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CONFERENCE REPORT

Advocacy, partnership and political commitment for TB vaccine research

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SUMMARY

The 4th Global Forum on TB Vaccines, convened in Shanghai, China, from 21 – 24 April 2015, brought together a wide and diverse community involved in tuberculosis vaccine research and development to discuss the current status of, and future directions for this critical effort. This paper summarizes the sessions on Advancing the Pipeline: A Vision for the Next Decade, Engaging the BRICS: Basic Research to Manufacturing, and Regulatory and Access Issues for New TB Vaccines. Summaries of all sessions from the 4th Global Forum are compiled in a special supplement of *Tuberculosis*. **[August 2016, Vol 99, Supp S1, S1–S30]**.

1. Introduction

When world leaders adopted the Millennium Declaration in September 2000, they included specific targets to halt and begin to reverse the incidence of tuberculosis (TB). The Millennium Declaration was followed by new initiatives to overcome the structural and financial obstacles for developing new TB vaccines, backed by support from public and philanthropic sources. These initiatives included the establishment of dedicated product development partnerships (PDPs) such as Aeras and the TuBerculosis Vaccine Initiative (TBVI), public–public partnerships like the European & Developing Countries Clinical Trials Partnership (EDCTP), and dedicated programs by major research funding agencies. Fifteen years later, the TB vaccine research field has arrived at the right moment—scientifically and politically—to review progress and reflect on the best ways to move forward. To anticipate the next decade of TB vaccine research and development (R&D), speakers at the 4th Global Forum presented perspectives on how scientific advances, advocacy and resource mobilization challenges, the increasingly important role of the BRICS (Brazil, Russia, India, China, South Africa) countries, and regulatory and access issues might affect research for new TB vaccines.

2. Advancing the pipeline: a vision for the next decade

During the final plenary session of the 4th Global Forum, Dr. Laurent Bochereau (Delegation of the European Union to China), Dr. Willem Hanekom (Bill & Melinda Gates Foundation, USA), Prof. Michel Kazatchkine (UN Secretary-General's Special Envoy on HIV/AIDS in Eastern Europe and Central Asia, Switzerland), Dr. Kei Katsuno (Global Health Innovative Technology Fund, Japan), and Dr. Ole Olesen (EDCTP, the Netherlands) discussed the global environment for TB vaccine R&D and how it could be improved in the next decade. This section summarizes key points from that discussion.

2.1. Mobilizing resources, promoting collaboration, and broadening the base of support

A large proportion of TB vaccine R&D funding comes from the public sector and from philanthropic organizations, while industry investments comprise less than 20% of global funding [1]. With an annual investment of approximately US$45 million, the Bill & Melinda Gates Foundation (Gates Foundation) is currently the world's largest funder of TB vaccine R&D, while the European

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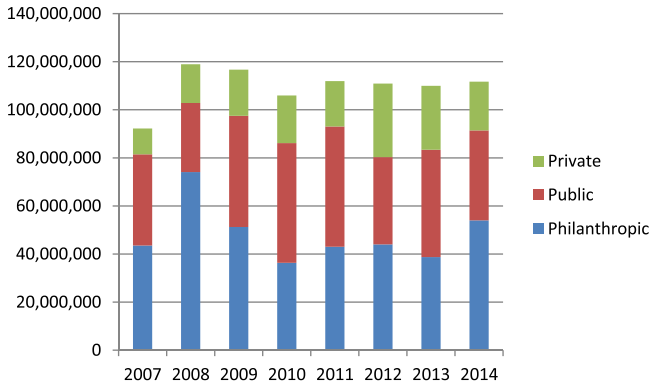

Figure 1. Funding for preventive TB vaccine R&D by year and funder category, 2007–2014.
Data source for figure: G-FINDER Public Search Tool [1].

Union (EU), and the United States (US), British, Dutch and Danish governments constitute the largest public funders of TB vaccine R&D. Together, these six sources provided 75% of total global funding for TB vaccine R&D from 2007 to 2014 [1]. During this period, total global investment for preventive TB vaccine R&D hovered around US$110 million per year (Figure 1) [1], which is only about 15% of the average investment in preventive HIV vaccines in that same timeframe [1]. Low- and middle-income countries contribute more than half of global gross domestic product (GDP) and carry the vast majority of TB disease burden, but their financial contribution to TB vaccine R&D remains negligible.

