



in pursuit of pathogens

— WILLIAM R. JACOBS —

TRAINED AS A MATHEMATICIAN, BILL JACOBS SAYS THAT HE LEARNS BIOLOGY ON A “NEED-TO KNOW-BASIS,” YET HIS NEED TO KNOW IS PRODIGIOUS. A PROFESSOR AT THE ALBERT EINSTEIN SCHOOL OF MEDICINE, JACOBS HAS SPENT MORE THAN 20 YEARS DEVELOPING NOVEL GENETIC TOOLS TO UNRAVEL THE DEFENSES OF MYCOBACTERIA, WHICH CAUSE TUBERCULOSIS AND LEPROSY. WE SPOKE WITH JACOBS IN WASHINGTON, D.C., AND MERIDA, MEXICO.

Mycobacterium tuberculosis has evolved to be the world's most successful pathogen. If you wanted to be a pathogen, I would argue that the strategy of just going in and killing your host is not a good one. It's not good to be like smallpox, which kills most mammalian hosts. You'd rather be like *M. tuberculosis* and infect everyone in the population, causing disease only when the patient is dying and you know it's time to get out. Prior to the HIV epidemic, the largest number of TB cases in the U.S. were in old folks homes where people had been infected with TB 50 years earlier, and it was controlled by their immune system. As a patient's immune system waned, *M. tuberculosis* caused disease in the lungs so it could be spread. In Africa and in Asia, where most everybody is infected with TB, the

way that people first learn they're infected with HIV is when they become immunosuppressed and get TB.

M. tuberculosis has evolved functions to persist in the face of innate and adaptive immunity as well as drugs. You can see this persistence phenotype very clearly if you look at its growth kinetics in a mouse. TB grows exponentially for the first two and a half weeks until you get the onset of adaptive immunity. Then TB enters a hunkered-down state where it's resistant to the killing mechanisms of the immune system. This is a typical biological reaction to an adverse condition—it's not any different from the trees in my backyard that are able to survive winter. We

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have to figure out how to kill the hunkered-down bacteria, to tear apart how TB evades the immune system.

To prove that a phenotype—a property like virulence or drug resistance—is caused by a specific genotype, you have to isolate a mutant, clone a genotype, and transfer it. I call this Koch's corollary, after Robert Koch, the man who discovered the cause of TB in 1882. Yet, for years we couldn't fulfill Koch's corollary. We didn't know the mechanism of attenuation for BCG—a live tuberculosis vaccine developed by two French scientists that has been given to half the world's population—until more than 70 years after it was introduced. We used drugs like isoniazid for more than 40 years without knowing their targets of action. We did not know the genetic basis for any TB virulence factor.

Over the years, my lab, in collaboration with Barry Bloom, has developed a fairly complete set of genetic tools to do genetics in mycobacteria and complete Koch's corollary. Every time I have had a problem overcoming a genetic obstacle, I went to mycobacteriophages—viruses that infect bacteria—to find solutions. In fact, our first big breakthrough came with the introduction of foreign genes into mycobacteria using chimeric phage vectors that I designed. Using a system based on this original chimeric vector, we can now systematically knock out every gene of *M. tuberculosis*. Recently, in collaboration with Graham Hatfull, an HHMI professor at the University of Pittsburgh, and David Fidock at Albert Einstein, we have developed an efficient complementation system for *Plasmodium falciparum*, the parasite that causes malaria, using genes from Bxb1 (alias the Bronx Bomber), a phage I isolated from my backyard in the Bronx.

I have always been interested in problems that affect the developing world. I went to Barry Bloom's lab because he wanted to make a recombinant BCG as a vaccine vector that could maybe protect against TB, malaria, and other diseases affecting the developing world. We have gone back now and remade BCG from virulent *M. tuberculosis* and *M. bovis*. Derivatives of these strains have shown promise in mice against *M. tuberculosis*. To get it into the clinic, we're going to have to prove that they

are safe in humans. Toward that goal, we have demonstrated safety in guinea pigs, immunocompromised mice, and recently in monkeys. Further studies are under way.

My life changed the first day I took a plane to Madras, India, on my way to visit a leper colony. I saw masses of humanity like I had never seen before in the U.S. I wish that I could take President Bush and his advisers with me to a leper colony because what we need in the U.S. is to be exposed to the rest of the world's problems. After all, 75 percent of the world's population is threatened by infectious diseases. ■

-Interview by Avice Meehan-