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CONFERENCE REPORT

TB vaccines in clinical development

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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 TB Vaccines in Clinical Development, and Clinical Research: Data and Findings. Summaries of all sessions from the 4th Global Forum are compiled in a special supplement of *Tuberculosis*. **[July 2016, Vol 99, Supp S1 - XX].**

1. Introduction

At the time of the first Global Forum for TB Vaccines, in 2001, there were not yet any candidate TB vaccines in the worldwide clinical portfolio [1]. In contrast, in 2015, at the time of the 4th Global Forum, there were at least 15 candidate TB vaccines and vaccine combinations being evaluated in clinical trials. This portfolio contains a variety of vaccine platforms, including recombinant BCGs, other whole cell mycobacteria or lysates, viral-vectored vaccines and adjuvanted subunit vaccines (Figure 1), although these candidates represent only modest diversity of immune mechanisms with most candidates designed to stimulate primarily a $CD4^+$ Th1 T-cell response. Most of the 15 candidates in the clinical pipeline are in relatively early stage evaluation (phases 1 through 2a) or are being used as "tools" to evaluate experimental medicine hypotheses. One candidate, MVA85A, has progressed to phase 2b efficacy evaluation [2] but unfortunately did not demonstrate an increase in efficacy of the BCG-MVA85A prime-boost regimen compared to BCG alone in South African infants. A correlates of risk analysis is ongoing on samples from this trial. Another phase 2b trial, with the GSK candidate M72/AS01$_E$, is underway in Africa [3]. A phase 3 trial is ongoing in China of a therapeutic vaccine, Vaccae®, for prevention of TB reactivation disease in those with latent *Mycobacterium tuberculosis* (Mtb) infection [4]; results should be available in the second half of 2016.

The results of the MVA85A phase 2b trial stimulated debate as to the value of efficacy trials with the current candidate vaccines. Some maintained that the probability of success for any of the current candidates is too low, and that the absence of a validated correlate of protection or predictive animal model makes it difficult to justify the resources required to conduct large, costly efficacy trials. Alternatively, however, without any level of human efficacy data the field cannot validate a correlate of protection or a relevant animal model, nor will it benefit from the iterative learning between clinical and preclinical studies that can only result when human efficacy data and animal model data are obtained and compared on a range of candidates.

Participants also discussed the merits of developing infant vaccines either to replace or boost BCG versus the development of vaccines targeted at adolescents and adults. While improved infant vaccines could provide enhanced safety and/or longer duration of protection than BCG, effective adolescent/adult vaccines, if delivered efficiently, would provide a more rapid public health impact because most transmission and the greatest burden of disease are seen in this latter age group. Ideally, novel TB vaccines will be developed for both these populations.

2. BCG-based whole cell vaccines

Prof. Stefan Kaufmann (Max Planck Institute for Infection Biology, Germany) discussed recombinant BCG (rBCG) vaccine candidates,

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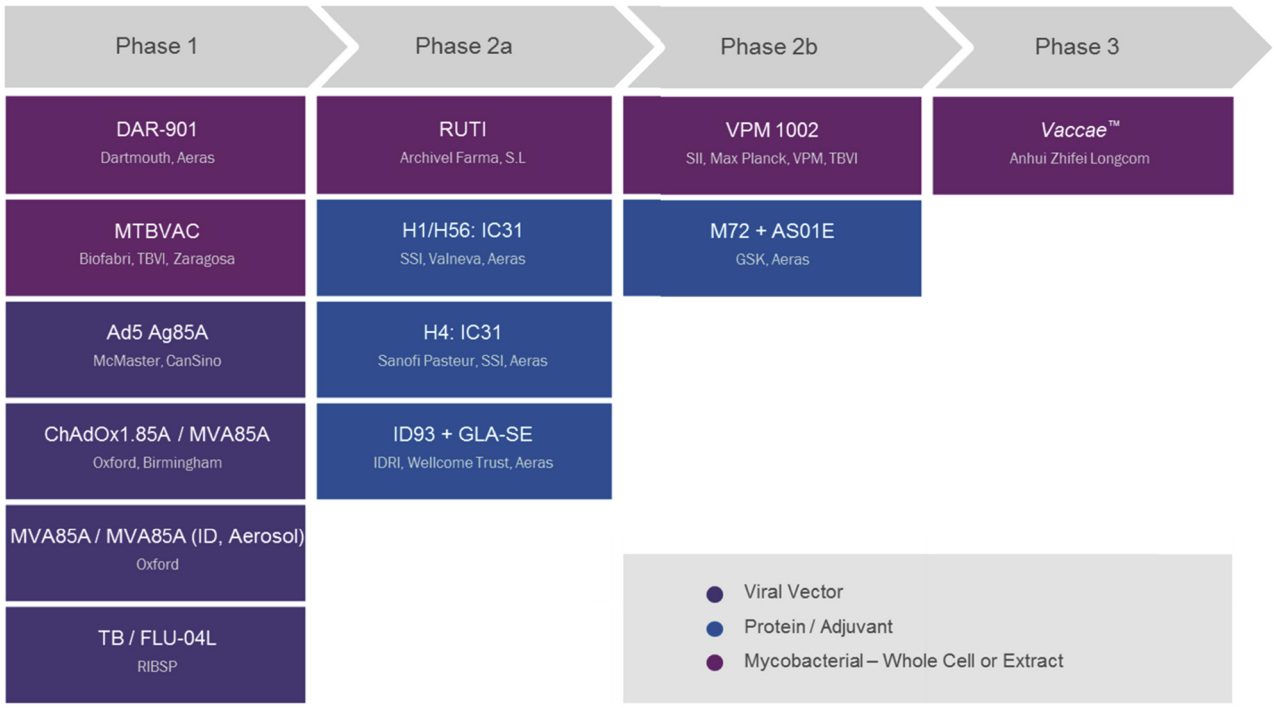

