The Tuberculosis Vaccines Pipeline: A New Path to the Same Destination?

By Mike Frick

Call it a paradigm shift, a pivot, or a turn – tuberculosis (TB) vaccine research and development (R&D) is entering a period of basic science. After years of focusing on phase II clinical trials, some of the field's largest players are now redirecting attention and resources to the beginning of the pipeline – basic discovery and preclinical development. This change is motivated by a growing consensus that the guiding assumptions of the last 10 years of TB vaccine research require updating in the face of emerging evidence from the clinic and the lab.

All along, some of the largest funders of TB vaccine research (e.g., the U.S. National Institutes of Health and the European Commission) have concentrated resources on basic-science and discovery activities. The momentum steering other funders in this direction picked up speed in 2014 when the Bill & Melinda Gates Foundation (BMGF), the largest funder of TB vaccine R&D globally, revised its TB vaccine R&D strategy, along with its overall TB R&D strategy, calling for efforts to "shift to the left" of the clinical development pipeline. As the BMGF envisions it, resources should transfer from a limited number of large, expensive phase IIb/III trials (events located on the far right side of the pipeline) to basic discovery, preclinical development, and phase I studies.[1,2] Whereas a phase III TB vaccine trial could cost $100 million to validate the efficacy of a single vaccine candidate,[3] investing in smaller, earlier-stage studies would enable the exploration of a wider array of vaccine concepts. This approach would "de-risk" vaccine development by winnowing vaccine concepts and advancing only those most likely to succeed in later clinical trials, where failure comes with a heftier price tag in terms of financial resources and community stamina for hosting large-scale research.[4]

The changes in TB vaccine R&D are a response to systemic weaknesses in the TB vaccines pipeline, which contains 16 candidates in active clinical development. Three of these candidates employ a single antigen of *Mycobacterium tuberculosis* (MTB), the bacterium that causes MTB infection and TB disease. Many candidates contain the same handful of antigens in different combinations; all together, the viral-vectored and protein/adjuvant vaccines in the pipeline include just 12 of the 4,500 targetable antigens encoded in the MTB genome.[5] Furthermore, in selecting these antigens, most current candidates are designed to trigger a strong cell-mediated immune response driven by CD4+ and CD8+ T cells. By contrast, most licensed vaccines work primarily through humoral immunity, or antibodies produced by B cells. In short, the antigenic repertoire targeted by vaccines in the pipeline is narrow, overlapping, and aimed at a single arm of the immune system.

Seasoned HIV/TB activists and investigators could be forgiven a feeling of déjà vu over this movement back to basic science. Present discussions in the TB vaccine world echo a call in 1993 for a return to basic science in HIV research. In TAG's *Basic Research on HIV Infection: A Report from the Front*, Gregg Gonsalves interviewed 36 scientists about key obstacles slowing basic research on HIV/AIDS.[6] The thematic areas that emerged from those interviews – correlates of immunity, research in vivo, pathology of HIV infection, viral life cycle, and events in host response – mirror the scientific sticking points in TB vaccine R&D today.

The central insight of Gonsalves's report holds true for TB prevention: the pipeline for new medical technologies is only as strong as the basic science and preclinical studies from which testable ideas emerge. In recognition of that, this chapter first reviews progress in basic science and preclinical development. Advances in these areas owe much to new ways of looking for clues to protective immunity in the blood, genome, and lung. The second section discusses ways of testing vaccine candidates through innovative clinical trial designs. The chapter closes with a call for researchers, funders, and vaccine developers to find new ways of working together – not just with each other, but also with an expanded definition of who counts as a partner, including activists, TB-affected communities, regulatory agencies, and developing-country vaccine manufacturers.

New Ways of Looking, but What Are We Seeing?

In January 2015, the biennial Keystone Symposia on TB, titled "Host Response in Tuberculosis," opened with one of the organizers admitting discomfort at making any distinction between MTB and its human host.[7] By the end of the meeting, a common refrain had emerged: the characteristics of host-pathogen interaction are more surprising, heterogeneous, and entangled than we had imagined. One speaker after another expressed his or her opinion that future research endeavors must look deeper, recognize increasing layers of complexity, and remember that what we think we know may have come from gazing at just a sliver of the full picture.

New visions from genomics

The full picture, it turns out, is painted with the complexity of tens of thousands of years of evolutionary back-and-forth between MTB and humankind. Over the long stretch of evolutionary time, MTB has transformed from a soil-dwelling microbe into the most lethal killer in human history.[8] Seventy thousand years of coevolution with *Homo sapiens* have given MTB sufficient time to learn to harness the human immune response to its benefit.[9] This ability upends traditional metaphors that relate the immune system to an army at war against pathogenic invaders. Rather than exist in either a state of full war (active TB disease) or an uneasy truce (latent MTB infection), MTB appears to establish a dynamic coexistence with the human host, the conditions of which give it fertile opportunity for persistence, replication, and onward transmission.[10]

These opportunities appear to hinge on MTB's attracting recognition by CD4+ T cells, a counterintuitive notion given that most pathogens hope to escape notice by the immune system.[11] Genomic analyses suggest that the parts of the MTB genome that code for the epitopes (cell-surface proteins) recognized by CD4+ T cells are hyperconserved, meaning they appear the least changed over time compared with other segments of the genome.[12] This genomic stability over 70,000 years suggests an evolutionary advantage to MTB being recognized by CD4+ T cells. That is, the cell-mediated immunity triggered by T cells may create a lung environment favorable to MTB under certain conditions.[13] One explanation implicates the release of type 1 helper T (Th1) cytokines such as interferon-gamma (IFNγ), tumor necrosis factor-alpha (TNFα), and interleukin-2 (IL-2) by CD4+ and CD8+ T cells responding to MTB. These cytokines are signaling proteins that help call and direct the behavior of other immune cells. However, certain cytokines also cause inflammation, and while some inflammation is necessary to mount a successful immune response, too much can have the unintended consequence of damaging lung tissue. This damage may create a microenvironment that favors MTB persistence by sheltering MTB from immune killing. Eventually, the scarring and cavitation (the formation of holes in tissue) produced by poorly controlled inflammation permit onward transmission by giving MTB a pathway to escape the lung into the air via aerosolized droplets.[14,15]

Consistent with the apparent hyperconservation of T-cell epitopes, clinical trials of TB vaccines have observed a repeated disconnect between strong IFNγ (Th1, T-cell-favored) responses and protection against TB disease. There is now widely shared agreement that IFNγ is a necessary but insufficient marker of protection.[16,17,18,19] However, a holistic picture of the biological markers that correlate with protection against either MTB infection or TB disease remains lacking. As a first step toward identifying biomarkers of protection, some researchers have turned their gaze to the human genome in search of correlates of risk. A subset of the broader set of biomarkers, correlates of risk serve as predictive signifiers composed of genes, biological processes, or clinical phenotypes that act as precursors to disease states or responses to vaccination or drug therapy.[20]

In the context of TB vaccine R&D, biomarker discovery is a tactic for informing and streamlining clinical development. The identification and validation of a biomarker (or biosignature comprised of multiple markers) would greatly aid TB vaccine R&D by giving investigators glimpses of efficacy earlier in a vaccine's development. These early suggestions of efficacy could improve the selection of candidates for late-stage trials and, once validated, might enable shorter, smaller trials by serving as surrogate endpoints for TB disease.[21] However, the identification of possible biomarkers would not transform the clinical pipeline overnight, as

any correlates would require validation in a successful phase III trial before they could function as reliable surrogate endpoints. In addition, biomarkers are by nature proxies for disease and may not fully represent the intricacies of host-pathogen interaction unfolding at sites of infection.[22]

