TB vaccines tested in humans

Clinical development will require extensive partnerships.

BY DAVID FILMORE

For the first time in 60 years, new tuberculosis (TB) vaccines are in clinical development in the United States. Two different vaccine candidates entered Phase I trials in February in various centers around the country, joining one other candidate that is in Phase I studies in the United Kingdom and Africa.

"Funding for TB has only been lucrative enough to produce some significant findings since the early 1990s," says Christine Sizemore, the TB program officer at the National Institute of Allergy and Infectious Diseases (NIAID). Having vaccines that now can be evaluated in humans, she contends, is "a phenomenal step."

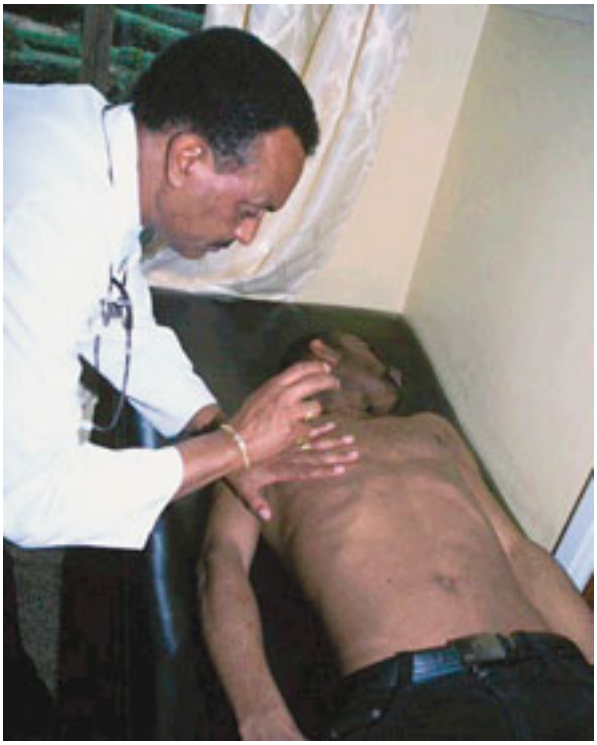
According to the World Health Organization (WHO), about 8 million people develop active TB infections each year, and, out of these, roughly 1.6 million die (not counting TB-related deaths in HIV–TB co-infected individuals).

Introduced over 80 years ago, the current vaccine, *Bacille Calmette-Guérin* (BCG), is a live attenuated organism closely related to *Mycobacterium tuberculosis*. It is administered throughout the world and is generally considered effective for protecting young children. But its efficacy in preventing pulmonary adult TB is inconsistent and, in certain environments, it has shown no protection at all.

"We have spent 12 years now trying to understand the disease and getting scientists interested in not just fundamental research but also research that leads to a product," Sizemore says.

This has been a major challenge, she points out, because TB doesn't represent a large market potential for the pharmaceutical industry. But as the ongoing trials highlight, some academic and not-for-profit institutions have become willing to take the extra step of product development, and several companies are getting involved as well.

The Aeras Global TB Vaccine Foundation, a nonprofit group with the sole goal of developing and distributing affordable new TB vaccines, is conducting one of the trials with the David Geffen School of Medicine at the University of California, Los Angeles. The Bill & Melinda Gates Foundation—which awarded Aeras $25 million in 1999 and, in February of this year, added another $82.9 million—is funding the trial.



A doctor at St. Peter's TB Clinic in Addis Ababa, Ethiopia, sounds the chest and lungs of an outpatient with HIV–TB co-infection. (Photo courtesy of WHO/TDR/Crump.)

Marcus Horowitz, professor of medicine, microbiology, immunology, and molecular genetics at UCLA, developed the vaccine candidate, rBCG30, which contains a strain of BCG recombinantly modified to overexpress ag85B. This TB antigen is a major target of cell-mediated immunity in a number of animal models, according to Scott Thaler, chief medical officer at Aeras. The trial, Thaler says, will monitor the safety and immunogenicity of 30 healthy volunteers for 9 months following inoculation.

Meanwhile, GlaxoSmithKline (GSK) and the Seattle-based biotechnology company Corixa are sponsoring a similar study for a subunit vaccine referred to as Mtb72f, which uses no live organism. The vaccine consists of a fusion protein of antigenic domains from *M. tuberculosis* combined with adjuvants. Steven Reed led the discovery and development of the fusion protein, first at the nonprofit Infectious Disease Research Institute and then at Corixa.

GSK and Corixa are two of only a handful of for-profit companies "that are dedicated to really making a difference in TB," Sizemore says. But making the investment in clinical development required a substantial partnership from NIAID, including early-stage research grants and a "challenge" grant, awarded to Corixa in 2000, specifically designed to speed new product development in industry.

"The challenge grant system," Sizemore says, "strongly contributed to this vaccine getting to the stage where it is."

