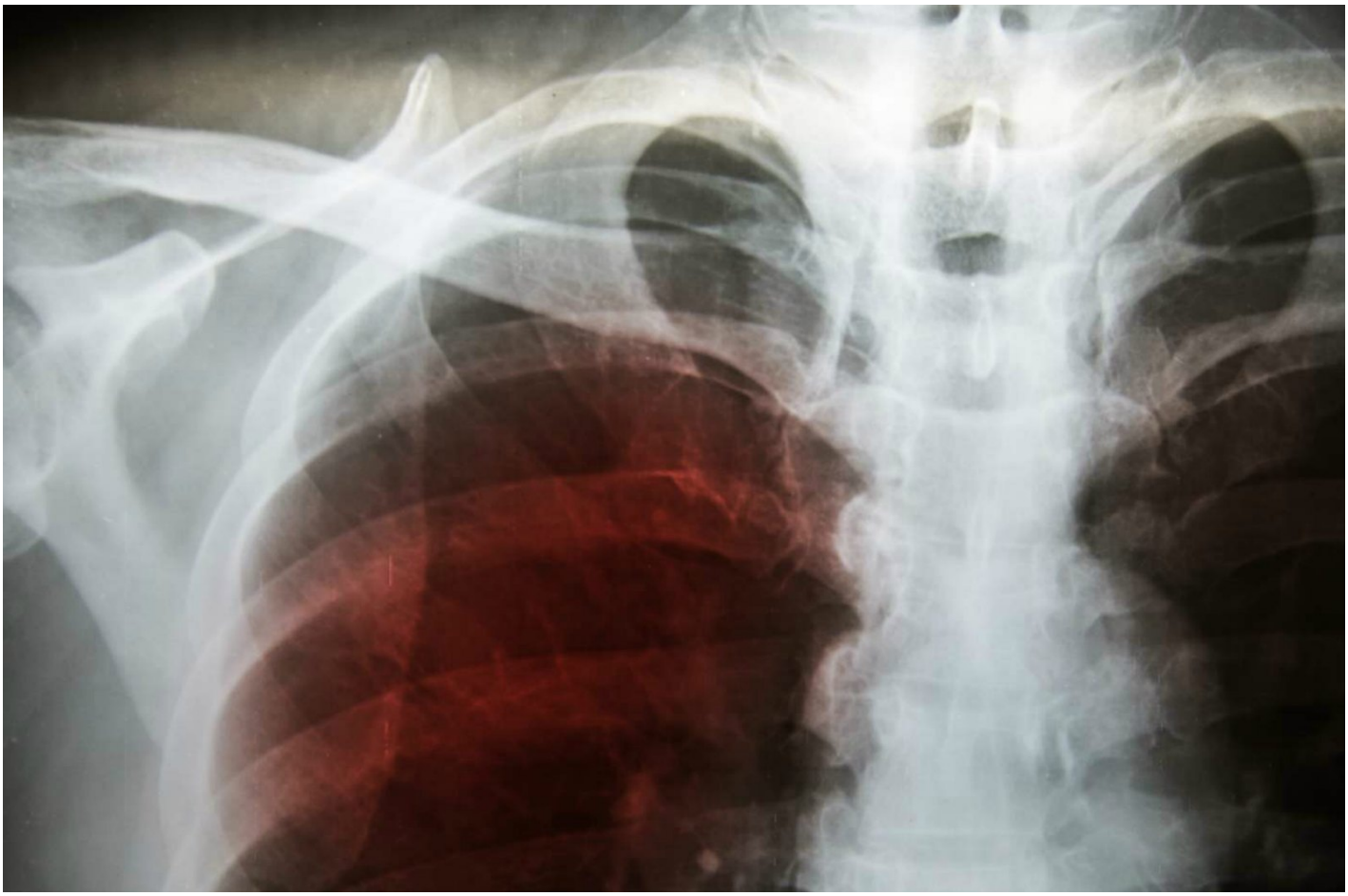
TB: Designing The Perfect Vaccine

Oregon Health
Oregon Health & Science University



At least from a bacterial survival standpoint, tuberculosis is the perfectly designed bug. Mycobacterium tuberculosis infiltrates the cell and then lurks within, identifiable by skin test, but not causing any symptoms.