Two major initiatives are pursuing biomarker identification from a genomics angle. The first is a prospective cohort study of South African adolescents spearheaded by the South African TB Vaccine Initiative (SATVI). The study enrolled over 6,300 adolescents with MTB infection and followed them over two years before looking for genes differentially expressed in those who developed TB disease and those who did not.[23] The second effort is the TB biomarker consortium organized under the BMGF-funded Grand Challenges 6 initiative that seeks to find correlates of risk of progression to disease among HIV-negative adult household contacts of people with TB in several African countries.[24] Investigators in the two projects have combined portions of their data and identified 1,531 genes that are differentially expressed between individuals who progress to active disease and those who remain healthy, although full analyses of this intriguing finding remain unpublished.[25]

New visions from radiography

Genomic and transcriptional analyses open a window onto the history of host-pathogen interaction and its effects across populations over time. Visions of what this complexity looks like within individuals appear through a very different kind of technology: PET/CT. The combination of positron emission tomography (PET) and X-ray computed tomography (CT) aligns the depiction of biochemical activity in the body with anatomical images represented in two or three dimensions. Researchers are taking advantage of PET/CT to map the appearance and growth of individual lesions in the lung. These lesions, or granulomas, are collections of macrophage cells that flock to sites in the lung where MTB is present. Traditionally, macrophages have been described as initial responders that huddle together to form immune fortresses that contain MTB. PET/CT has helped to overturn the idea of granulomas as stolid, stable fortresses by showing that a dynamic range of activity exists across lesions, even during so-called latent phases of MTB infection.

PET/CT imaging has been applied in at least one TB treatment trial – a phase II study of linezolid functional monotherapy in patients with chronic extensively drug-resistant (XDR-TB) in South Korea.[26] In a substudy nested into this trial, 19 participants received three PET/CT scans at different times before, during, and after treatment with the linezolid-containing regimen. Among the five participants who had PET/CT scans before the linezolid-containing therapy, all had evidence of progressing, regressing, and newly forming lesions over a two-month period. The implication is that TB activity varies throughout the lung and that the response to MTB, whether driven by drug therapy or the body's adaptive immune response, is locally heterogeneous as well.[27] With these data, as well as results from autopsy studies of granuloma patterns,[28] the previous assumption that all lesions within an individual behave similarly has been disproved.

In vaccine research, the application of PET/CT has focused on preclinical work in cynomolgus macaques, the field's dominant nonhuman primate model. PET/CT imaging is being used to study immune activity (i.e., inflammation) in macaques whose quiescent, latent infection with MTB is reactivated by treatment with anti-TNF, an immunosuppressant. Findings so far suggest that macroscopic granuloma patterns seen during primary MTB infection may differ from those observed during re-activated disease.[29] Whether anti-TNF treatment can stand in for the immunosuppressing conditions (e.g., HIV, diabetes, and silicosis) that increase the risk of MTB infection progressing to TB disease in people remains unknown.

Researchers have also sought to overlay granuloma patterns observed through PET/CT imaging with T-cell responses measured by intracellular cytokine staining to better understand whether and how T cells and the cytokines they produce are responsible for inflammation. This work points to marked variability in the T-cell response to MTB across granulomas – even within granulomas located in the same lobe of the same lung of the same macaque.[30] While each granuloma contains many T cells making a variety of cytokines, most individual T cells appear to produce just one type of cytokine. This stands in juxtaposition to the common

practice of judging TB vaccine candidates by their ability to trigger polyfunctional T cells that produce multiple cytokines. Notably, granulomas with T cells producing both pro- and anti-inflammatory cytokines appear more likely to reach sterilization. In addition, levels of granuloma inflammation in macaques are more strongly predictive of whether MTB infection will progress to active disease than the number of bacteria present (bacterial burden).[31]

By revealing the expansive range of granuloma activity in the lung, PET/CT has helped to replace the idea that MTB infection and disease exist as distinct binary states with the notion that a continuum of host-pathogen responses underlies infection and disease. While distinguishing latent from active TB may still hold clinical relevance when diagnosing patients, within the lung, distinctions between active and latent TB dissolve in the face of heterogeneous, localized activity between MTB and a range of immune cells. Using PET/CT to create macroscopic composites of inflammation unfolding across the lung raises the tantalizing possibility of defining inflammation-based markers of response to drugs or vaccines for use in future clinical trials.[32] In short, radiography has made a compelling case for casting aside old ideas that treat MTB and the host response as discrete and uniform and has offered a way to look at host-pathogen interaction outside of the strict cellular context of traditional immunology work.

New visions from blood and bronchial samples

One of the guiding principles of the field's shift to earlier phases of research is the need for iterative learning between experiments in the laboratory and trials in the clinic. Instead of progressing in a strict linear fashion from lab to clinic, vaccine research should move back and forth between these two stages of research. Samples collected in human studies should be studied in the lab to better understand the biology of MTB infection and TB disease, the knowledge of which can then be used to refine the preclinical models that will inform future clinical development. This iterative approach entails making use of observational cohort data alongside evidence from randomized, controlled trials.[33] Several presentations at the Santa Fe Keystone Symposia demonstrated the potential of using blood and lung samples collected in cohort studies to investigate specific questions of immunologic importance.

One of these questions concerns the role of antibodies produced by B cells in preventing, controlling, and clearing MTB infection. Efforts to understand humoral, B-cell-based immune responses to MTB have trailed investigations of cell-mediated immunity generated by T cells. This overshadowing is so extensive that all of the speakers in the "B-cell responses to TB" session at the Santa Fe Keystone meeting emphatically assured the audience that their research focus lay elsewhere. The last presenter, however, did something unexpected: she turned a room of B-cell skeptics into cautious believers. Using plasma samples from 120 South Africans with TB, some with latent MTB infection and others with active TB disease, Galit Alter and her lab at the Ragon Institute showed how MTB-specific immunoglobin (IgG), a type of antibody, is capable of recruiting other immune cell types – including macrophages and natural killer cells – to the site of infection, and that differences observed in the structural properties of IgG can even distinguish patients with latent MTB infection from those with active TB disease.[34]

Although B cells may attract more attention moving forward, findings about the role of humoral immunity in controlling MTB are likely to augment, rather than supplant, efforts to better understand cell-mediated immunity. The emphasis on designing vaccines that trigger robust cell-mediated immunity rests on the incontrovertible observation that CD4+ T-cell depletion in people with HIV hugely increases their risk of developing TB disease. Even this long-established story is adding chapters as researchers look closely at the mechanisms at play in the lungs of people with TB/HIV coinfection. Observational cohort data from Malawi show there is a delayed recovery of MTB-specific CD4+ T cells in adults with HIV on antiretroviral treatment (ART) – even among individuals taking ART for at least four years. This suggests that HIV makes the lung environment more susceptible to MTB infection and progression.[35] People with HIV also appear to face a higher risk of TB disease before CD4+ T-cell depletion. One recent study from South Africa found that HIV

infection increases the risk of TB disease even at high CD4+ T-cell counts. Individuals with HIV with CD4+ T-cell counts greater than 600 cells/μL had half the frequency of MTB-specific immune responses compared with study participants without HIV, as measured in both blood and airway samples.[36] This growing literature argues for the importance of considering how comorbidities may change characteristics of host-pathogen interaction from the outset of TB vaccine development.

