

**WHY RISK EXPOSURE  
TO BIOWEAPONS  
WHEN YOU CAN  
BANISH!**

**Better  
than  
antibiotics!**

**Absorbs through pores  
to boost nonspecific  
immunity!**

**Protects against  
diseases such as  
anthrax and plague!**

**Also guards against  
all synthetic threats,  
even those that don't  
yet exist!**

# BANISH

Just one spray keeps the germs away!

## BODYSPRAY

### WARNING

*Could trigger cytokine overproduction, a potentially fatal immune reaction. Could activate autoimmune diseases, including, but not limited to, primary biliary cirrhosis, multiple sclerosis, pernicious anemia, type 1 diabetes and celiac disease. If the following symptoms develop, contact your doctor immediately: dizziness, fatigue, a general ill feeling, low-grade fever, intolerance to cold, dry skin, hair loss, weight gain, weight loss, difficulty concentrating or thinking or concentrating, joint stiffness, facial swelling, shortness of breath, rapid heart rate, loss of appetite, unsteady gait, impaired sense of smell.*

Antipestilence deodorant spray

IN A WORLD OF BIOTERROR, WHAT SHOULD WE FEAR MOST:

Brand-new life forms engineered for deadliness // Existing germs “heated up” to increase virulence // Or those same germs just as nature made them?

# Once and Future Threats

■ BY WENDY ORENT // ILLUSTRATIONS BY MONDOLITHIC STUDIOS

**T**hese days, there are lots of things you can do with a strand of DNA. You could sequence the genetic code of a particular organism, then reconstruct it in the lab. Or you could transfer a gene from one species to another—to make a strain of corn that’s resistant to herbicides, say, or to produce bacteria that digest oil spills. You could “knock out” genes in laboratory mice, rendering the animals less prone to a particular disease. Or, if you’re a bioterrorist bent on mass destruction, you could try to engineer a virus so contagious and so deadly that it could quickly lay waste to entire populations.

It’s that last possibility, synthetic biology, that worries such people as Michael G. Kurilla, director of the Office for Bio-defense Research Affairs at the National Institute for Allergy and Infectious Diseases. Whereas many experts think the real bioterror threat involves well-known agents—smallpox, pneumonic plague and, of course, anthrax, which infected 22 people and killed five in the attacks of fall 2001—Kurilla and others are more frightened by the specter of diseases that don’t yet exist. They envision designer pathogens that could be created in the bioweapons laboratories of rogue states or terrorist camps, and whose spread we would be powerless to stop. To these people, the risks posed by engineered germs and

emerging infections mean that our strategies must change. “It has become abundantly clear that the one-bug, one-drug approach is not sustainable,” says Kurilla. “Nature throws potential threats at us much faster than we can deal with them, and terrorists don’t have to contend with the FDA.”

Kurilla points out that the traditional tools—vaccines and antibiotics—have obvious shortcomings. Vaccines are an inherently limited solution to disease threats because they’re difficult to develop and deploy. Drug companies don’t make money on them; many people, both in Africa and the West, don’t want to take them; and many vaccines need to be kept in cold storage or they spoil. What’s more, you can’t develop a vaccine for a disease that doesn’t yet exist. Antibiotics are problematic because germs so often develop resistance to them and because, of course, they work only against bacteria, not viruses.

For Kurilla and others, the solution is to develop whole new ways of treating disease, approaches that fundamentally modify not germs, but our response to them. They want to try something radically new—to enhance innate, or nonspecific, immunity, which kicks in as soon as a host is exposed to an unfamiliar germ. They’re convinced that nonspecific immunity could be boosted sufficiently to treat any disease, new or old, natural or designed.

But will bioterrorists actually be able to build deadlier

germs than those that exist in nature? And if bioterror agents are created, is revving up our highly evolved system of innate immunity a viable way to counter these threats? Igor V. Domaradskij, for one, is skeptical—both about synthetic agents and enhancing general innate immunity. When asked by visiting U.S. congressmen in Moscow several years ago whether he thought such therapies might work, the former co-designer of the entire Soviet bioweapons system remarked, “Certainly—if you could design an entire new *Homo sapiens*.”

**D**omaradskij, a foremost expert on the plague germ, insists that despite advances in synthetic biology, the real bioweapons threats have not changed. In his view, they remain smallpox, anthrax and plague. Decades of work in the Soviet bioweapons system convinced Domaradskij that these agents are unparalleled, supremely dangerous pathogens. Anthrax and plague are extraordinarily lethal bacteria. Untreated inhalational anthrax and pneumonic plague kill close to 100% of their victims. Except for rabies and untreated HIV, no other pathogens are as deadly. Anthrax also is amazingly durable in the external environment. When buried in soil, its spores remain viable and infectious for decades, perhaps even centuries. Anthrax contamination can make a large area virtually uninhabitable.