"People estimate that one-third of the world has at least been exposed to tuberculosis," says David Lewinsohn, M.D., Ph.D., associate professor in pulmonary and critical care medicine at Oregon Health & Science University and Portland VA Medical Center. "We think that many of them are latently infected. So they have the bacteria and the bacteria is kind of there, but not causing any trouble. And 90-plus percent of the time that works just fine-people don't get sick." When the disease does become active, though, tuberculosis can inflict significant harm-to the infected individual and others. Symptoms include chest pain, hemoptysis (coughing up blood), fever and weight loss. Someone with active disease, who goes untreated, can unknowingly infect 10 to 15 people annually by coughing, sneezing, or even talking, according to the World Health Organization (WHO).

In 2006 alone, 9.2 million people worldwide became ill and 1.7 million people died, according to WHO data. And some

regions of the developing world have been particularly devastated by the bacterial infection.

> *Five countries in Africa and Asia-India, China, Indonesia, South Africa and Nigeria-rank among the top five countries worldwide, in their total number of tuberculosis cases.*

The highest rate of new cases occurs in Africa, with nearly 350 cases per 100,000 population. Residents in Africa also suffer from the highest mortality rate compared with other regions of the world.

While medications typically can treat the disease, multi-drug resistant (MDR) strains are of increasing concern. An estimated 0.5 million cases of MDR tuberculosis worldwide were identified in 2007 alone and vaccine protection remains limited at best. The Bacille Calmette-Guerin (BCG) vaccine provides limited protection, particularly among adults, who are most likely to transmit the infectious bacteria.

The vaccine isn't typically recommended in the United States because it can interfere with skin testing and because TB is primarily controlled by active surveillance and drug treatment. The best solution, in short, is a better vaccine, one that mimics the immune system's natural ability to wall off the life-threatening bacterium. Solving that immune system riddle has become a driving passion for Lewinsohn and his research partner and wife, Deborah Lewinsohn, M.D., a pediatric infectious disease specialist and OHSU associate professor at Dorenbecher Children's Hospital.

"We think the TB is kind of hidden within this [cellular] structure," David Lewinsohn says. "The TB is not dead-it's there. And the immune system has got it contained. ...If we really understood how the human immune-response contained tuberculosis, then that would be our model for a better vaccine."

Fighting TB—Progress to Date

Along with the inherent cellular complexity, researchers describe a number of other hurdles involved with designing a tuberculosis vaccine. Since the disease develops slowly, it's difficult to assess the relative effectiveness of any given vaccine prototype. Plus, triggering a broad population-wide immune response is complicated by the natural variability in individuals' immune responses. "What your immune system will recognize is determined by your genetic makeup," says John Fulkerson, Ph.D., head of vaccine discovery at Aeras Global TB Vaccine Foundation, (Areas) a not-for- profit organization.

In tackling this issue, the Lewinsohns have applied more than 15 years in infectious disease research, with a particular interest in immune responses. David Lewinsohn's work related to tuberculosis dates back more than a decade. Deborah Lewinsohn, who initially focused more on HIV, started working more closely on tuberculosis once the pair joined the Oregon Health & Science University (OHSU) in the late 1990s.

Traditionally, tuberculosis researchers have been particularly focused on one component of the immune system, CD4 T-cells, which are believed to play a crucial role in keeping active tuberculosis at bay. (The depletion of CD4 T-cells in those infected with HIV, for example, makes them more vulnerable to developing tuberculosis.) But the Lewinsohns have become increasingly intrigued by another immune system component, the CD8 T-cells, which they also believe to be influential. They describe those cells as uniquely designed to locate foreignseeming antigens hiding within a cell.

