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Taking care of bio s

The U.S. government's Project BioShield allots $5.6 billion to the quest for new and better vaccines.

BY DAVID FILMORE

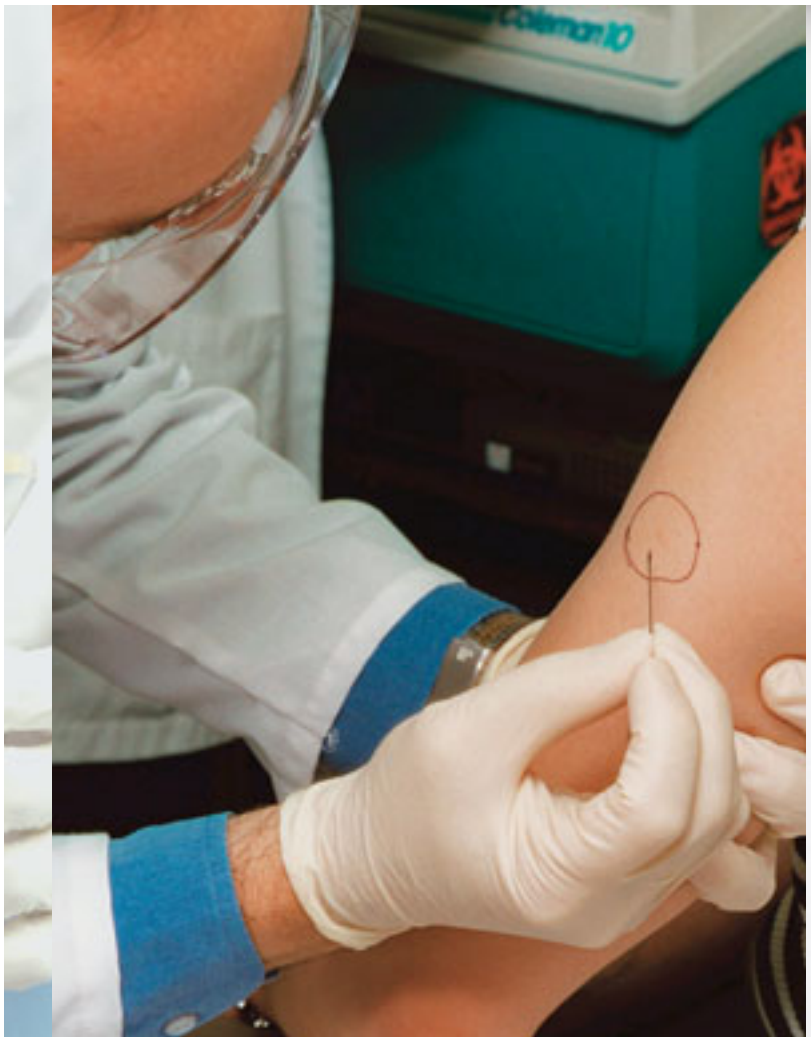
Plague, anthrax, smallpox: In our post-9/11 terrorist-ridden world, such diseases have leapt from the history books to the front page. With this leap comes an urgent need for new defenses against these ancient maladies, and with that need comes a potential market.

Although approved vaccines already exist for smallpox and anthrax, their use has been curtailed by safety concerns and, in the case of anthrax, complicated dosing schedules. Few outside the military have received either vaccine in the 25 years since naturally occurring smallpox was eradicated.

Moreover, there are no vaccines and limited treatment options for other conditions such as pneumonic plague, botulism, tularemia, and viral hemorrhagic fevers like Ebola, which round out what the Centers for Disease Control and Prevention refer to as Category A bioterrorism threats. This classification is based on their ease of dissemination, risk for high mortality rates, and potential to cause substantial social disruption (*www.bt.cdc.gov/agent/agentlist-category.asp#catdef*).

The U.S. government has begun sending out strong signals of its interest in filling these gaps to protect the general public. And the pharmaceutical and biotechnology industries are starting to respond.

"The industry is cautiously optimistic that we are in the throes of the emergence of a new industry in America, called biodefense—



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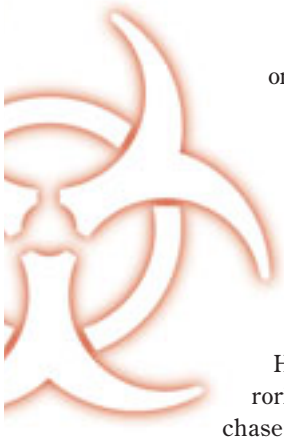


one that the federal government will commit to funding the purchase of countermeasures," says Frank Rapoport, a partner in the McKenna, Long & Aldridge law office in Philadelphia.