The importance of providing such incentives for projects deemed particularly significant was underscored by Corixa's decision, in November 2003, to refocus its resources "on programs with the greatest opportunity for near-term commercial success." The restructuring included discontinuing a number of R&D programs and the departure of Reed, the company's chief scientific officer and co-founder.

NIAID is currently making a lot of calls looking for contributions from pharma-

ceutical companies, Sizemore says, both through challenge grants and, since TB is now considered an emerging bioterrorism threat, through the Institute's new biodefense initiative (*www.niaid.nih.gov/biodefense*).

A TB vaccine called MVA85A, which uses a nonreplicating vaccinia virus as a vector for another immunogenic TB antigen, Ag85A, is the furthest along in clinical development. Adrian Hill, professor of human genetics, and colleagues at the University of Oxford developed the vaccine. They recently completed a Phase I trial at Oxford and have another one under way in The Gambia in western Africa. In the first trial, the candidate was shown to be safe and to elicit a robust T-cell immune response in healthy volunteers, particularly when given as a boost after the BCG vaccine.

The Mtb72f vaccine is also envisioned as an agent to boost the body's defenses after the use of BCG to prime the immune system. However, rBCG30 is designed to replace BCG in this "prime-boost" equation.

But before this formula can be realized, the candidates have a long and challenging path ahead.

TB vaccine candidates in or approaching clinical development

Candidate	Status	Developer
rBCG30	Phase I	Aeras/UCLA
Mtb72f	Phase I	Corixa/GlaxoSmithKline/Infectious Disease Research Institute
MVA85A	Phase I	University of Oxford
M. tuberculosis with RD1 deletion	Preclinical	Yeshiva University/Howard Hughes Medical Institute
Peptide vaccine	Preclinical	Intercell/Sequella/EpiVax

Aeras hopes to conduct a similar rBCG30 study in South Africa after it completes the first one and then follow a traditional development path of Phase II and Phase III trials. The Foundation, Thaler says, wants "to drive as much of the development process as we can."

In addition, the recent $82.9 million Gates Foundation grant specifically targets funding Phase II trials for two different vaccine candidates—rBCG30 and an unspecified fusion protein. Aeras will not divulge the specifics of this second product, because of the nature of its agreements.

To make the most of its funds, Aeras plans to follow a so-called industrial model of vaccine development by prioritizing its pipeline, adhering to strict timelines, and making predetermined "go/no-go" criteria for each stage of development. Furthermore, it will seek partnerships with both the public and private sectors to implement research, development, and manufacturing.

Meeting the demands of performing later-stage testing in endemic areas for any TB vaccine candidate, Sizemore says, will require "the works" in terms of big funders and international collaborations between the public and private sector. The ultimate question, she says, is, "Does the vaccine really reduce the burden of the disease in communities?" It is a matter of effectiveness, not simply efficacy, Sizemore explains.

One challenge to finding the answer is limited access to patients. "In endemic countries, the few times you have access to an individual is at birth and then maybe later on during school age," Sizemore says. But since the vaccine is supposed to reduce adult pulmonary TB, individuals will have to be followed for many years afterward to judge a vaccine's true effect on a community.

In addition, Phase III trials will have to be very large to accurately measure protection. They will also need to be multinational. "It is already known from trials with the old BCG vaccines that, depending on what continent you are on, the efficacy of that vaccine varies," Sizemore notes.

Another issue that remains from BCG inoculations is ensuring safety in individuals with immune systems compromised by HIV.

One thing that might make late-stage trials go smoothly would be the establishment of surrogate biomarkers indicative of better TB protection than with the BCG vaccine. Such markers could act as end points to support efficacy measurements in clinical trials. Immunogenicity data derived from the initial Phase I studies will be the first step toward identifying such markers.

Aeras, according to Thaler, is working hard at screening for alternative measures of immunity. "The better in vitro surrogates we can develop, the easier it is going to be to develop the product," he says.

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Furthermore, NIAID has a contract with the Tuberculosis Research Unit at Case Western Reserve University to perform trials expressly for finding surrogate markers. "These are not clinical trials in the sense of product development," Sizemore stresses, "but they are absolutely needed to facilitate the product development trials."

These efforts are also important for the preclinical development of new TB vaccine candidates, because the biomarkers discovered in humans will provide insight into what needs to be looked for in animals for an effective vaccine. "There will be a lot of back-and-forth between human studies, animal studies, and further refinement of the vaccine candidates," Sizemore says.

Several other products are currently getting closer to clinical testing. They include a multiepitope vaccine developed by Sequella and EpiVax and licensed to Intercell that contains peptides derived from immunogenic TB proteins and an attenuated strain of *M. tuberculosis* from Yeshiva University.

Sizemore believes it is hard to say how long it will be before there is a TB vaccine ready for Phase III testing. But Jerald Sadoff, CEO of Aeras, has his own ideas. "Our goal—and we believe it is achievable—is to license and deliver a more effective TB vaccine within 10 years." ■