In 2004, the Lewinsohns received $4.6 million to further study the antigens, or proteins, believed to be influential in the onset of active tuberculosis. The substantial five-year contract was one of 14 contracts, totaling more than $73 million, awarded by the National Institute of Allergy and Infectious Diseases as part of its Large-Scale Antibody and T Cell Epitope Discovery Program. The program's goal is to stimulate breakthroughs in the understanding of epitopes-

small portions of antigens-that can lead to vaccine breakthroughs against infectious diseases, including bioterrorism targets. With the infusion of funding, the Lewinsohns have been delving further into identifying differences in antigens and epitopes between people with active tuberculosis and those with latent, or inactive, tuberculosis. Their goal: to identify specific cellular markers that the CD8 T-cells must recognize in order to swing into action against the lurking tuberculosis bacterium within.

Identifying Vaccine Components

By 2006, the Lewinsohns had identified a dozen antigens that showed sufficient promise, leading OHSU to file a provisional patent application. The following year, in late 2007, OHSU granted to Aeras an exclusive license to develop and market OHSU's antigen based vaccine for human vaccination against TB.

"From the initial discussions with Aeras, which occurred at the 2007 AUTM Annual Meeting, they were excited about the opportunity to in-license and work on these antigens," says Andrew Watson, Ph.D., Licensing Associate in OHSU's office of Technology & Research Collaborations. "The licensing of OHSU's technology was an important step towards the development of a broad-based vaccine containing multiple epitopes," says Rita Khanna, Ph.D., J.D., General Counsel at Aeras. Aeras, which is funded by the Bill & Melinda Gates Foundation, the Dutch government and others, was founded in 2003 with the goal of developing a more effective TB vaccine by the middle of the next decade. "OHSU is pleased to be a partner in helping achieve this objective and meeting the global need for low-cost or at-cost vaccines, especially in the developing world," says Watson.

Along with addressing a vital public health need, the market incentives are substantial. The potential payoff, depending upon the type of tuberculosis vaccine developed, ranges from $450 million to nearly $1 billion annually, according to a 2006 analysis by BIO Ventures for Global Health, a Washington, D.C.-based nonprofit organization. Aeras, based in Rockville, Md., has numerous vaccine development resources including partner clinical trial sites and a manufacturing plant. "We are functionally modeled like a pharma or a biotech, even though we are a non-profit," Fulkerson says. "Aeras can conduct more of the required vaccine development activities in-house than most big companies can." Aeras is pursuing a number of vaccine strategies, some of which are already in Phase I and II clinical trials. Aeras officials also have started working with the 12 antigens they've licensed from OHSU.

In the coming years, Aeras will evaluate vaccine constructs encoding the identified antigens in rodent models and then in non-human primates on the most promising candidates prior to initiating trials in humans. "Aeras is excited about using OHSU's antigens for developing an effective vaccine against TB," says Khanna.

Moving Forward

Collaboration is key to making the project succeed. Aeras' scientists and the Lewinsohns continue to work in partnership on the development of vaccine candidates involving these antigens. In addition, Aeras will continue to track the Lewinsohns' progress as they identify other intriguing antigens in the future. In discussing the significance of the Lewinsohns' research, Fulkerson circles back to their ability to isolate specific epitopes, or pieces of antigens. Fulkerson believes that identification of those epitopes-specifically the ones that help trigger an immune response in individuals of diverse genetic backgrounds-may open the door to a broader-spectrum vaccine, one that could contain a dozen or possibly more epitopes.

"What this will allow is the capacity to design a vaccine that contains, instead of a large antigen or several large antigens, one that will instead use portions of many different antigens that you know are recognized by people of many different backgrounds," Fulkerson says. "And by doing this you can make a vaccine that will drive a strong

immune response in people of any genetic makeup.

I think their approach to antigen discovery is absolutely spectacular. Some of the most interesting results we've seen have come out of the Lewinsohns' work." OHSU sees the relationship with Aeras as a promising opportunity for continued growth in the future. "Our hope is that as new antigens and/or antigenic epitopes are identified by the Lewinsohns, Aeras will continue to be an exceptional development partner," says Watson

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