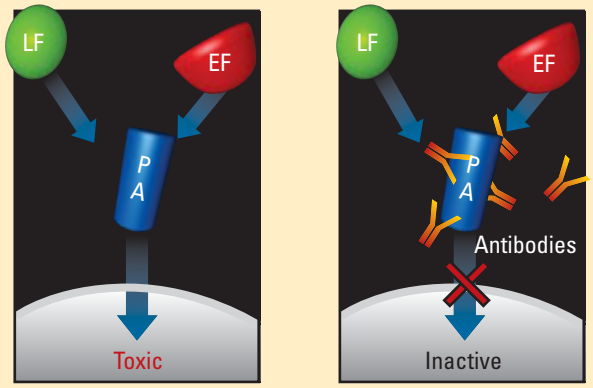
A major source of this optimism is, undoubtedly, the federal government's new Project BioShield initiative. In the FY 2004 appropriations process, Congress budgeted $5.6 billion over the next 10 years to the Department of Homeland Security to procure stockpiles of bioterrorism countermeasures. This is in addition to purchases the Department of Defense will make for protecting the military.

Although separate legislation that technically authorizes the spending has not actually made it through Congress yet (passed the House, still pending in the Senate), an already appropriated $885 million for FY 2004 is presenting a significant incentive to companies, particularly biotech firms. The funds are not slated for any R&D but solely seek to guarantee industry a market by committing government to purchases of stockpiles of Category A vaccines (and to a smaller extent, antitoxins and monoclonal antibodies).

Rapoport coordinates a fund called Biodefense Link, which serves as a clearinghouse for the legal advice, government affairs, and venture capital needs of pharma and biotech firms interested in securing government contracts. The fund, he says, "is going to be sending signals that they are interested in this business." Rapoport describes a blossoming community of companies coming forward with a lot of energy and myriad biodefense proposals. "It's kind of like watching a circus unfold," he says, "in a positive way."

Competition begins

Several companies are already seeking to become the main act in biodefense vaccines. A prime example is VaxGen, originally founded in 1995 by famed AIDS researcher Donald Francis to develop an



Antibody attack. An rPA vaccine will produce PA antibodies to block anthrax toxin—including lethal factor (LF), edema factor (EF), and PA—from entering cells. (Illustration courtesy of VaxGen.)

HIV vaccine. After Phase III AIDSVAX vaccine trials failed in 2003, the company shifted its focus to anthrax, smallpox, and plague. (Francis and two colleagues left in February of this year to form a not-for-profit foundation for HIV vaccines.)

VaxGen's most advanced candidate is rPA102, a recombinant form of *Bacillus anthracis* protective antigen licensed from the U.S. Army Medical Research Institute of Infectious Diseases. PA is a crucial component of the toxin released by anthrax bacteria in the body. According to the mechanism of anthrax infection, antibodies against PA should block the toxin from entering cells.

In September 2002, the company received a $20.9 million contract from the National Institute of Allergy and Infectious Diseases (NIAID) to conduct animal efficacy studies and Phase I human trials for the candidate. It also began to plan for large-scale manufacture of the vaccine, which is produced from a *B. anthracis* cell line. VaxGen completed these goals and, a year later, NIAID awarded it $80.3 million to further develop rPA102, including funding for Phase II trials and the manufacture of 3 million doses.

The size and nature of these contracts highlight the expanded role NIAID has taken since early 2002 in pushing biodefense activities forward, not just with early-stage research but with later-stage development as well. "Unlike most smaller R&D grants from NIAID, this contract was specifically designed to develop a biodefense vaccine as soon as possible that could become part of the strategic national stockpile," says Carmen Betancourt, VaxGen's vice president of regulatory affairs.

The currently approved anthrax vaccine, called BioThrax, is a bacterial extract from an attenuated anthrax strain that requires 6 doses over a period of 18 months to afford protection.

The purer rPA, however, offers the ability to alter the PA concentration and, therefore, reduce the necessary doses. Project BioShield, according to a May 2003 Congressional Budget Office estimate (*www.cbo.gov/showdoc.cfm?index=4203&sequence=0*), is intending, with approximately $1.4 billion over 10 years, to purchase and keep an rPA stockpile requiring fewer doses per patient and offering the potential for quick postexposure protection. VaxGen has its sights on this contract. "We feel very good about our chances of participating in this supply agreement," Betancourt says.

But the company is not the only one with a prominent interest in this stockpile award, which will not necessarily be limited to a single supplier. Avecia, a fine and specialty chemicals company based in the United Kingdom, also has an rPA candidate in development—produced from *E. coli* cells. The company has traditionally focused its business on contract manufacturing, says Kevin Cox, vice president of Avecia's biotechnology business unit. "Defense vaccine development is a relatively new departure for us," he adds.