From a bioterrorist’s point of view, it’s highly desirable for a disease to spread quickly. Contagion is a chief virtue of smallpox, which kills an estimated 30% of those infected and leaves many of the rest scarred or blinded. Officially deemed eradicated from nature in 1979, smallpox is a highly adapted human pathogen; plague (one form of which is contagious) and anthrax are both animal diseases that are deadly to humans.

If terrorists wanted to go beyond these three, there are plenty of other less formidable but still dangerous natural germs—tularemia, brucellosis, Q fever, glanders and the reconstituted 1918 flu virus, among others. All are so-called select agents, kept under tight constraints by the government to limit possible misuse, accidental or otherwise, by researchers with access to them.

But some scientists contend that the whole idea of a long select-agent list, with the attendant tortuous restrictions, background checks and reams of paperwork, is rendered meaningless by the threat of synthetic biology. What’s the point of curbing access to particular agents if you can just produce endless new forms of life in the laboratory?

Roger Brent, president and research director of the Molecular Science Institute, an independent, nonprofit research organization in Berkeley, thinks we face a future of numberless synthetic microbes, the products of what he terms a revolution in biological competence. “It’s inevitable that somebody will deploy an infectious organism that has been hacked,” Brent says. He points out that scientists already routinely use altered agents—viruses as vectors for vaccines, for example. Like a designer pathogen, Brent says, vaccine vector viruses are constructed to infect human tissue and replicate, and he doesn’t see any qualitative difference between a virus altered to vaccinate a patient and a bug created to make people sick.

Steven Block, a biophysicist and biodefense expert at Stanford University, also sees a threat from synthetic agents. “Nature is creating pathogens all the time,” Block says. “If someone is bent on destruction, it should become possible to synthesize whole new genes, to create chimeras through mix and match. These germs don’t have to work at all well. They don’t even have to be very successful in the wild. They just have to kill a lot of people.”

Yet so far, there have been only a few instances in which altered microbes have been produced, and none gives much support to the idea that such an approach would be a

35

Number of years ago that a treaty was signed by more than 100 countries to ban biological weapons

350

Number of U.S. labs authorized by the CDC to work with select agents (biological agents or toxins that have the potential to pose a severe threat to public health and safety) for research purposes

150

Approximate dollar amount, in millions, spent on U.S. biodefense in 1997

7.5

Approximate dollar amount, in billions, spent on U.S. biodefense in 2005



## Engineering antibiotic resistance requires considerable scientific sophistication. It's hard to imagine anyone making plague germs in a cave in Waziristan.

bioterrorist's dream. For example, there's evidence that the Soviet Union's bioweapons program created antibiotic-resistant strains of the plague germ *Yersinia pestis*. Scientists did this by adding genetic information conferring antibiotic resistance from *E. coli*, a distant relative of *Yersinia pestis*, to the plague germ, via tiny rings of DNA called plasmids. But Domaradskij, who originated these engineered plague strains, points out that altering bacteria even in this straightforward way is problematic: The plasmid can fall out, and the germ will lose its resistance. Moreover, though quite basic as genetic modifications go, engineering antibiotic resistance requires considerable scientific sophistication. It's hard to imagine anyone making antibiotic-resistant plague germs in a cave in Waziristan.

Another data point: An Australian team reported in 2001 that while it was trying to develop fertility control for mice, it introduced into mousepox virus DNA a gene that codes for

interleukin 4 (IL-4), a protein that stimulates the immune system. Sixty percent of mice that got the gene died, including those that had been vaccinated against mousepox or were normally immune. The experiment caused an uproar, primarily because mousepox is related to smallpox, and experts feared introducing IL-4 into the smallpox genome could likewise override human immunity.

Strict World Health Organization oversight on all smallpox work ensures that no American scientists will be "heating up" the closely restricted smallpox virus to see whether IL-4 might make it deadlier. But Mark Buller of Saint Louis University replicated the Australian mousepox experiment with a few enhancements of his own, and his modified IL-4 virus achieved a 100% kill rate. When he tried to get his chimeric mousepox to spread from mouse to mouse, however, Buller found that the infected mice generally died too quickly to pass on the disease. And although mousepox normally spreads

“When you mix and match genes, you tend to lose some function,” says Brown, who doubts that hacked germs will be able to compete with natural disease agents.

