says he views the biodefense initiative as "complementary" to, and "much more applied" than, NIAID's work. As for Lerner, he seems delighted that molecular biology may have a new sponsor, as the Pentagon shifts its research focus from nuclear Armageddon to what Lynn calls "our war with Mother Nature." "Wouldn't it be nice," Lerner muses, "if one of the peace dividends is this kind of research?"

**–Eliot Marshall**

FRANCE

# Archaeologists Take to the Streets

**PARIS**—A dispute sparked when construction work threatened an archaeological site in the southern French city of Rodez has become a rallying cause for French archaeologists. Last month, many researchers staged a weeklong strike, and 250 archaeologists and their supporters occupied the culture ministry's archaeology offices in Paris. These protests culminated in a demonstration that brought more than 1000 people onto the streets of Paris last week. Their goal: to persuade the government to pass new laws to protect vulnerable historic sites.

They got a swift response. On 29 January, French culture minister Philippe Douste-Blazy—who a week earlier agreed to temporarily halt construction in Rodez to allow rescue work to go on—told the protesters he would open a "great national debate" on the future of French archaeology.

Researchers initially put down their tools in mid-January to protest the potential destruction of vestiges of medieval, Gallo-Roman, and Iron Age structures in Rodez. The action came when it was revealed that French Prime Minister Alain Juppé had written to a local official 2 months earlier giving a developer the green light to continue construction of an apartment building at the site. Juppé's intervention circumvented efforts by the culture ministry, which had been negotiating with the developer to allow researchers to perform a brief mission of "rescue archaeology," to carefully record remains before construction proceeded. But the negotiations had stalled because the developer balked at paying for the study, which is the custom in France and many other countries.

Because France has regulations to protect sensitive sites, Juppé's action was "completely against the law," claims archaeologist Vincent Krier, leader of one of France's four archaeologists' unions, all of which participated in the strike. Officials, stung by the strength of the reaction, quickly backtracked, and on 23 January, Douste-Blazy announced that construction work at Rodez would be halted. But the strikers were not mollified. They are now pressing for stronger laws to protect historic remains from the bulldozers, including a formal requirement that developers pay for rescue archaeology. "The [current] law doesn't specify who must pay," says Françoise Audouze, director of the Center for Archaeological Research, a network of labs associated with the CNRS public research agency. "The developers are starting to refuse" to provide the necessary funds, she adds.

Another key demand is for a change in the legal status of the Association for National Archaeological Excavations (AFAN), a 2000-member private organization that carries out most rescue archaeology in France under contracts with the government. The strikers are calling for AFAN to be turned into a public organization, a move that would formalize the government's responsibility for protecting threatened remains. As for the national debate promised by Douste-Blazy, its scope has yet to be defined. But researchers involved in the action of the past several weeks have their own ambitions: "We are going to change the landscape of archaeology in France," says Krier.

**–Michael Balter**