New Ways of Testing, but Have the Measurements Changed?

People with HIV, on and off ART, are underrepresented in TB drug trials. So are children, although the historic exclusion of younger age cohorts from TB drug research is beginning to change. In the coming period, these two patient populations may also play a less central role in TB vaccine trials, which until recently focused on infants and people with HIV in phase II investigations. Future TB vaccine clinical trials, particularly those supported by the BMGF, will focus instead on adolescents and adults without HIV or other comorbidities. This new emphasis by some funders reflects a move toward preventing MTB infection, as opposed to TB disease, in the design of clinical trials. Two lines of thinking are motivating this shift.

First, for a new TB vaccine to interrupt MTB transmission, the target population must be adolescents and adults, as disease in these age groups drives the majority of MTB transmission globally. Children, who typically have paucibacillary and nonpulmonary forms of TB, are less likely to transmit TB to others. Similarly, people with TB/HIV coinfection have lower bacterial loads, though recent work challenges the notion that they do not contribute to TB transmission.[37] Mathematical modeling commissioned by Aeras suggests that an adolescent or adult vaccine with 40% efficacy against TB disease would avert 70% of the expected TB burden in low-income countries between 2024 and 2050.[38] An infant vaccine of equal efficacy and duration, however, would avert less than 12% of the TB burden – partly because many infants in the vaccinated groups would not have reached adolescence, an age when the risk of TB disease increases markedly, by the end of the 20-year period under simulation. Buried in the paper presenting these scenarios is this sentence: "A vaccine targeted at adolescents and adults . . . is likely to prevent, before 2050, more infant cases of TB than a vaccine targeted at infants due to the reduction in transmission."[39] This claim rests on the promise of vaccines to protect not just those persons directly vaccinated but also neighboring individuals who may not be immunized. Future modeling exercises and in vivo studies should interrogate the validity of this statement as our understanding of the biological and social drivers of TB transmission evolves.

Second, using prevention of infection as the primary endpoint will enable smaller, faster, and cheaper clinical trials. In any given population, rates of MTB infection typically exceed those of TB disease. This difference is even more pronounced in high-risk groups such as household contacts of newly diagnosed TB cases, health care workers, and miners. Because the outcome of interest occurs more frequently, prevention-of-infection trials require smaller sample sizes and shorter durations of follow-up than prevention-of-disease trials.[40] Consequently, prevention-of-infection studies may offer a more efficient way of testing vaccine concepts before deciding which ones to advance to phase IIb/III trials, where prevention of TB disease is likely to remain the primary endpoint. For this strategy to work, the mechanisms of protection against infection and disease must overlap – which seems far from guaranteed given the increasingly complex picture of host-pathogen interaction emerging from basic-science work.

Although heralded as a paradigm shift, prevention-of-infection trials may simply transpose the current strategy to an earlier event in TB pathology. As designed, prevention-of-infection trials do not circumvent the thorny issue of how to judge vaccine efficacy if classic Th1 cytokines such as IFNγ are important but only partial aspects of protective immunity. All TB vaccine trials described below continue to assess immunogenicity by measuring IFNγ. Rather than replace the object of measure with a more relevant marker, prevention-of-infection studies merely shift our measurement of it to earlier points in the infection process.

Further complicating things, this moment (incidence of MTB infection) is difficult to measure with available diagnostic technologies. There is no gold standard diagnostic for MTB infection, and the best currently available tools, interferon gamma release assays (IGRAs), come with serious limitations. The repeatability of the QuantiFERON Gold In-Tube (QFT) blood test, the most common IGRA used in TB vaccine R&D, has come under scrutiny for the tendency of QFT tests taken on the same individual at different times to produce discordant results, whereby initial tests read MTB-positive and follow-up tests read MTB-negative.[41,42] This poor reproducibility creates a risk that prevention-of-infection trials using QFT may overestimate the true incidence of MTB infection among trial participants. This could occur if a high proportion of MTB-positive test results reflect QFT variability rather than true infection with MTB.[43] Compensatory efforts to measure sustained IGRA positivity at multiple times in clinical trials allay but do not resolve concerns about the fragility of QFT-defined endpoints. Alternatives, such as using PET/CT to assess infection and disease by inflammation and lesion activity, are not yet ready for routine use in clinical trials. Given these limitations, the most we can hope is that prevention-of-infection studies will unveil insights into the biology of MTB infection and that this information will give us the tools we need to truly do things differently.

Table 1. Tuberculosis Vaccines Pipeline

Agent	Strategy	Type	Sponsor(s)	Status
M. vaccae	Immunotherapeutic	Whole-cell M. vaccae	AnHui Longcom	Phase III
M72/AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
Hybrid 4 + IC31	Prime-boost	Protein/adjuvant	Statens Serum Institut (SSI), Sanofi Pasteur, Valneva, Aeras	Phase II
Hybrid 56 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva, Aeras	Phase IIa
Hybrid 1 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva	Phase IIa
MTBVAC	Prime	Live genetically attenuated M. tuberculosis (MTB)	University of Zaragoza, Biofabri, TuBerculosis Vaccine Initiative (TBVI)	Phase IIa
VPM1002	Prime	Live recombinant bacille Calmette-Guérin (rBCG)	Serum Institute of India, Vakzine Projekt Management, TBVI, Max Planck Institute for Infection Biology	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
Crucell Ad35 + MVA85A	Prime-boost	Viral vector	Crucell, Oxford University, Aeras	Phase I
ChAdOx1.85A + MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
Dar-901	Prime-boost	Whole-cell M. obuense	Dartmouth University, Aeras	Phase I
MVA85A (aerosol)	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A-IMX313	Prime-boost	Viral vector	Oxford University, Imaxio	Phase I
ID93 + GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research Institute, Aeras	Phase I
TB/FLU-04L	Prime-boost	Viral vector	Research Institute for Biological Safety Problems	Phase I

Hybrid 4 and Hybrid 56 flex their immunogenicity in phase I/IIa

Hybrid 4 + IC31 has the distinction of being the first TB vaccine candidate tested under the new prevention-of-infection approach. This vaccine pairs a fusion of MTB antigens Ag85B and TB10.4 with the IC31 adjuvant owned by the French company Valneva. In 2014, Aeras announced a three-arm phase IIa study to evaluate the safety and immunogenicity of Hybrid 4 + IC31 and bacille Calmette-Guérin (BCG) revaccination in nearly 1,000 BCG-vaccinated, HIV-negative adolescents in South Africa.[44] BCG, the existing TB vaccine first introduced in 1921, protects infants and children against severe forms of disseminated TB but does not confer significant protection against pulmonary TB to adolescents and adults.[45] One-third of participants will receive two doses of Hybrid 4 + IC31; one-third will be revaccinated with one dose of BCG; and the final third will receive two doses of placebo. The first 90 participants will constitute a safety and immunogenicity cohort with intensive data collection on safety, adverse events, and immunogenicity using the standard assays that assess the frequency and magnitude of Th1 cytokines like IFNγ. The remaining 900 participants will form a correlates cohort and undergo evaluation for safety, biomarker discovery, and prevention of MTB infection. This will be the first randomized controlled trial to assess whether BCG revaccination can prevent MTB infection in adolescents.