Avecia initially got involved with the product over five years ago, working with the U.K. Ministry of Defence to develop a vaccine for the U.K. military. "Over time," Cox says, "we determined that NIAID was interested in developing an anthrax vaccine for civilian needs." This led Avecia on a very similar path of contracts and milestones as VaxGen's and, in September 2003, resulted in a $71.3 million NIAID award to pursue Phase II trials and make 3 million doses.

Animal efficacy

Always a complicated endeavor, proving efficacy for FDA approval of biodefense vaccines comes with a unique challenge: Without a terrorist attack, there is generally no risk of infection under the targeted conditions, and it is unethical to expose inoculated human subjects to deadly pathogens.

In some cases, proof of effective vaccination exists, such as the pock lesion in smallpox (although the highly attenuated MVA does not produce a pock), but in others, such as anthrax and plague, no definitive standard has been established. For this reason, the FDA has come up with the "animal rule", in which pathogenic-challenge tests in at least two different animal models, paired with Phase I and II studies that measure safety and immunogenicity in humans, can take the place of large-scale Phase III human trials.

This easing of regulations is considered an important incentive in its own right for biodefense development, but the industry is still apprehensive.

"How the two-animal rule is going to unfold, God only knows," says Vijay Samant, CEO of Vical. Samant's biggest question is precisely what animals—mice, rabbits, nonhuman primates, or others—will be required.

Besides this general uncertainty, there are other concerns. "For vector vaccines, it is a clumsy rule," says Avant Immunotherapeutics CEO Una Ryan. She points out that her company is using attenuated human pathogens as vectors; thus, the level of efficacy could be misrepresented in animals. Partly because of this concern, Avant is going ahead with Phase I human trials before animal studies "to show quickly in humans what we expect to be impressive immunogenicity."

Despite these worries over the animal rule, Ryan says, "of course, we'll live with it."

NIAID released an official request-for-proposal document for the anthrax vaccine purchase in March. Even as they await a decision, both Avecia and VaxGen are sufficiently pleased with the U.S. government's support so far in the anthrax program that they are looking to start a similar process over again. Each company has bid for an initial NIAID contract to develop its respective plague vaccine candidate.

Smallpox payoffs

The U.S. government already has a smallpox vaccine stockpile consisting of live vaccinia virus grown on the skin of calves. In November 2001, Acambis, a U.K.-based vaccine company, was awarded a contract to supply the U.S. government with 209 million doses of the same strain of vaccinia virus as used in the old vaccine (called Dryvax), but manufactured using modern cell culture techniques. "The principle that Secretary Thompson set right after 9/11 was that there would be a dose of vaccine for every American," says Acambis Chief Scientific Officer Thomas Monath.

ACAM2000, Acambis's vaccine, is currently going through Phase III trials to determine its "noninferiority" to Dryvax. Monath says the company has already delivered "large amounts of vaccine to the strategic national stockpile."

Most ongoing development, however, focuses on producing an attenuated vaccine that is safe and effective for the large segment of the population for which the conventional vaccines are contraindicated, primarily that with eczema or with weakened immune systems. Modified vaccinia Ankara (MVA) has surfaced as a strain that might fulfill this need, and several companies—including Acambis and Bavarian Nordic, both of which have received an approximately $9 million NIAID contract for Phase I studies—are developing MVA-based vaccines.

VaxGen, on other hand, is co-developing, with the Japanese company Kaketsuken, another attenuated vaccine called LC16m8, which is also in Phase I trials. This strain is currently approved in Japan after being tested on approximately 50,000 children, according to VaxGen. "It now constitutes the Japanese stockpile for smallpox vaccine," VaxGen CEO Lance Gordon says.

According to Gordon, LC16m8 is associated with fewer side effects than the conventional vaccines, and, unlike MVA, it can be effective in only one dose. "We believe LC16m8 would be a useful means of protecting members of the general population against the threat of smallpox, particularly in situations where the adverse reactions associated with the conventional vaccine outweigh the benefits of protection against theoretical or remote risks of smallpox."

The May 2003 budget office estimate explicitly refers to MVA as the initial target of the approximately $1.9 billion slated for smallpox purchases over the next 10 years. But based on ongoing conversations VaxGen has had with various government authorities, the company believes there would also be an interest in alternatives such as LC16m8.

Estimated 10-year Department of Homeland Security expenditures on stockpile purchases of preventive vaccines

Smallpox	$1.9 billion
Anthrax	$1.4 billion
Botulinum toxin	$1.8 billion[a]
Ebola	$260 million
Plague	$220 million

[a]Includes spending for antitoxins and monoclonal antibodies, as well as a vaccine.
Source: S. 15: Project BioShield Act of 2003; Congressional Budget Office, May 7, 2003.

