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## Blue Light, Red Light

By Jeffrey Klineman December 2003/January 2004

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It's a Frankenstein-monster-type conceit, but biologist Todd H. Rider '91, SM '91, SM '94, PhD '95, has never shied away from the idea that he might be a mad scientist. In fact, he embraces it. His role models have been the wild-haired scientists of the movies, the ones with renegade aspirations and a reluctance to stand on methodological ceremony. He even borrows their lines. Before one experiment that required him to flip a switch, he shouted, "Give my creation life!" "I think I startled a lot of people," he says now.

The 35-year-old Arkansas native specializes in hunting down something that many people find more terrifying than Frankenstein's monster: deadly germs and viruses.

Rider and his team from Lincoln Laboratory received national attention in July for their work on a novel system for detecting potentially deadly pathogens, such as anthrax or Legionnaire's disease, that have long been feared in their own right but have become even more frightening for their possible use in biological weapons. Known as "cellular analysis and notification of antigen risks and yields," or Canary for short, the detector Rider developed uses white blood cells—the body's first line of defense against disease—to test substances for the presence of certain pathogens.

Unlike current detection systems that use DNA-amplifying reactions that can take an hour or more, Rider's technique provides information in seconds. With the public rubbed raw over the threat of biological warfare and bioterrorism, and cities quarantined due to fast-spreading viruses like SARS, the detector's potential to provide on-the-spot readings could lead to a variety of "first-response" uses, from reading mucus supplied by a mysteriously ill emergency-room visitor to testing white powder shortly after it flies out of an envelope. Rider also believes the detector can be adapted to pull particles from the air, to determine if biological weapons have been released on the field of battle.

### Tweaking a Natural Reaction

Nature, Rider says, already demonstrates that white blood cells detect pathogens. When the antibodies on such a cell bind to a virus or bacterium, they trigger a calcium signal. That causes the cell to go "on the warpath" and combat the invaders. Rider believed that if he could find a simple way to detect the calcium signal, he could develop a pathogen sensor.

"It's clever," says Dr. David Relman, a Stanford University professor who studies pathogen detection. "I love the idea of coopting a biological system that's already hard-wired for rapid response."

But when Rider first started working on the idea, soon after coming to Lincoln Lab in 1997, people were not so receptive. "A lot of people at Lincoln Lab hadn't taken it very seriously," he says. On top of that, Lincoln Lab had no biology laboratory. So the youthful scientist-28 at the time, with just a year in the "real world" after nine years at MIT—was forced to find bench space on campus until he could engineer a white blood cell that would reveal the calcium reaction.

Rider found that space in the lab of biology professor Jianzhu Chen. Chen, who researches immunology, also helped Rider secure early funding from the cloak-and-dagger crowd that has gone on to bankroll much of Canary's development.

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The U.S. Defense Advanced Research Projects Agency (DARPA), a U.S.-military-affiliated source of funding for scientific projects, was interested in pathogen detection, and Rider's team went down to Washington to make what was ultimately a successful presentation.

With adequate resources behind him, Rider could begin investigating a protein that he had long considered promising: aequorin, which is derived from the glowing jellyfish *Aequaria victoria* and has a well-documented ability to produce light in response to calcium. Rider used electricity to blow holes in white blood cells that had been extracted from a mouse, then infused those cells with the jellyfish's genetic instructions for the manufacture of aequorin. The theory was that when antibodies on the cells' surfaces locked onto their pathogens, they would trigger a calcium signal, which would activate the aequorin and make the cells glow blue. That blue light, while not visible to the naked eye, could be measured by a luminometer, which would send the results to a computer, which would generate a readout.

By mid-1998, Rider had programmed the cells to emit light in response to phosphorylcholine-ovalbumin, a safe chemical stand-in for viruses and bacteria. But the principle was the same, and this initial success lent the concept the credibility Rider needed to continue.

He and his team then moved back into Lincoln Lab and began "shopping" for pathogen antibodies, drawing on the panoply of disease-causing bacteria and viruses studied in other labs. After much trial and error, biologist Martha Petrovick developed a new version of a genetic-engineering tool known as a "DNA vector" that allowed Rider and his team to produce white blood cells with antibodies on their surfaces that responded to specific pathogens. These included anthrax, bubonic plague, the pathogenic strain of *E. coli*, chlamydia, smallpox, and a half-dozen other viruses and bacteria feared for their potentially negative effects on public health or use in bioterror weapons.