The Statens Serum Institut (SSI) of Denmark continues to advance the development of Hybrid 56 + IC31 in partnership with Aeras. Hybrid 56 + IC31 is an adjuvanted subunit vaccine that combines three MTB antigens (Ag85B, ESAT-6, and Rv2660c) with Valneva's IC31 adjuvant. Hybrid 56 + IC31 is currently undergoing several clinical evaluations at trial sites in South Africa. One phase I/IIa study nearing completion is investigating three different doses of Hybrid 56 + IC31 in BCG-vaccinated, HIV-negative adults with and without MTB infection who have no history or evidence of TB disease. A second phase of this study will evaluate the dose formulation selected in phase I in two-dose and three-dose regimens in individuals with and without MTB infection as measured by QFT.[46] A second trial is comparing the safety and immunogenicity of Hybrid 56 + IC31 with Hybrid 4 + IC31 and BCG revaccination in HIV-negative South African adolescents. This trial will enroll 84 participants with the objective of identifying immune responses to vaccination for further evaluation as potential correlates of risk or protection.[47] A third phase I study is evaluating the safety and immunogenicity of Hybrid 56 + IC31 in a different population: HIV-negative adults who have recently completed treatment for drug-susceptible TB. The trial will enroll 24 participants and compare two intramuscular doses of Hybrid 56 + IC31 versus placebo to see whether the vaccine should be evaluated in larger studies aimed at preventing disease recurrence (defined as either relapse or reinfection). Investigators have vaccinated the last participant in the trial and have reported no safety concerns so far.[48]

SSI is also exploring opportunities to study Hybrid-56 + IC31 as an adjunct to drug therapy. A study planned for early 2016 will evaluate whether vaccination with Hybrid-56 + IC31 in combination with COX-2 selective inhibitors, a type of nonsterile anti-inflammatory drug (NSAID), helps reduce harmful inflammation in the lungs of patients undergoing treatment for active TB disease.[49] As envisioned, the study will contain three arms: the first giving COX-2 inhibitors alone, the second giving Hybrid-56 + IC31 alone, and the third combining Hybrid-56 + IC31 with COX-2 inhibitors. This approach grows out of basic science and preclinical work suggesting that modulating lung inflammation may help generate a positive host response to TB. The initial study will probe the safety of this approach, but the larger goal is to see whether vaccination as an adjunct to chemotherapy can shorten treatment duration as measured by faster sputum conversion.[50] Participants in the planned study will receive Hybrid-56 + IC31 after their sputum samples convert from positive to negative out of concern that vaccination at an earlier time might pose a safety issue by increasing the MTB antigen load in the lung when the body is still awash in actively replicating bacteria.

M72/AS01 moves into phase IIb

In August 2014, Aeras and GlaxoSmithKline Biologicals (GSK) announced the opening of a phase IIb trial of M72/AS01,[51] an adjuvanted subunit vaccine that combines MTB antigens 32A and 39A with GSK's AS01 adjuvant. This phase IIb study follows a raft of phase IIa evaluations of M72/AS01 in infants in Gambia; adults with MTB infection in the Philippines; adults with HIV in Chennai, India; adults with TB disease in Taiwan and Estonia; and adolescents and adults in South Africa.[52,53,54] The phase IIb trial will enroll 3,500 HIV-negative adults with MTB infection in South Africa, Kenya, and Zambia. Participants will be randomized to receive either two doses of M72/AS01, administered intramuscularly, or two doses of placebo spaced 30 days apart. As a primary outcome, the trial will assess whether M72/AS01 offers participants significant protection against progressing to TB disease up to 36 months of follow-up.[55] A subcohort study will evaluate the cell-mediated immune response to M72/AS01 by measuring the frequency of CD4+ and CD8+ T cells expressing the cytokines IFNγ, TNFα, and IL-2, either singly or in combination, as well as M72-specific antibody responses. An independent, optional substudy sponsored by Aeras will collect biological samples for future biomarker investigations.[56] Investigators expect to complete follow-up and release results in 2018.

MVA85A is down but not out

Despite disappointing results from a second phase II trial published in March 2015, MVA85A, the first TB vaccine to enter efficacy trials since 1968, still has a lot to teach us. That trial, which took place in South Africa and Senegal, gave two intradermal doses of MVA85A spaced six to 12 months apart to adults with HIV.[57] (Participants randomized to the placebo arm received a *Candida* skin test antigen instead of vaccine.) Participants not on ART had to have a CD4+ T-cell count greater than 350 cells/µL at study entry, and those with latent MTB infection had to have completed at least five months of isoniazid preventive therapy. The primary outcome was the safety of MVA85A; as a secondary outcome, investigators evaluated the vaccine's efficacy for preventing TB disease. The trial showed that MVA85A is safe to give to people with HIV but does not afford them significant protection against TB disease.[58]

One caveat to keep in mind when interpreting these findings: the sample size of this trial was revised down from 1,400 to 650 participants after the trial of MVA85A in South African infants published negative results in February 2013.[59] In that trial, MVA85A did not confer significant added protection against either TB disease or MTB infection to infants vaccinated with BCG.[60] Consequently, investigators in the adult trial revised the study design to test safety, not efficacy, as the primary outcome using a smaller sample size and a shorter duration of follow-up of six months instead of two years. Additionally, the immune response MVA85A provoked in adults with HIV was qualitatively different than the response seen in the infant trial. In the adult study, CD4+ T cells stimulated by MVA85A were primarily monofunctional (single-cytokine-producing) rather than polyfunctional, as observed in infants vaccinated with MVA85A. Whether a vaccine built around a single MTB antigen, such as MVA85A, can provoke a strong enough immune response to prevent TB disease or MTB infection remains an open question.[61]

These results do not foreclose a future for MVA85A. Helen McShane, the lead developer of MVA85A, and colleagues at Oxford University are studying MVA85A in combination with other vaccine candidates and on its own using aerosolized administration. Delivering MVA85A by aerosol makes intuitive sense given that MTB is an airborne pathogen. It also builds on evidence from mouse and nonhuman primate models suggesting that delivering a vaccine directly to the mucosal tissues lining the respiratory tract might increase protective immune responses at the site of infection.[62,63] To test this idea, McShane's group conducted a phase I study comparing the safety and immunogenicity of MVA85A administered by aerosol versus intradermal injection to 24 BCG-vaccinated adults in the United Kingdom.[64] The first two participants who received aerosolized MVA85A displayed such potent cellular immune responses – higher than those seen in nonhuman primates – that the investigators revised the protocol to reduce the dose by a full order of

magnitude. By study's end, aerosolized MVA85A appeared to be safe and produced a stronger CD4+ T-cell response than intradermal MVA85A in circulating blood and the lung, as measured by production of the Th1 cytokines IFNγ, TNFα, IL-2 and IL-17.[65]

McShane's group is also pairing nonaerosolized MVA85A with other vaccine candidates in novel prime-boost combinations. A phase I trial combining MVA85A with Crucell Ad35 recently concluded among 40 adult participants at Oxford University.[66] Crucell Ad35, a viral-vectored vaccine using the MTB antigens Ag85A, Ag85B, and TB10.4, was originally devised as a stand-alone TB vaccine and, at one point, was poised to enter a phase IIb study with a projected enrollment of 4,000 BCG-vaccinated, HIV-negative infants.[67] After an early look at immunogenicity data, investigators cut the sample size of that trial to just 500 participants.[68,69] The combination of Crucell Ad35 and MVA85A seeks to pair the strong CD8+ T-cell response provoked by Crucell Ad35 with the robust CD4+ T-cell response generated by MVA85A.[70]