New approaches

As companies like VaxGen, Acambis, and Avecia vie for the first spoils of BioShield, other companies see opportunity in later rounds with new and improved vaccine technologies, often based on work they have already developed for nonbiodefense applications.

"A multidose injectable, even if multi means two, is never going to be used for mass vaccinations in the United States," says Una Ryan, CEO of Avant Immunotherapeutics. Logistically, Ryan thinks that large populations could only be vaccinated for anthrax, for instance, with a single-dose oral vaccine. Avant has single-dose orals for anthrax and a combination anthrax/plague oral vaccine in preclinical development.

According to Ryan, Avant is trying "to make vaccines that people will actually take." Also, she says, the intestines are a "marvelous place to present a vaccine to the immune system, as opposed to a tiny hole in someone's arm."

Avant's anthrax project is being supported by NIAID, whereas its anthrax–plague project was initiated in 2003 when DynPort Vaccine Company, the main vaccine contractor for the Pentagon, awarded the company $8 million to make a combination vaccine that would protect against two Category A threats. The technology relies on cholera or salmonella vaccines—that is, attenuated versions of the organisms—as vaccine vectors. "These are waterborne infections that get into the intestines by what I call natural means," Ryan says. "They know how to bypass stomach acids and all those things." Avant scientists are able to insert up to three foreign antigens—PA and two plague antigens, F1 and V—into these bacteria.

The company plans on taking a plague-only oral vaccine to Phase I trials this year, even before animal challenge studies (the "empty" cholera and salmonella vaccines have already been shown to be safe and effective in late-stage human trials), to establish safety and immunogenicity. Right now Avant has a line-item appropriation on the Department of Defense budget, but the company has its eye on eventual Homeland Security purchases. "I think that when we are ready for a procurement phase, we will be competing," Ryan says.

Other small biotech companies are concentrating preclinical studies on a different route of delivery that might be preferable to injection: intranasal administration. This route potentially provides protection right at the expected entry point for most bioterrorism agents, preventing infection before the organisms can become estab-

lished. Siga Technologies, for instance, is investigating natural mucosal bacteria for effectiveness in expressing a potentially protective vaccinia virus antigen. ID Biomedical has a similar strategy for a plague vaccine using its Proteosome delivery technology, which, according to the company, acts as both an intranasal delivery system and a vaccine adjuvant.

"Naked" DNA formulations are another up-and-coming vaccine technology by Vical, which encodes specific gene sequences for targeted antigens in plasmid rings. A nonviral (e.g., cationic lipid) formulation of the plasmids is injected into muscle cells, where the antigens can be expressed and presented to the immune system. According to CEO Vijay Samant, these vaccines are much safer and easier to manufacture than live bacteria or cell culture vaccines, and they generally have been well tolerated in cancer vaccine trials.

Vical's anthrax candidate, which is receiving NIAID support for preclinical studies, contains two gene sequences, one for PA and another for a second component, lethal factor (LF), of the three-component anthrax toxin. The PA–LF combination, Samant says, "has been shown in extensive experiments with rabbits to provide the broadest cross-protection."

But Samant is still hesitant about moving forward with the project, because of the holdup in the BioShield legislation. "We haven't gotten it into humans, because we are trying to figure out where the money is going to come from."

BioShield II?

Companies like VaxGen feel confident that the Homeland Security vaccine procurement money will come through soon, but, Gordon says, "We will all benefit from the passage of Project BioShield legislation. It will lend further clarity on how much money will be spent, in what period of time, and on what products."

Some, however, wonder if BioShield will be enough. "There are 52 biological agents we can get hit with," Rapoport says. Most of these agents, including the ricin toxin found in Senate Majority Leader Bill Frist's (R-TN) office in January, a number of water safety threats, and viral encephalitis agents, are on the CDC's Category B list. And others are emerging threats not previously associated with bioterrorism, such as multidrug-resistant tuberculosis and influenza.

NIAID, as part of its biodefense initiative (*www.niaid.nih.gov/biodefense*), is performing and encouraging R&D in these areas, but there isn't much industry involvement at this point.

According to Rapoport, he, along with partners in industry, are lobbying Congress on what he calls "BioShield II" to broaden the goals and start attracting Big Pharma to the endeavor. Such a bill, Rapoport says, would contain "huge money" and other incentives, like offering to extend a company's patent if it diverts significant resources to a biodefense project.

"The biodefense initiative is going to fuel a new industry in America, and that isn't just for biodefense, it is for infectious diseases [in general], like SARS and monkey pox," Rapoport believes.

Companies like Avant are already aware of this. "There is a huge collateral benefit," Ryan says. "Whatever comes down the pike, we will have the base technology." ■