Figure 1. Global Clinical Pipeline of TB Vaccine Candidates.

being developed primarily to replace BCG as a priming vaccine in infants. He noted two current approaches to improving BCG efficacy: improvement of a beneficial effect or reduction of a potentially disadvantageous one. The lead rBCG candidate, VPM1002 (BCGureΔC::hly), which expresses listeriolysin, was discovered in the Kaufmann laboratory, licensed to Vakzine Projekt Management GmbH and sub-licensed to Serum Institute of India [5]. It is designed to enhance immunogenicity and efficacy by increasing antigen cross-presentation to MHC Class I-restricted $CD8^+$ T-cells and induction of IL-17 responses. This involves apoptosis and autophagy in antigen presenting cells. In phase 1/2a studies in adults and infants, VPM1002 has demonstrated an acceptable safety and immunogenicity profile. A larger phase 2 study that will compare safety and immunogenicity of VPM1002 and BCG in newborns delivered by HIV + mothers has subsequently been initiated in South Africa. A multicenter therapy trial using VPM1002 to treat bladder cancer has also been initiated. Additional improvements to VPM1002 continue to be explored by the Kaufmann laboratory.

Recombinant BCG30 (rBCG30) was designed by the Horwitz laboratory at UCLA to enhance antigenicity by over-expressing the 30kd complex of Mtb and completed a first-in-human trial in 2008 [6]. Another rBCG, AERAS-422, was developed to enhance both antigenicity and immunogenicity via addition of a mutated perfringolysin from *Clostridium perfringens* and over-expression of the Mtb antigens Ag85A, Ag85B and Rv3407. The development of AERAS-422 was halted, however, by the reactivation of latent Varicella Zoster virus (VZV) infection in two subjects during the first-in-human, phase 1 trial. A third rBCG, rBCGΔzmp1 from the Sander/Böttger laboratories in Zürich, Switzerland is designed to reduce immune subversion but has not yet advanced into clinical testing [7]. In addition to replacing BCG, vaccine developers are considering rBCGs as a potential BCG booster, particularly in adolescents and adults, with the aim of blocking transmission and providing longer duration protection for this key age group.

3. First-in-human phase 1 study results of MTBVAC, a live-attenuated vaccine from human origin

Dr. Francois Spertini (University of Lausanne, Switzerland) presented data from a first-in-human phase 1 trial in Lausanne, Switzerland with MTBVAC, an attenuated Mtb strain based on the deletions in the *phoP* and *fadD26* genes [8]. The trial consisted of three cohorts, each with three subjects administered BCG and nine subjects administered MTBVAC at 5×10^3, 5×10^4 or 5×10^5 colony forming units (CFU), where the upper dose was chosen to be equivalent to the licensed BCG dose. Initial analysis of the trial data demonstrated an acceptable safety profile, and in particular, the absence of conversion towards positive response to ESAT-6 and CFP-10 at the end of the trial in all volunteers. Immunogenicity showed a trend towards a stronger $CD4^+$ T-cell antigen specific response, a strong polyfunctional memory response and an enlargement of the polyfunctional response over time in comparison to BCG. However, the group sizes are still too small to support statistical analysis, waiting for future phase 2 studies. Memory T-cells were detectable 210 days post-vaccination; a follow-up in three to five years is planned. Globally, MTBVAC was at least as immunogenic as BCG. These data support advanced clinical development in high-burden tuberculosis endemic countries.

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