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quite easily, the few IL-4 mice that lived long enough to infect others seemed to transmit the disease less effectively than do mice infected with naturally occurring mousepox.

All of that suggests a serious flaw in any plan to use IL-4 to make smallpox a more efficient killer. Engineered smallpox might improve on the typical 30% fatality rate of natural smallpox strains, but it likely wouldn't cause an epidemic—and if not reliably contagious, it would be no better as a bioterror agent than, say, anthrax.

There are two other potentially relevant pieces of research. In 2002, Eckard Wimmer and his colleagues at the State University of New York at Stony Brook synthesized a poliovirus strain by using a documented poliovirus sequence—but they were only recreating an infectious virus that still exists in the wild, rather than developing any kind of artificial germ. Perhaps more disturbing was the experiment published in 1997 by two Russian scientists who added hemolytic genes from a related bacterium, *Bacillus cereus*, to *Bacillus anthracis*, the anthrax germ. These genes caused blood cells to break open, or lyse, and the Russian scientists reported that the introduced genes also allowed the altered anthrax germ to evade vaccination. But so far, this work has not been replicated, so it's impossible to know whether vaccine-resistant anthrax represents a genuine threat.

**B**ased on this handful of experiments, there seems little proof that engineered bioterror agents can work better than natural pathogens. According to the Molecular Science Institute's Brent, however, the science of synthetic biology is still in its infancy, and he cites viruses that are used as vaccine vectors and bacteria created to make plastics as examples of synthetic life forms that can survive and multiply.

Yet others don't consider such examples

as having much to do with the prospect of creating disease agents. “Vaccine viruses are great for vectoring, but they are not pathogens,” says Earl Brown of the University of Ottawa, who studies virulence genes in viruses. “Vaccine viruses are attenuated and neutered.” Brown also points out that in his lab, when a gene is added to viruses, it generally weakens them, because the gene isn't in its normal context. “When you mix and match genes, you tend to lose some replicative and growth function,” says Brown, who doubts that extensively hacked germs will be able to compete with highly evolved, effective natural disease agents. “Natural pathogens that have the ability to be weapons have evolved to deliver their toxins and survive,” says geneticist and biodefense expert Roy Curtiss of Arizona State University. “Changing the venue of these toxins means they may not do any harm.”

Still, because it's impossible to know for sure what kind of bioterror threat we may face, there's an obvious appeal to the idea of improving our immune system so that it could shrug off any attack. If you could rev up non-specific immunity, which releases a torrent of immune chemicals—interferons, interleukins and other cytokines—you could wash out new threats immediately, without waiting for the body to produce antibodies. Yet the immune system, like natural pathogens, has been finely tuned by natural selection, and tinkering with it could have devastating results.

One problem is that heightening innate immunity might itself cause disease. Many pathogens manipulate the human immune system for their benefit, weakening or killing their host by generating an overproduction of innate immune chemicals. In recent research on the 1918 flu virus, recreated in several laboratories, the virus killed mice by generating a toxic storm of cytokines. Several current diseases, too, kill by sparking overreactions of the immune system. For example, a liver

41

Number of select agents and toxins, as defined by the U.S. Department of Health & Human Services

60

Percentage of mice killed in one experiment after they were infected with bioengineered mousepox

100

Percentage of mice killed in a later experiment with a modified mousepox whose swift deadliness limited its spread beyond the directly infected population

disease, primary biliary cirrhosis, can be triggered by repeated bladder infections with gram-negative bacteria. Multiple sclerosis, another autoimmune disease, is also thought to result from the overreaction of the innate immune system to microbial assault.