Developing an effective TB vaccine represents a global endeavor, requiring broad ownership, a wider and more diverse funding base, and further involvement of and collaboration between researchers, clinicians, manufacturers, civil society, and affected communities. To make this goal a reality, the EU has recently supported two large four-year collaborative projects on preclinical TB vaccine research, TBVAC2020 and EMI-TB, utilizing €26 million from the Horizon 2020 program. In addition, the EDCTP2 program is expected to disburse more than €1.4 billion over the next 10 years for clinical trials in sub-Saharan Africa, including TB vaccine trials. At the time of the Global Forum, the Global Health Innovative Technology Fund (GHIT Fund) had invested over US$35 million in nearly 40 collaborative research projects between Japanese and non-Japanese organizations with a focus on infectious diseases prevalent in developing countries, including funding of US$5.7 million for work on a novel vaccine candidate to combat TB. The Gates Foundation has established a new consortium called the Collaboration for TB Vaccine Discovery (CTVD) to promote innovation in the upstream research space through discussion forums and early data-sharing, by leveraging co-funding of the TB vaccine field by various funding stakeholders, and by providing service platforms to facilitate state-of-the-art science.

While dedicated funding opportunities exist for TB vaccine R&D, they are far from sufficient to support the intensive basic science, preclinical and clinical investigations necessary to efficiently move the field forward in a manner commensurate with the extent of disease and death caused by TB. TB vaccine R&D has to compete for sufficient attention with many other diseases and social problems. Funders and decision-makers must be convinced that new, more effective TB vaccines would not only be a highly cost-effective tool for improving global public health, but also that their investments will return value for funding. Further, speakers voiced the need to establish a global advocacy plan which would allow a broad array of stakeholders to communicate with policy makers in a coherent, consistent, and more efficient manner, while avoiding the fragmentation and rivalry that sometimes has hindered progress in other scientific areas. Speakers also emphasized the need for the TB vaccines community to advance a bolder, more innovative research agenda, learning from experiences in other disease areas, such as HIV.

2.2. *Advancing the science*

Funding and broader ownership of R&D will be driven by scientific innovation, by progress in developing new TB vaccines, and by demonstrating that TB vaccine research can be deployed in a cost-efficient manner. To achieve this, vaccine candidates should be de-risked at earlier stages of development to ensure that limited resources are applied to the advancement of candidates with the greatest likelihood of success. Target product profiles should guide the product development pathway. At the same time, the potential for generating more diversity in the types of immunologic responses beyond classical $CD4^+$ and $CD8^+$ T-cell responses generated by TB vaccine candidates needs to be explored. The potential effect of heterogeneity in both human populations and tuberculosis strains on the efficacy of candidate TB vaccines should also be addressed. Better animal models, the identification of correlates of protection, and early proof-of-concept vaccine trials will help determine if a vaccine has the desired clinical profile before entering large and costly phase 2b/3 clinical efficacy trials. This ideally would be done through an efficient, transparent, and rigorous gating system to compare, select, and advance the most promising vaccines candidates towards a final product. In 2012, TBVI and Aeras took the first step in this direction by developing a set of consensus stage-gating criteria to inform advancement of TB vaccine candidates at each step of the development pipeline—from discovery work to phase 3 trials [2]. At the time of the Global Forum, discussions were underway to establish a Global TB Vaccine Partnership (GTBVP), which would adopt and expand this stage gate approach to provide advice to a broader constituency of funders, researchers and industry groups involved in TB vaccine R&D across the globe.

3. Engaging the BRICS: from basic research to manufacturing

During a plenary session focused on better engaging the BRICS countries in TB vaccine R&D, Dr. Luciana Leite (Butantan Institute, Brazil), Dr. Soumya Swaminathan (Indian Council for Medical Research, India), Dr. Bi Lan (China National Biotech Group, China), and Prof. Gavin Churchyard (Aurum Institute, South Africa) discussed the respective BRICS countries' capacities for research, development, manufacturing and clinical trials of TB vaccines. Together the BRICS countries comprise 40% of the world's population and 20% of the world's GDP, and share socio-economic and environmental issues that contribute to the high burden of TB. Collectively, the BRICS countries account for almost 50% of reported TB cases globally [3]. Each of these countries, however, has significantly different levels of experience and capabilities for conducting TB vaccine R&D.

In Brazil and India, most TB vaccine R&D is conducted in academic and government research centers and is focused on discovery and preclinical phases. China and South Africa have development programs through national grants for R&D of novel TB vaccines. China is supporting the development of new or improved TB vaccine candidates, including recombinant BCG (rBCG) as a BCG replacement, and prime/boost vaccines in collaboration with international partners. South Africa has established the Strategic Health Innovation Partnerships (SHIP) program, under the Medical Research Council (MRC), with the mission to seek, fund and manage multi-disciplinary and multi-institutional product research, development and innovation projects from prototype to