

# taming tb

Weill Cornell immunologists fight one of the world's most intractable diseases.

**C**all tuberculosis a killer. Call it a scourge on the developing world. But don't call it a "reemerging" disease. "I find that offensive and narrow-minded," says immunologist Dr. Carl Nathan, "because it is the single leading cause of death from bacterial infection worldwide—and has been for time out of mind."

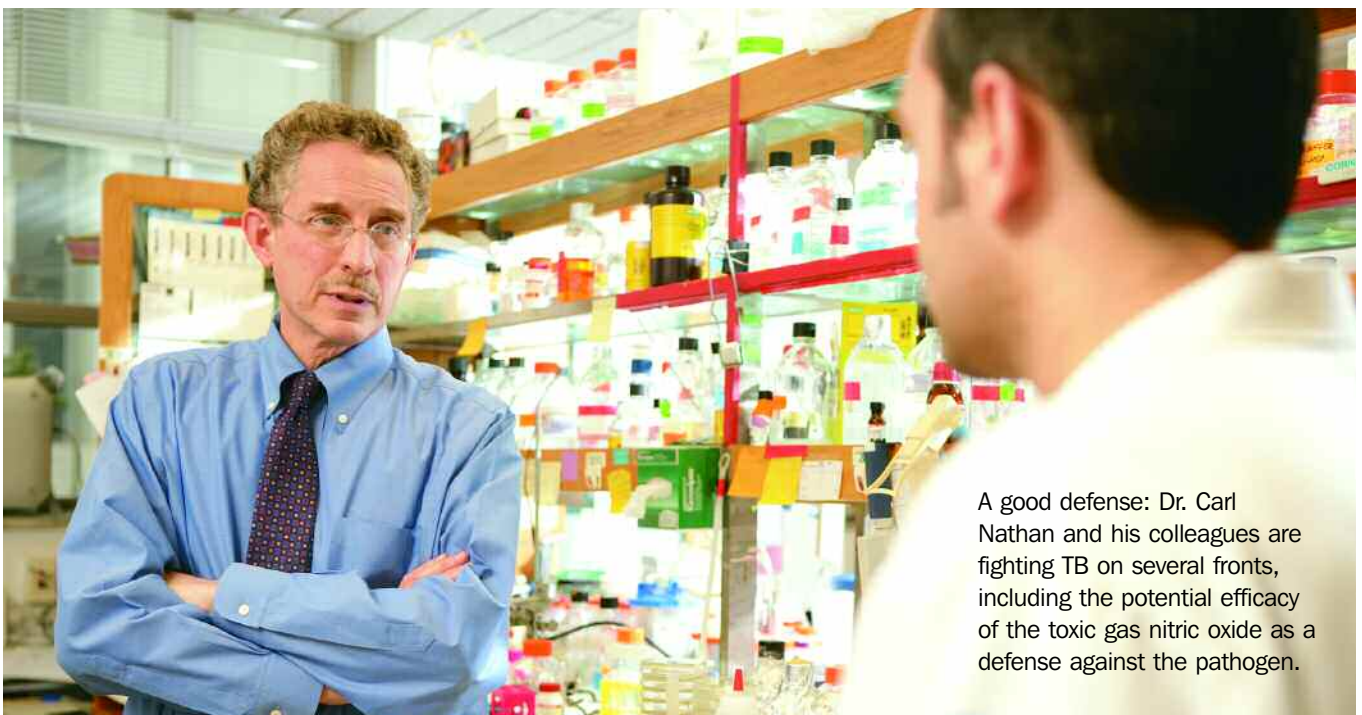
Although Americans may occasionally be alarmed by news stories on drug-resistant TB flourishing in prisons and other enclosed populations—and the disease recently made headlines with the Gates and Buffett foundations' multi-billion-dollar commitment to combat it, along with malaria and HIV—for the most part, it has lapsed from the first-world radar. "TB stopped being a major public health problem in the areas of the world that supported pharmacological research, but it never stopped being a problem in other areas," Nathan says. "It's the leading cause of death in HIV-infected people, and the leading cause of death in women in the middle years of life around the world. It's a huge problem."