But the team still faced one crucial problem: the white blood cells and pathogens had trouble locating each other during the testing. The reaction was taking too long and the signal from the luminometer was too low. "We had to come up with some way to make the reaction faster and more apparent," says James Harper, PhD '98, the Lincoln Lab staffer who headed hardware engineering for Canary.

The solution was to use a centrifuge to spin a sample's cellular material toward the bottom of its container, add the white blood cells, and spin them down on top of the sample, forcing the two into close contact with each other. What had taken minutes now took seconds.

"In a lot of these systems, the limitation is 'mass transport,'" says Duane Lindner '72, deputy director for chemistry and biology programs at Sandia National Laboratories in Livermore, CA, which is developing its own pathogen detection systems. "It takes a lot of time for these big things to get on top of each other. Their work has highlighted just how fast the systems can be."

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### Fast and Simple...Maybe?

It's that speed that has both the military and private companies interested in the potential of the new detector. Even before the terrorist attacks of Sept. 11, 2001, the military had been interested in something that could analyze the air for biological weapons. Public-health agencies were also eager for something that could quickly check a shipment of food for E. coli. Recent concerns about mysterious, possibly anthrax-laden "white powders" sent through the U.S. mail and the fear of fast-spreading viruses, like SARS, have made emergency responders and clinicians as interested in pathogen detection as the military.

The technology used in Canary is close to being adaptable to many of those uses already, say its developers, who believe that the current prototype of a centrifuge, luminometer, and computer could be included in a field testing kit about the size of a suitcase, at a hardware cost of somewhere between \$7,000 and \$10,000.

"We're intentionally designing it so it will be very easy to use," Rider says. "Some of the current systems use quite a lot of training. We want it usable for army soldiers, medical personnel, emergency responders. You'll simply add the sample to the cell and see if it glows."

Rider is also developing what he playfully terms a "giant snorfler-thingy" to suck particles from the air in sensitive locations and test them. Detector cells used in the device can now survive for up to two weeks before they need to be exchanged. Although Rider calls the cells "surprisingly hardy," others say that they aren't rugged enough, particularly for one major civil-defense goal, a system that will autonomously collect samples from the air and test them for pathogens.

Still others believe his process is overmatched by the competition. DNA-based detection technologies, while not as fast as Canary, will eventually be able to test for a broad array of pathogens simultaneously, and even reveal the genetic characteristics of those organisms that cannot be readily identified. Canary has "too much focus on specific organisms," says Calvin Chue, a researcher with the Center for Civilian Biodefense Strategies at Johns Hopkins. "If I gave you an unknown pathogen, you would have to run all of your specific 'rapid' tests. Since this could encompass a dozen or more runs, the analysis is no longer so rapid. Even at the completion of your run...you might still have an unknown on your hands, and you cannot assume it is benign."

However, Rider hopes that in the future Canary will be capable of doing any sort of analysis that competing DNA-based technologies can do. In the meantime, Harper, for one, believes that the benefits of being able to take a quick reading are apparent.

"DNA is good for looking for the needle in the haystack when you don't know what the needle is," Harper says. "But in terms of sensitivity and speed, it doesn't appear that there's anything that can match Canary. It has the potential to, at bedside, determine whether someone has a bacterial or viral infection, before they even get up to leave [for] the hospital. It's not good for looking at what's happening in a thousand different genes, but it's good at giving you the fastest and most sensitive answer."

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Indeed, while much of DARPA's early motivation for funding the project came from its interest in using the reactive properties of different cells to determine the characteristics of unknown pathogens, rather than testing samples for those that are already known, the agency remains pleased with the technology. "DARPA is one of those places where you're not confined by one theme," says Alan Rudolph, the scientist overseeing the project for the agency.

That's a good thing for Rider, who has had difficulty remaining confined to a single theme in academic or research settings. His doctoral work, in fact, involved fusion reactors, but he migrated through several minors-including biomedicine-while completing it. He turned to microbiology after his dissertation demonstrated problems with various fusion reactors-making him, he admits, a bit unpopular in the reactor business.

"I upset some people, so I decided to move into a different field," Rider says. "I was lucky to have a degree in biomedicine."

Dr. Frankenstein might agree.

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