A separate phase I study will combine MVA85A with IMX313, a carrier protein created by fusing a small DNA sequence to an antigen-coding protein. IMX313 is a proprietary technology of Imaxio, a biopharmaceutical company based in Lyon, France, and is designed to enhance the immune response to different vaccine constructs. The phase I evaluation will compare the safety of two escalating doses of MVA85A-IMX313 with that of MVA85A alone in BCG-vaccinated healthy adults.[71] Preclinical work showed that MVA85A-IMX313 induced quantitatively higher cell-mediated immune responses in mice and rhesus macaques than either MVA85A or BCG.[72] This will be the first human evaluation of IMX313, although Imaxio has hinted at plans to evaluate it in vaccines against flu and malaria.[73]

Finally, MVA85A is being evaluated as a boost to ChAdOx1.85A, a simian adenovirus vector that expresses MTB antigen Ag85A. A phase I study is evaluating the safety of ChAdOx1.85A vaccination alone and in combination with MVA85A in BCG-vaccinated adults in the United Kingdom.[74] ChAdOx1 may offer advantages over other adenovirus vectors because it primarily infects nonhuman primates, reducing the likelihood that vaccine recipients will demonstrate preexisting immunity to the vector due to previous exposure.[75]

Other candidates in phase I

Phase I is the most well populated and diverse stage of the TB vaccine pipeline. In addition to the studies of MVA85A in combination with Crucell Ad35, IMX313, and ChAdOx1.85A, phase I includes other viral-vectored vaccines (Ad5Ag85A, TB/FLU-04L), an adjuvanted subunit vaccine (ID93+GLA-SE), a whole-cell mycobacterial vaccine (Dar-901), and a vaccine using genetically attenuated MTB (MTBVAC).

Developed by the University of Zaragoza, Spain, and the Spanish biotech company Biofabri, the MTBVAC vaccine uses live, genetically attenuated MTB weakened through the deletion of two genes related to MTB virulence: phoP and fadD26.[76] While the majority of vaccines in the pipeline are constructed using one or more MTB antigens and aim to boost BCG, MTBVAC is a live, whole-cell vaccine (and thus contains all the antigens of MTB) and could either replace or boost BCG. A phase I dose escalation study recently concluded in Lausanne, Switzerland. Three cohorts of 12 adult participants tested the safety and immunogenicity of escalating doses of MTBVAC versus BCG. There were no vaccine-related serious adverse events. Investigators observed a dose-response relationship between higher doses of MTBVAC and the expression of polyfunctional CD4+ T cells.[77] Based on these favorable results, MTBVAC is completing a second phase I study in newborns less than a month old in South Africa and preparing for a phase II trial in South African adults.

TB/FLU-04L is the newest vaccine to come to international attention and the first viral-vectored vaccine candidate to employ a live, attenuated flu virus to deliver MTB antigens. Developed by the Research Institute for Biological Safety Problems (RIBSP) in Almaty, Kazakhstan, TB/FLU-04L uses replication-deficient, recombinant influenza virus A to present two MTB antigens, ESAT-6 and Ag85A, intranasally using a delivery

platform similar to the FluMist vaccine.[78] A phase I study in 36 BCG-vaccinated, QFT-negative adults tested the safety and immunogenicity of two doses of TB/FLU-04L spaced 21 days apart. There were no serious adverse events, and no infectious flu virus could be recovered from nasal swabs taken after vaccination. RIBSP and its collaborators in St. Petersburg, Russia, are planning to further evaluate TB/FLU-04L as a boost to BCG in a phase IIa trial in QFT-positive adults.[79]

A whole-cell mycobacterial vaccine called Dar-901 is nearing completion of a phase I dose escalation study in BCG-vaccinated adults in the United States. Developed at Geisel School of Medicine at Dartmouth University, Dar-901 consists of inactivated *Mycobacterium obuense*, a nontuberculous mycobacterium. The phase I study contains six groups; participants in each will receive three intradermal injections of either vaccine or placebo spaced two months apart. The first three cohorts enrolled HIV-negative adults and have completed all doses of vaccine or control. The 1 mg dose judged safe in these groups is now being evaluated in three cohorts enrolling both HIV-positive and HIV-negative participants.[80] Dar-901 is very similar to an earlier TB vaccine candidate developed at Dartmouth, SRL-172, which was studied in the phase III DarDar trial. Both Dar-901 and SRL-172 are manufactured from the same strain of *Mycobacterium obuense*; the primary difference is that Dar-901 is grown in broth rather than agar, a more scalable production method.[81]

New Ways of Working Together, but Who Counts As a Partner?

The changes in TB vaccine R&D make this a moment of significant potential. The defeatist, inward-looking rhetoric of the last few years is ceding ground to the optimism of concrete plans and revised, if not totally new, thinking. This scientific momentum, however, stands at odds with a remote, almost regressive approach toward engaging civil society and TB-affected communities in TB vaccine research. The early-phase state of TB vaccine science is no excuse for the lack of community engagement in TB vaccine R&D. Quite the opposite – now is the time to ensure that the next chapter of TB vaccine R&D is more inclusive than the last.

Over the past year, major funders and vaccine developers have taken steps to form the Global TB Vaccine Partnership (GTBVP). So far, this body includes all the usual suspects – vaccine developers (Aeras, the TuBerculosis Vaccine Initiative), funders from high-income countries (BMGF, the European Commission, the European Investment Bank), and research networks (the European and Developing Countries Clinical Trial Partnership).[82] Although the recent addition of the South African Medical Research Council is a move toward greater representation of TB-endemic nations, development of the GTBVP has proceeded without input from members of civil society and TB-affected communities.[83]

This oversight would be problematic for any global health research endeavor but is particularly troubling in the case of TB vaccine R&D. As the writer Eula Biss has noted, immunity is a public space; vaccines promise to protect not just a single body, but also the collective body of a whole community.[84] Research, too, is a public space in that clinical trials of new TB vaccines are hosted by communities, supported overwhelmingly by public funds, and designed to produce technologies that will need to garner the trust and acceptance of societies affected by TB. The noticeable lack of community voices in the governance structures of TB vaccine R&D ignores this reality.

Community voices also remain absent from the design and conduct of TB vaccine trials. In last year's *Pipeline Report*, TAG noted the absence of community engagement programs in TB vaccine R&D – the exemplary community advisory boards of SATVI and the Kenya Medical Research Institute excepted.[85] A year later, there is still no global community advisory board that can connect vaccine developers to community priorities, concerns, and perspectives, although Aeras has taken exploratory steps to create such a mechanism.[86] The pace of these steps must quicken. Communities have a right to participate in research as more than just trial participants,[87] and the early state of TB vaccine R&D means that they will be asked to do so time

and again. Guidelines such as the *Good Participatory Practice Guidelines for TB Drug Trials*, and the field experiences of TB drug developers implementing community engagement programs, offer TB vaccine developers plenty of models for how to begin this important work.[88,89]

The current concentration of TB vaccine funders, developers, and university-based research labs in North America, Europe, and Japan makes it easy to forget that vaccines were originally a South-to-North technology transfer. For example, inoculation against smallpox came to colonial America through the knowledge of slaves brought from Africa and to Europe from the Ottoman Empire.[90] (Upon returning to London from her husband's diplomatic posting at the Ottoman court, Lady Mary Wortley Montague inoculated her own children against smallpox, prompting the English crown to further study the procedure in a "trial" among six prisoners).[91] The conditions of these transfers were far from equal. It is imperative that TB vaccine R&D, even as it turns toward basic science and earlier stages of clinical development, keep considerations of equity at the fore.[92] One way to achieve this is to establish governance structures for the sharing of intellectual property (IP), knowledge, and technology to ensure that once a new vaccine is judged safe and effective in phase III trials, it can be made quickly and equitably available to the communities that need it the most.