Nathan, chairman of the Department of Microbiology and

Immunology, has many research interests, including the potential for the toxic gas nitric oxide (produced by inducible nitric oxide synthase, or iNOS) to aggravate Alzheimer's disease, and the possibility of harnessing the power of the immune system to fight cancer. But battling tuberculosis is an abiding passion. "What fascinated me about this particular pathogen is that it's one of a select group that has no natural host other than humans, and it has the capacity to kill," Nathan says. "In fact, the untreated infection has a mortality rate of 50 percent in people with normal immune systems. And it's extremely prevalent: one-third of the people in the world are infected subclinically, meaning they have no active disease but are infected for life."

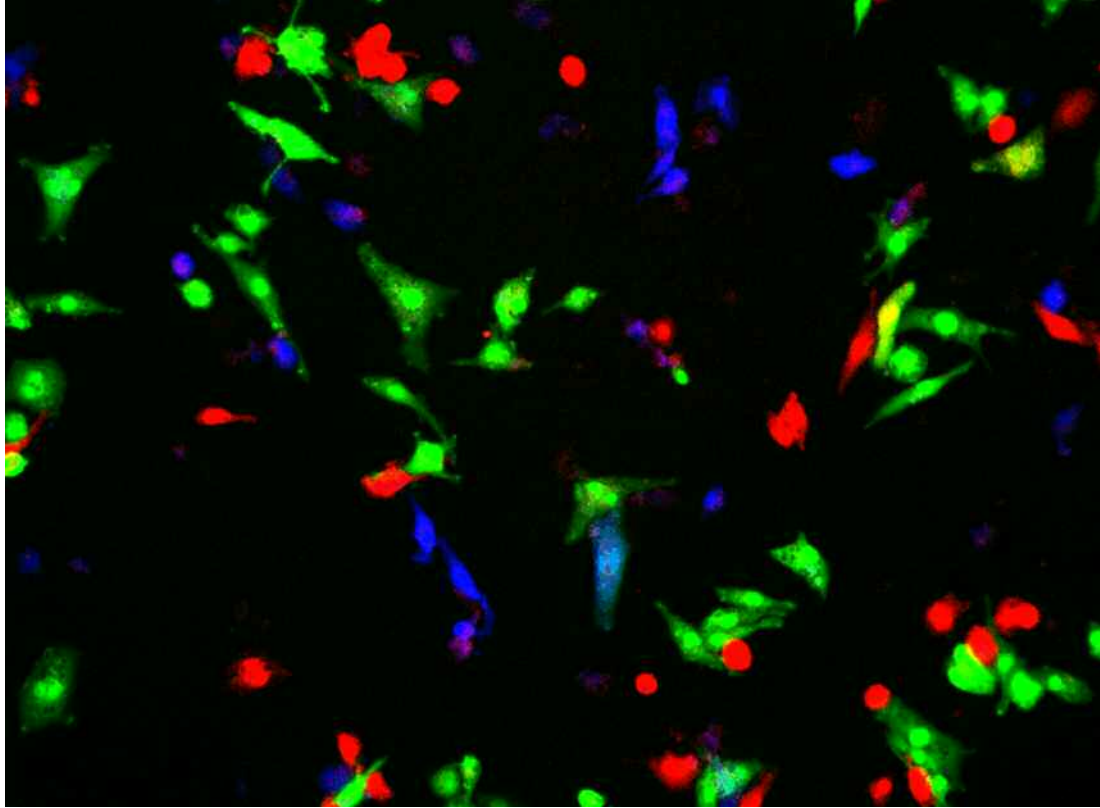
After medical school, Nathan trained in both internal medicine and oncology, and for years he was active in the field of tumor immunology. The fact that *Mycobacterium tuberculosis* (Mtb)

ABBOTT



A good defense: Dr. Carl Nathan and his colleagues are fighting TB on several fronts, including the potential efficacy of the toxic gas nitric oxide as a defense against the pathogen.

