A Good Vaccine Is Hard to Find: Nonprofit Biotechs Tackle Tuberculosis

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In the developed world, the tuberculosis sanitariums were shuttered when antibiotics became widely available. But tuberculosis (TB), a disease of poverty, still festers across wide swaths of the developing world. The World Health Organization's 2008 report estimated that in 2006, 1.5 million people died of TB, as well as 0.2 million people also infected with HIV. TB is slow growing and can remain latent in the lungs for years, complicating diagnosis. The WHO estimates that 2 billion people in the world have latent TB, whereas 14.4 million people live with active TB (http://www.who.int/tb/publications/global_report/2008/key_points/en/index.html).

Public health experts worry about two trends: the blistering rate of HIV infection, which makes people more susceptible to TB, and the growing realization that our "antibiotics honeymoon" may be over. Half a million cases of multidrug resistant TB were reported in 2006. "Obviously, this is extremely worrying for everybody, because if they get a hold they are difficult to treat and the cure rate is very low," said Dr. Tanya Parish, professor of mycobacteriology at Queen Mary's School of Medicine and Dentistry (UK) and senior scientist/principal investigator at the Seattle, WA, based Infectious Disease Research Institute (IDRI [http://www.idri.org]). "In parts of Eastern Europe and Russia, these resistant strains are becoming a big problem, so it is not necessarily going to be confined to … developing countries." Her group collaborates with the TB Global Alliance, validating proteases as drug targets.

New Trends, Old Foe

"TB is really an underdog," said Peg Willingham, senior director for external affairs at Rockville, MD, based Aeras Global TB Vaccine Foundation (http://www.aeras.org), which develops TB vaccines. "It kills so many people each year and is the leading cause of death for people with HIV/AIDS in Africa. Because it has been around for literally thousands of years, it is part of the background or wallpaper in public health." According to Willingham, TB is only now getting increased attention.

Organizations like the Gates Foundation and the National Institutes of Health (NIH) are now pouring money into public health measures for TB but are emphasizing "translational research." By investing in not-for-profit biotechs and product development partnerships (PDPs) that use private sector strategies, they hope that know-how borrowed from industry can be turned to the public good.

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Normally, TB is curable by a cheap, daily 2–4 drug regimen that takes 6–9 months. But when people don't adhere to treatment, multiple-drug-resistant (MDR) or extensively drug-resistant (XDR) strains of TB can result. Treating drug-resistant TB can take years, and the available drugs do not work for everybody.

The only TB vaccine available, Bacillus Calmette-Guerin (BCG), developed in 1921 and still used in the developing world and parts of Europe, fails to protect most people beyond childhood, as it doesn't stop pulmonary transmission. Additionally, most diagnosis in developing countries is done by a sputum smear test developed by Robert Koch in 1882. The smear test is not as sensitive as a culture—it only picks up TB about half the time—but it is much faster, as a negative culture can take from 3 to 4 weeks to determine.

Bootstrapping a Cure

Steve Reed, PhD, founded IDRI, "to bring biotech and research together focusing on diseases of poverty." Reed has appointments as professor of medicine at Cornell University Medical College in New York and research professor of pathobiology at the University of Washington, but his calling is as a serial entrepreneur, establishing parallel for-profit and nonprofit biotechs. In 1993, Reed started IDRI, where he is chief scientific officer. The next year, Reed cofounded Corixa, a for-profit biotech. "That company ended up developing adjuvants that were of benefit to IDRI," Reed said. "There was scientific and business synergy between the two organizations. Basically, the institute provided a challenge and a way to do good for the company, and the company provided developmental, manufacturing, and clinical expertise that a small research organization doesn't fill."

When Corixa was bought by GlaxoSmithKline in 2005 for $300 million, Reed refocused his energies on IDRI. The organization started pulling in substantial NIH funding and Gates Foundation grants: $47 million to develop a leishmaniasis vaccine through clinical trials and, in 2007, $29 million to develop adjuvants for a malaria vaccine (in collaboration with the PATH Malaria Vaccine Initiative [http://www.malariavaccine.org] and the World Health Organization). This year, IDRI received a $6.3 million grant from the National Institute of Allergy and Infectious Diseases (NIAID) to develop adjuvants for TB vaccines. Corporate collaborators include 3M, which donated IP from its toll-like receptor TLR7 and TLR8 agonists for vaccine adjuvants.

"We started our antigen program with Glaxo and Corixa in 1995 and identified more than 100 mycobacteria antigens," said Rhea Coler, Ph.D., vice president of preclinical biology. "The vaccine candidate resulting from this collaboration is now in phase II trials. Building on this experience, IDRI is working on its own TB vaccine, intended for drug-resistant TB as well. IDRI has also developed in-house

a vaccine candidate against leishmaniasis that is in phase I evaluation. On the diagnostics front, IDRI is collaborating on new tests for leishmaniasis, leprosy, and tuberculosis. We also have a program for chlamydia as well as programs developing vaccine adjuvants and TB antibiotics.''