Without concerted efforts, equity in access is far from guaranteed. Traditionally, more than a decade can elapse between the licensure of a vaccine by a stringent regulatory agency in the United States or Europe and widespread introduction of that vaccine in developing countries.[93] Reducing this gap will require that vaccine developers license IP and transfer technology and expertise to developing country vaccine manufacturers (DCVMs) to enable local vaccine production.[94] It is encouraging to see major TB vaccine developers such as Aeras establish relationships with vaccine manufacturers, regulators, and scientific partners in India, China, and South Africa.[95] This work to identify developing country partners should continue under a more open, transparent, and strategic framework. A more inclusive GTBVP — one that includes civil society and community representatives in governance roles and throughout the organization's structures — might be the right platform for bringing together the range of stakeholders with financial, legal, or medical interests in vaccine access. This work must start now, before any particular candidate enters phase III trials or prepares for regulatory approval.[96,97] Fulfilling the promise of new TB vaccines to end the TB epidemic's grip on humanity will depend on orienting TB vaccine R&D along the twin axes of meaningful engagement of communities in research and equity in access from the very beginning.

Recommendations

- **Capitalize on the shift to the left to increase funding and support for basic science.** Much basic-science work remains to be done but, broadly speaking, efforts that look at host-pathogen interaction from new angles — moving beyond frameworks that see events in MTB infection and the host response as binary, uniform, and discrete — deserve support. Initial areas of investigation should include identifying new vaccination targets, exploring arms of the immune system beyond cell-mediated immunity, interrogating the at-times deleterious effects of inflammation, and understanding the geography and kinetics of immune processes unfolding in the lung. These endeavors should go beyond exploring mechanisms of protection driven by the host response to considering mechanisms of evasion from the perspective of the MTB pathogen itself.

- **Create opportunities for robust immunology work in clinical trials.** Immunology substudies are often the first thing cut from a trial protocol when funding is scarce. Yet these substudies are instrumental for bridging preclinical work in the lab and results from clinical trials.[98] A growing chorus of voices is calling for more experimental medicine studies that, nested within clinical trials of any phase, probe hypotheses in fine-grained immunologic detail.[99] These experimental medicine studies would sit within and alongside product development efforts and create opportunities to iteratively test new concepts in what has formerly

been a linear product-development pathway.[100] These channels for testing vaccine concepts in addition to candidates should become more established.

- **Adapt clinical trial designs to enable iterative, parallel learning between laboratory and clinic.** The application of PET/CT in clinical trials of TB drug therapy and preclinical models of MTB infection in macaques offers a model for this type of integration. Another approach would involve conducting human studies in phase I in parallel with challenge studies in nonhuman primates to simultaneously learn about immune responses under different experimental conditions. Small-animal models will remain important, and the predictive value of animal models for vaccine selection should be thoroughly evaluated based on findings from the clinic. In addition, the application of adaptive trial designs to larger clinical trials would allow for real-time modification of study protocols in response to emerging safety and efficacy data.[101]

- **Establish meaningful partnerships with civil society organizations and TB-affected communities.** The first step to engaging the broader public in TB vaccine R&D is engaging TB-affected communities in all aspects of research – from clinical trial design to trial conduct to the delivery of new vaccines. Advocates who understand the science of TB vaccine R&D will be best positioned to advocate in its support before governments and funders. Major milestones toward this goal include the formation of a global TB vaccine community advisory board, the development of active community engagement programs at trial sites, and the inclusion of representatives from civil society in the governance of joint initiatives like the GTBVP.

- **Be guided by principles of equity and prepare for access to tomorrow's vaccines today.** Achieving this objective will require action on both global and country levels. Globally, the creation of a patent pool to share TB vaccine IP and the formation of a central clearing house for the transfer of technology and expertise would reduce financial risks for both vaccine developers and the communities that will host and pay for TB vaccine research. These platforms would also help developers prepare to create equitable access to new TB vaccines in the event of success. Vaccine developers will also need to identify DCVMs to receive IP, technology, and information and build country capacity to regulate, manufacture, and introduce new TB vaccines.

Many thanks to all the researchers for the information that made this chapter possible and to Christine Sizemore and Richard Jefferys for thoughtful reviews of early drafts.

REFERENCES

Unless noted otherwise, all links were accessed on June 10, 2015.

HRTBKS: Host Response in Tuberculosis Keystone Symposia

1. Hanekom W. Vaccines against TB: where are we going? Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

2. Frick M. TB R&D's shift to the left. TAGline;22(1):14–5. 2015 April 9. http://www.treatmentactiongroup.org/tagline/2015/spring/tb-rd%E2%80%99s-shift-left.

3. Kaufmann S, Evans T, Hanekom W. Tuberculosis vaccines: time for a global strategy. Sci Transl Med. 2015;7(276):276fs8. doi: 10.1126/scitranslmed.aaa4730.

4. Hanekom W. Vaccines against TB.

5. Rao M, Zumla A, Maeurer M. Host-directed therapy: tuberculosis vaccine development. Lancet Respir Med. 2015 Mar;3(3):172–3. doi:10.1016/S2213-2600(15)00055-7.

6. Gonsalves G. Basic research on HIV infection: a report from the front. New York: Treatment Action Group; 1993. http://www.treatmentactiongroup.org/publications/1993/basic-research-hiv-infection-report-front.

7. Flynn J. Opening remarks at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

8. Cambier CJ, Falkow S, Ramakrishnan L. Host evasion and exploitation schemes of Mycobacterium tuberculosis. Cell. 2014;159:1497–1509. doi: 10.1016/j.cell.2014.11.024.

9. Comas I, Coscolla M, Luo T, et al. Out-of-Africa migration and Neolithic expansion of Mycobacterium tuberculosis with modern humans. Nat Genet. 2013 Oct;45(10):1176–82. doi: 10/1038/ng.2744.

10. Cambier CJ. Host evasion and exploitation schemes.

11. Ibid.

12. Comas I, Chakravartti J, Small P, et al. Human T cell epitopes of Mycobacterium tuberculosis are evolutionarily hyperconserved. Nat Genet. 2010 Jun;42(6):498–503.

13. Ramakrishnan L. Revisiting the role of the granuloma in tuberculosis. Nat Rev Immunol. 2012;12(5):352–66. doi: 10.1038/nri3211.

14. Barber D, Mayer-Barber K, Feng C, et al. CD4 T cells promote rather than control tuberculosis in absence of PD-1-mediated inhibition. J Immunol. 2011;186(3):1598–1607. doi: 10.4049/jimmunol.1003304.

15. Cooper A, Mayer-Barber K, Sher A. Role of innate cytokines in mycobacterial infection. Mucosal Immunol. 2011 May;4(3):252–60. doi: 10.1038/mi.2011.13.