Down to the DNA: Nathan, with PhD candidate Aimee Beaulieu and former postdoc Marianne Imhof, has taken a genetic approach to the immunology of tuberculosis. The macrophage cells seen in this micrograph have been engineered to express red, green, or blue fluorescent proteins, corresponding to three different host genes whose expression is stimulated by a mutant form of *Mycobacterium tuberculosis*. Ultimately, Nathan's lab hopes to find a combination of mutations that could lead to a vaccine.



PROVIDED BY DR. CARL NATHAN

often lives for decades as a foreign genome in the human body, he notes, is “reminiscent of the cancer problem, where a genome that once was identical to our own becomes slightly different—and then persists for years, in many cases, before breaking forth and causing disease.” It’s this persistent state—where Mtb lurks in a relatively inaccessible cellular structure called a granuloma—that researchers find both fascinating and vexing: although the immune system temporarily forces the bacterium into a non-replicating state, it doesn’t sterilize it. Nathan’s research focuses on the immune factors that keep TB at bay—and the potential for using them to defeat the disease.

One possible weapon in the fight against TB is iNOS; Nathan’s lab was the first to recognize it as a distinct enzyme, then cloned it and knocked it out in mice. The enzyme appears to play a role in the biology of most living organisms—and its production is a major host defense against TB. Breaking down the products of iNOS, in turn, is a way in which tuberculosis withstands the immune system’s counterattack. “When the body tries to kill Mtb, it basically tries to oxidize it to death—and Mtb regulates a pathway to resist that oxidation,” says Christopher Lima, an associate professor of biochemistry and structural biology at Sloan-Kettering who regularly collaborates with Nathan. “It looks like there are unique enzymes in those pathways, and if we could develop a drug against them we might be able to block the ability of tuberculosis to survive in our immune system.”

In the developing world, conquering TB is a matter of life and death. In 2006, notes Nathan’s colleague Sabine Ehrhart, the first strain of Mtb resistant to all current treatments emerged in South Africa. “If you open up Google News, you can read about cases of extremely drug-resistant tuberculosis (XDR-TB) that affected more than a hundred people and killed eighty-one of them within the last few months,” says Ehrhart, an associate professor of microbiology and immunology. “And it’s not just multi-drug resistant—it resists all first- and second-line drugs and leaves patients virtually untreatable. It’s really terrible.”

Tuberculosis treatments have long had their limitations. For one thing, even in the best-case scenario, a complete course requires patients to take antibiotics for a minimum of six months. “Very few people comply with that,” Ehrhart says. “So if you had a drug that could work in six weeks, it would be fantastic. It would change the whole problem.”

But the search for a short-term, effective treatment requires a switch from conventional pharmaceutical research—and Nathan’s work has found much-needed support with the recent gift of \$7.25 million by Abby and Howard Milstein for the creation of a Chemistry Core Facility and a Program in Chemical Biology at the Medical College. Nathan is convinced that this type of philanthropy, outside of the pharmaceutical industry, is key to developing drugs with the ability to target TB.

Typically, Nathan notes, potential drug compounds are tested under optimal growth conditions, where the bacterium is replicating quickly. That may be the most efficient way of running an experiment, but in the case of diseases like TB it has a serious drawback. “The question you’re asking isn’t, ‘What kills Mtb?’ ” Nathan says. “It’s, ‘What keeps Mtb from growing under conditions where it otherwise can grow at its fastest possible rate?’ ”

Not only are those conditions vastly different from what exists in the body—where Mtb lives inside macrophages whose environment is quite harsh, including a deficiency of oxygen and an abundance of acid—they’re the opposite of what’s going on in the subclinical patient, where Mtb is not actively replicating. And while those people may not be in imminent danger of death, from a public health standpoint their cases are no less urgent. “Five to 10 percent of them will eventually develop active disease—and then before they are successfully treated or die, whichever happens first, it’s estimated that they each will infect fifteen to twenty additional people a year,” Nathan says. “So you never catch up. The current approach to TB drug treatment just can’t work to reduce the proportion of the population that’s infected.”

— Beth Saulnier