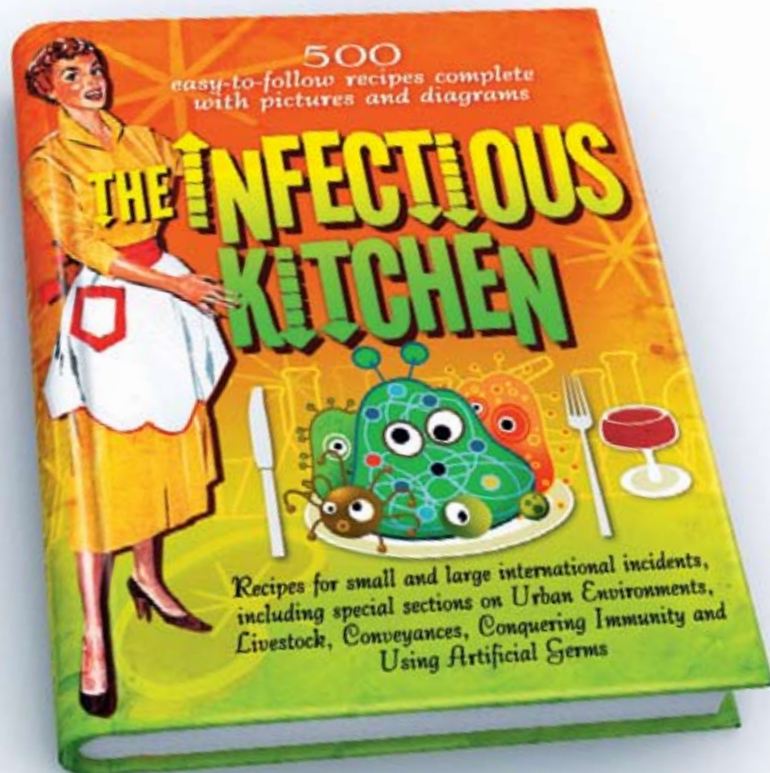
Then there's the argument that if augmenting innate immunity were the ticket to fighting new pathogens, natural selection would already have achieved it. Something so fundamental to our existence as the ability to fight off pathogens is likely as enhanced as it could be, and any tweaking could destroy the delicate balance between under- and overreaction of innate immunity. Moreover, if innate immunity were the key to fighting infection, why did we evolve an entire system of humoral immunity, of antibody production?

There are, however, specific instances in which delicate, precise intervention to improve innate immunity may work well. Carolyn Hovde-Bohach of Idaho University has done intriguing research with the plague germ, *Yersinia pestis*, which has the ability to shut off innate immunity and "convince" a host it isn't under attack. After inactivating the body's normal inflammatory response, the cytokine production system, *Yersinia pestis* uses something called the type 3 protein injection system to stick tiny needles into immune-killer cells and destroy them.

Hovde-Bohach's work interrupts this deadly message from pathogen to host. Using a nontoxic mimetic of a harmful compound known as lipid A, Hovde-Bohach managed to save 40% of her test mice. When she added gentamicin, a common antibiotic, to her compound, she saved 85%. Without this protection, plague would have killed all the mice. The lipid A mimetic binds to human immune cell receptors of a class known as toll-like receptor 4, stimulating production of the inflammatory compounds *Yersinia pestis* has evolved to turn off. The strategy works directly around the bacterial tactic that allows *Yersinia pestis* to silence innate immunity.

Still, Hovde-Bohach's approach is far from a simple, universal fix. "We aren't just ratcheting up the innate immune response—and this isn't going to be a panacea for everything," she says, noting that the lipid A mimetic did nothing, for example, to save the test mice from tularemia infection.

So, though enhancing innate immunity may work in certain carefully calibrated ways, for particular agents that have evolved the ability to turn off critical aspects of that system, it's unlikely to be the magic bullet some proponents seem to think it could be. For the foreseeable future, at least, it seems



likely the bioterror threat will come from finely honed and deadly natural pathogens, perhaps with added antibiotic resistance, rather than from engineered synthetic agents. "The biggest bang for our buck in public health and bioterror countermeasures are still broad-spectrum drugs, antibiotics and antivirals," asserts microbiologist Richard Ebright of the Waksman Institute of Rutgers University. "It's not betting on Captain Kirk and Mr. Spock." ■

## → DOSSIER

1. *Germs: Biological Weapons and America's Secret War*, by Judith Miller, Stephen Engelberg and William Broad (Simon & Schuster, 2001). Its publication, which coincided with September 11, 2001, propelled a book intended for a relatively small audience into an instant international bestseller. The book remains a useful introduction to biological weapons, clearly explaining the threat and its dimensions.
2. *Unit 731: Japan's Secret Biological Warfare in World War II*, by Peter Williams and David Wallace (Simon & Schuster, 1989). This responsible and deeply horrifying book describes the largest-scale use of biological weapons in history, in which the Japanese military managed to get weapons to work despite primitive technology.
3. *Scourge: The Once and Future Threat of Smallpox*, by Jonathan Tucker (Atlantic Monthly Press, 2001). Tucker, an expert in biological and chemical warfare, presents a lucid account of the struggle between those who want to destroy the remaining virus stocks and those who want to preserve them to develop countermeasures against an attack.