16. Walzl G, Ronacher K, Hanekom W, et al. Immunological biomarkers of tuberculosis. Nat Rev Immunol. 2011 May;11(5):343–54. doi: 10.1038/nri2960.

17. Andersen P, Kaufmann S. Novel vaccination strategies against tuberculosis. Cold Spring Harb Perspect Med. 2014;4:a018523. doi: 10.1101/cshperspect.a018523.

18. Kaplan G. Changing the perspective of research to end TB: a global venture. Paper presented at: Stop TB Partnership Symposium at the 44th Union World Conference on Lung Health; 2013 October 30; Paris, France.

19. Abebe F. Is interferon gamma the right marker for bacilli Calmette-Guérin-induced immune protection? Clin Exp Immunol. 2012 Sep;169(3):213–9. doi: 10.1111/j.1365-2249.2012.04614.x.

20. Lock M. Eclipse of the gene and the return of divination. Current anthropology. 2005 Dec;46(S5):S47–S70. doi: 10.1086/432452.

21. Ottenhoff T, Ellner J, Kaufmann S. Ten challenges for TB biomarkers. 2012 Mar;92(11):S17–S20. doi: 10.1016/S1472-9792(12)70007-0.

22. Lock M. The Alzheimer conundrum: entanglements of dementia and aging. Princeton: Princeton University Press, c2013. p. 110.

23. Scriba T. Prospective correlates of risk of TB disease. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

24. Weiner J. TB biomarkers across cohorts and sample types. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

25. Ibid.

26. Myungsun L, Jongseok L, Matthew W, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012 Oct;367(16):1508–18. doi: 10.1056/NEJMoa1201964.

27. Lenaerts A, Barry C, Dartois V. Heterogeneity in tuberculosis pathology, microenvironments and therapeutic responses. Immunol Rev. 2015;264(1):288–307. doi: 10.1111/imr.12252.

28. Kaplan G. Lesion-specific immune activation in granulomas of patients with pulmonary tuberculosis. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

29. Lin P. Spatial patterns of granuloma development differ between infection and reactivation. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

30. Flynn J. Heterogeneity: global and local. Paper presented at: Host Response in Tuberculosis Keystone Symposia; 2015 January 24; Santa Fe, NM.

31. Ibid.

32. Barry C. Quantifying TB treatment response using PET/CT. (Abstract 109). Paper presented at: TB: Looking to the Future: Resistance Persistence Monitoring and Control. 2014 Conference on Retroviruses and Opportunistic Infections; 2014 March 3–6; Boston, MA.

33. Hanekom W. Vaccines against TB: where are we going?

34. Alter G. A case for antibody Fc-effector function in TB containment. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

35. Mwandumba H. TB/HIV interactions in the airways. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

36. Burgers W. Defects in multiple mycobacterial T helper subsets in blood and lungs in early HIV infection. Paper presented at: HRTBKS; 2015 January 22–27; Santa Fe, NM.

37. Glynn J, Guerra-Assunção J, Houben R, et al. Does HIV infection reduce the probability of transmission of pulmonary tuberculosis (Poster 816)? Poster session presented at: 2015 Conference on Retroviruses and Opportunistic Infections; 2015 February 23–26; Seattle, WA.

38. Knight G, Griffiths U, Sumner T, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. Proc Natl Acad Sci U S A. 2014 Oct;11(43):15520–25. doi: 10.1073/pnas.1404386111.

39. Ibid.

40. Evans T. Testing novel concepts through clinical trials. Paper presented at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

41. Zwerling A, van den Hof S, Scholten J, et al. Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. Thorax. 2012 Jan;67(1):62–70. doi: 10.1136/thx.2010.143180.

42. Metcalfe J, Cattamanchi A, McCulloch C, et al. Test variability of the QuantiFERON-TB Gold In-Tube assay in clinical practice. Am J Respir Crit Care Med. 2013 Jan 15;187(2):206–11. doi: 10.1164/rccm.201203-0430OC.

43. Behr M, Schwartzman K, Pai M. Tuberculosis vaccine trials. Comment on Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomized, placebo-controlled phase 2b trial. Lancet. 2013 Jun 29;381(9885):2252–3. doi: 10.1016/S0140-6736(13)61481-6.

44. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT02075203, A randomized, placebo controlled, partially blinded phase II study to evaluate safety, immunogenicity and prevention of infection with Mycobacterium tuberculosis of Aeras-404 and BCG revaccination in healthy adolescents; 2015 May 26 (cited 2015 April 2). https://clinicaltrials.gov/ct2/show/NCT02075203.

45. McShane H. Tuberculosis vaccines: beyond bacilli Calmette–Guérin. Philos Trans R Soc Lon B Biol Sci. 2011 Oct 12;366(1579):2782–9. doi: 10.1098/rstb.2011.0097.

46. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01865487, Phase I/IIa safety & immunogenicity of Aeras-456 in HIV-negative adults with & without latent tuberculosis infection; 2014 November 11 (cited 2015 June 10). https://clinicaltrials.gov/ct2/show/NCT01865487.

47. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT02378207, Phase 1b safety and immunogenicity trial of BCG revaccination, H4:IC3, and H56:IC31 in healthy, HIV-1-uninfected adolescents; 2015 February 22 (cited 2015 April 2). https://clinicaltrials.gov/ct2/show/NCT02378207.

48. Morten Ruhwald (Statens Serum Intitut, Copenhagen, Denmark). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2015 April 23.

49. Ibid.

50. Ibid.

51. Aeras. Large trial will evaluate vaccine's ability to prevent tuberculosis disease (Press Release). 2014 August 28 (cited 2015 April 1). Available from: www.aeras.org/pressreleases.

52. Idoko O, Owolabi O, Owiafe P, et al. Safety and immunogenicity of the M72/AS01 candidate tuberculosis vaccine when given as a booster to BCG in Gambian infants: an open-label randomized controlled trial. Tuberculosis (Edinb). 2014 Dec;94(6):564–78. doi: 10.1016/j.tube.2014.07.001.

53. Montoya J, Solon J, Cunanan S, et al. A randomized, controlled dose-finding phase II study of the M72/AS01 candidate tuberculosis vaccine in healthy PPD-positive adults. J Clin Immunol. 2013 Nov;33(8):1360–75. doi: 10.1007/s10875-013-9949-3.

54. Day C, Tameris M, Mansoor N, et al. Induction and regulation of T-cell immunity by the novel tuberculosis vaccine M72/AS01 in South African adults. Am J Respir Crit Care Med. 2013 Aug 15;188(4):492–502. doi: 10.1164/rccm.201208-1385OC.

55. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01755598, Study to evaluate the efficacy of GlaxoSmithKline Biologicals' candidate tuberculosis vaccine in adults; 2015 March 19 (cited 2015 April 1). https://clinicaltrials.gov/ct2/show/record/NCT01755598.

56. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT02097095, Substudy of protocol Tb-018 (NCT01755598): collection and storage of biological samples for evaluation of correlates of TB (C-041-972); 2014 October 8 (cited 2015 May 18). https://clinicaltrials.gov/ct2/show/NCT02097095.

57. Ndiaye B, Thienemann F, Landry M, et al. Safety, immunogenicity and efficacy of the candidate tuberculosis vaccine MVA85A in healthy adults infected with HIV-1: a randomized, placebo-controlled, phase 2 trial. Lancet Respir Med. 2015 Mar;3(3):190–200. doi: 10.1016/S2213-2600(15)00037-5.