Paying for It All

Aside from grants, IDRI sustains itself by leveraging internally generated IP. ''To sustain an organization that we believe is fundamentally important, you have to use innovative public-private partnership practices,'' Reed said. ''We think that our work is of high enough quality that it should be commercializable.''

According to Reed, the main impact would be in the developing countries, but the world is changing quickly. Brazil, India, Russia, and China are at an interesting crossroad as being real markets as well as real customers. ''But we always retain the rights for what we call public sector marketing, so the technology we develop doesn't get priced out of reach of those who need it the most,'' Reed said.

Recently, Reed cofounded another company, Immune Design, to develop selective vaccines and synthetic adjuvants targeted at dendritic cells. ''Immune Design is probably the first biotech to be started with a global access strategy inherent in its mission,'' said Reed.

IDRI is now being run by Steve Davis, former CEO of Corbis, a Gates-backed company. ''We are basically trying to create something new here,'' said Davis. ''Some of the most critical early and translational science is done by federal and philanthropic grants. You need to use a nonprofit model to secure these grants. In our instance, we would not take it to market. You need the for-profit community for marketing.''

While the NIH and the Gates Foundation are IDRI's largest source of funding, according to Davis, global licensing and commercial partnerships can give IDRI a revenue stream and milestone payments. An emerging concept in the global health field is that organizations have a global access plan and can enter into arrangements to get royalties for tax exempt research so it is accessible at cost to developing countries.

Aeras: One-Stop Shopping for TB Vaccines

The Aeras Global TB Vaccine Foundation was founded in 2003 as a spinoff of Maryland BIOTECH Sequella. The 130 person nonprofit biotech intends to develop a TB vaccine by 2016. ''The word everybody uses in the nonprofit TB drug field is accessibility,'' said Peg Willingham. ''People have got to afford them, or have somebody pay for them, so that they can afford the therapies.''

In 2007, The Gates Foundation awarded Aeras $200 million over 5 years to push a TB vaccine through phase II, building on a 2003 grant. Aeras estimates it will cost $120 million to bring a TB vaccine candidate to phase III trials. Aeras has six vaccine candidates in the pipeline, two in preclinical, two in phase I/II, and one in phase II.

''Our ideal would be a vaccine that would prevent initial infection and later reinfection,'' said Willingham. ''At a minimum … it should be 60% effective. No vaccines on the market are 100% effective.'' Production has to scale very cheaply to 100 million doses a year. To that end, Aeras has its own in-house vaccine manufacturing facility.

''Our strategy is called a prime boost strategy,'' said Dr. Lewellys Barker, senior medical advisor. Aeras is developing an improved BCG vaccine for newborns. According to Barker, BCG is a live vaccine, and Aeras's goal is to modify it so it overexpresses certain antigens to make it safer, particularly for patients with HIV. Long-term follow-up studies suggest that TB vaccine protection doesn't last, so a booster is necessary.

Aeras, along with Nevada-based Crucell, has developed AERAS-402/Crucell Ad35, a replication-deficient adenovirus that expresses TB antigens meant to elicit high levels of CD8+ T cell responses. AREAS-402/Crucell AD35 completed a phase I clinical trial in the US in 2006. Another phase I trial started in South Africa in 2007 in healthy adults vaccinated at birth with BCG.

Aeras is currently partnering with the South African Tuberculosis Vaccine Initiative of the University of Capetown (http://www.satvi.edu) to test the Oxford University MVA viral-vector vaccine. According to Willingham, South Africa has good technical capabilities and infrastructure. It also has a high rate of endemic TB, which is necessary for testing the vaccine in large and varied populations to get significant data. Aeras also has agreements in Kenya, India, Uganda, and Cambodia.

''First we have to get a vaccine that works well,'' said Barker. ''And that is the challenge in TB. We don't know what kind of immune response we need to get for a recipient to be protected.'' According to Barker, cell-mediated responses are thought to be important, but the role of antibodies is unknown. A major accomplishment will be the ability to gauge T cell responses. ''Aside from a better regime for immunizing against TB, we would like it to work for people infected with HIV,'' Barker said.

Aeras also has a few preclinical projects: an oral vaccine using a bacteriophage capsid inserted in attenuated shigella bacteria as well as an inhaled vaccine being tested on animals at Tulane University in New Orleans. Barker noted that it is uncertain whether animal tests could predict vaccine performance in people or what would be the indication of the immune response needed for animals. Researchers do not know what immune response is needed to judge the effectiveness of early childhood immunization. ''Clinical testing will be difficult, as diagnosis of TB in early childhood is difficult,'' said Barker.

''We have relatively little drug-resistant TB in this country, but this not really true in the rest of the world,'' said Barker.

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