58. Ibid.

59. Ibid.

60. Tameris M, Haterhill M, Landry B, et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomized, placebo-controlled phase 2b trial. Lancet. 2013 Mar 23;381(9871):1021–8. doi: 10.1016/S0140–6736(13)60177–4.

61. Rao M. Host-directed therapy: tuberculosis vaccine development.

62. Santosuosso M, McCormick S, Zhang X, et al. Intranasal boosting with an adenovirus-vectored vaccine markedly enhances protection by parenteral Mycobacterium bovis BCG immunization against pulmonary tuberculosis. Infect Immun. 2006 Aug;74(8):4634–43.

63. White A, Sibley L, Dennis M, et al. Evaluation of the safety and immunogenicity of a candidate tuberculosis vaccine MVA85A delivered by aerosol to the lungs of macaques. Clin Vaccine Immunol. 2013;20(5):663–72. doi: 10.1128/CVI.00690-12.

64. Satti I, Meyer J, Harris S, et al. Safety and immunogenicity of a candidate tuberculosis vaccine MVA85A delivered by aerosol in BCG-vaccinated healthy adults: a phase I, double-blind, randomized controlled trial. Lancet Infect Dis. 2014 Oct;14(10):939–46. doi: 10.1016/S1473-3099(14)70845-X.

65. Ibid.

66. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01683773, Safety study of tuberculosis vaccines Aeras-402 and MVA85A; 2014 September 16 (cited 2015 April 2). https://clinicaltrials.gov/ct2/show/NCT01683773.

67. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01198366, Study of Aeras-402 in healthy infants; 2014 April 17 (cited 2015 April 6). https://clinicaltrials.gov/ct2/show/NCT01198366.

68. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01198366, Changes to NCT01198366 on 2012_11_13; 2012 November 13 (cited 2015 April 6). https://clinicaltrials.gov/archive/NCT01198366/2012_11_13/changes.

69. Tameris M, Hokey D, Nduba V, et al. A double-blind, randomized, placebo-controlled, dose-finding trial of the novel tuberculosis vaccine AERAS-402, an adenovirus-vectored fusion protein, in healthy, BCG-vaccinated infants. Vaccine. 2015;33(25):2944–2954. doi: 10.1016/j.vaccine.2015.03.070.

70. McShane H. TB vaccine development using recombinant viral vectors. Paper presented at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

71. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01879163, Phase I trial evaluating safety and immunogenicity of MVA85A-IMX313 compared to MVA85A in BCG vaccinated adults; 2014 December 15 (cited 2015 April 2). https://clinicaltrials.gov/ct2/show/NCT01879163.

72. Spencer A, Hill G, Honeycutt J, et al. Fusion of the Mycobacterium tuberculosis antigen 85A to an oligomerization domain enhances its immunogenicity in both mice and non-human primates. PLoS One. 2012 Mar;7(3):e33555. doi: 10.1371/journal.pone.0033555.

73. Imaxio (Press Release). Imaxio announces the first human clinical trial using its pro-immunogenic technology IMX313 in tuberculosis. 2013 September 3. http://www.imaxio.com/upload/editorHTML/130828 IMX313 first in human EN.pdf.

74. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT01829490, Safety study of ChAdOx1 85A vaccination with and without MVA85A boost in healthy adults; 2015 February 18 (cited 2015 April 2). https://clinicaltrials.gov/ct2/show/NCT01829490.

75. da Costa C, Walker B, Bonavia A. Tuberculosis vaccines—state of the art, and novel approaches to vaccine development. Int J Infect Dis. 2015 Mar;35:5–12. doi:10.1016/j.ijid.2014.11.026.

76. Martin C. Searching for the mechanisms of protection and attenuation of MTBVAC. Paper presented at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

77. Spertini F. First-in-human phase 1 study results of MTBVAC, a live attenuated vaccine from human origin. Paper presented at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

78. Stukova M. Randomized double-blind placebo-controlled phase I trial of intranasal TB/FLU-04L tuberculosis vaccine in BCG-vaccinated healthy adults aged 18–50 years. Paper presented at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

79. Ibid.

80. von Reyn F. DAR-901 inactivated whole cell mycobacterial booster vaccine: phase I dose escalation study. Paper presented at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

81. Ibid.

82. Olesen O. Global TB Vaccine Partnership. Satellite session at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

83. Kaufmann S. Tuberculosis vaccines: time for a global strategy.

84. Biss, E. On immunity: an inoculation. Minneapolis, Minnesota: Graywolf Press; c2014. p. 95.

85. Frick M. The TB vaccines pipeline: back to basic science. In: Clayden P, Collins S, Daniels C, et al.; i-Base/Treatment Action Group. 2014 pipeline report. Edited by Andrea Benzacar. New York: Treatment Action Group; 2014. p. 233–53. http://www.pipelinereport.org/2014/tb-vaccine.

86. Kristin Coucher and Gavin Robertson (Aeras, Cape Town, South Africa). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2015 January 6.

87. DeLuca A, Lessem E, Wegener D, et al. The evolving role of advocacy in tuberculosis. Lancet Respir Med. 2014 Apr;2(4):258–9. doi: 10.1016/S2213-2600(14)70035-9.

88. Stakeholder and Community Engagement Workgroup of the Critical Path to TB Drug Regimens. Good participatory practice guidelines for TB drug trials. Washington, D.C.: Critical Path to TB Drug Regimens; 2012. http://www.cptrinitiative.org/downloads/resources/GPP-TB%20Oct1%20 2012%20FINAL.pdf.

89. Boulanger R, Seidel S, Lessem E, et al. Engaging communities in tuberculosis research. Lancet Infect Dis. 2013 Jun;13(6):540–5. doi: 10.1016/ S1473-3099(13)70042-2.

90. Niven S. Onesimus (fl. 1706–1717), slave and medical pioneer [Internet]. Cambridge (MA): Hutchins Center for African & African American Research, Harvard University. http://hutchinscenter.fas.harvard.edu/onesimus-fl-1706-1717-slave-and-medical-pioneer-was-born.

91. Riedel S. Edward Jenner and the history of smallpox vaccination. Proc (Bayl Univ Med Cent). 2005 Jan;18(1):21–5. http://www.ncbi.nlm.nih.gov/ pmc/articles/PMC1200696/.

92. Frick M. TB's shift to the left.

93. Crager S. Improving global access to new vaccines: intellectual property, technology transfer, and regulatory pathways. Am J Public Health. 2014 Nov;104(11):e85–91. doi: 10.2105/AJPH.2014.302236.

94. Ibid.

95. Aeras (Press Release). Chinese CDC and Aeras sign agreement to collaborate on tuberculosis vaccine R&R.

96. Friede, Martin (World Health Organization, Technology Transfer Initiative, Geneva, Switzerland). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2015 March 31.

97. Crager, Sara (University of California, Los Angeles, Department of Emergency Medicine, Los Angeles, CA). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2014 November 14.

98. Hanekom W. Vaccines against TB: where are we going?

99. Ibid.

100. McShane H. Experimental medicine. Global TB vaccine partnership. Satellite session at: 4th Global Forum on TB Vaccines; 2015 April 21–24; Shanghai, China.

101. Kaufmann S. Tuberculosis vaccines: time for a global strategy.