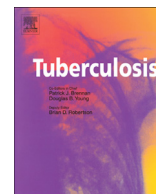




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CONFERENCE REPORT

TB vaccines in clinical development

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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].

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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/AS01E, is underway in Africa [3]. A phase 3 trial is ongoing in China of a therapeutic vaccine, Vaccacae®, 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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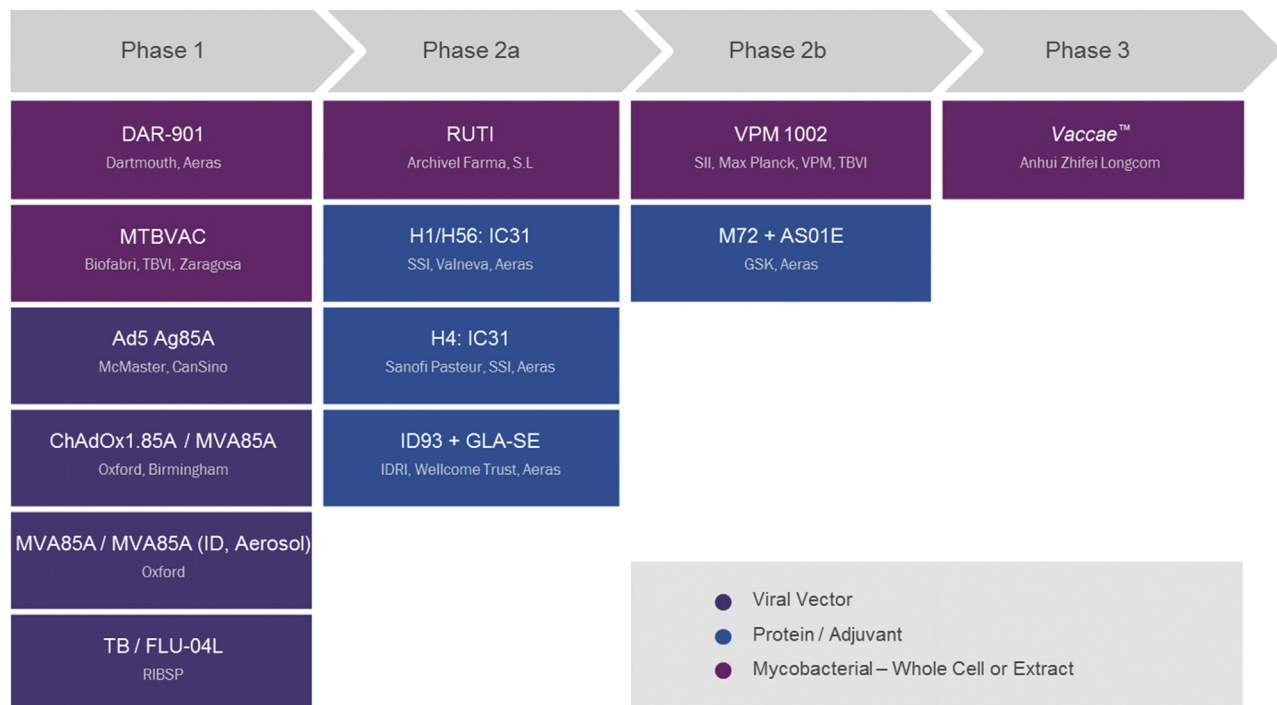


Figure 1. Global Clinical Pipeline of TB Vaccine Candidates. The information in Figure 1 is as of December 2015 and is reported by vaccine sponsors. Image courtesy of Aeras.

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 (BCG_{ur}eΔC::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.

4. TB vaccine development using recombinant viral vectors

Prof. Helen McShane (University of Oxford, UK) described using recombinant viral vectored TB vaccines, including MVA85A, as boosts to BCG. MVA was chosen as the vector for its safety record and ability to induce both humoral and cellular immune responses. The phase 2b efficacy study of this vaccine demonstrated that the modest immune responses induced in South African infants by this vaccine when given as a boost to BCG were not adequate to provide protection beyond that provided by BCG alone [2]. The quality and quantity of induced immune responses

that would be adequate to provide protection, however, remain open questions. McShane and colleagues are conducting further analyses of study samples to identify correlates of risk of TB disease in this population [9]. These analyses are also being conducted with samples from a recently conducted phase 2 safety and immunogenicity trial of MVA85A in HIV + adults in Africa [10]. McShane discussed three strategies for improving efficacy of viral-vectored recombinant TB vaccines: 1) combination boosting strategies, such as an adenovirus-vectored vaccine (induces primarily CD8⁺ T-cells) followed by an MVA-vectored vaccine (induces primarily CD4⁺ T-cells), which has been efficacious in a malaria human challenge model and appears promising for Ebola; 2) inclusion of additional and/or different antigens; and 3) alternate routes of vaccine administration, particularly aerosol delivery. McShane's group has conducted a phase 1 study of aerosol vs. intradermal MVA85A [11]. Aerosol vaccination demonstrated an acceptable safety profile, with one case of reactivation of latent VZV infection in a young adult subject who received 10⁸ plaque-forming units (pfu) of aerosol MVA85A. Aerosol MVA85A also resulted in robust antigen-specific CD4⁺ and CD8⁺ immune responses, with greater CD4⁺ responses in the bronchoalveolar lavage (BAL) fluid following aerosol compared to intradermal delivery and comparable systemic CD4⁺ T-cell responses. Systemic CD8⁺ responses were also higher following aerosol compared to intradermal delivery, although CD8⁺ responses were comparable following the two delivery methods in BAL specimens. Lastly, McShane discussed three potential approaches to improving TB vaccine selection models: 1) developing pre-clinical models that more closely resemble natural infection; 2) conducting experimental medicine studies to better elucidate human immunology in the target population; and 3) developing a human mycobacterial challenge model.

5. TB subunit vaccines, memory and immunity in the lung

Prof. Peter Andersen (Statens Serum Institut – SSI, Denmark) discussed adjuvanted subunit vaccines. The rationale supporting this vaccine approach included: 1) excellent safety profiles; 2) they are molecularly well-defined; 3) responses are not complicated by immune responses targeting the vector, thereby permitting the possibility of boosting; and 4) delivery devices allow for slow antigen release. An argument against their use is their composition of multiple antigenic components, and complex adjuvant formulations, which result in challenges to GMP manufacture and analysis. Andersen highlighted that, in both preclinical and clinical studies, and unlike BCG, several subunit vaccines induce IL-2⁺TNF⁺ double positive CD4⁺T-cells indicative of a central memory phenotype.

Andersen presented results of the evaluation of the SSI H56 vaccine in non-human primate (NHP) models. Based on analyses of inflammatory markers, chest radiology, PET-CT scanning and lung pathology, the CAF01-adjuvanted H56 vaccine appears to promote early protection from low dose Mtb challenge with minimal pulmonary inflammation/pathology and with efficient control of bacterial growth in regional lymph nodes. CAF01 and IC31, the adjuvant systems used in the H56 vaccine in clinical development, prevent ESAT-6 specific IFN- γ responses post infection, which may indicate an ability to prevent interferon gamma release assay (IGRA) conversions in humans. Increasing the magnitude of the vaccine-induced Th1 response with stronger adjuvants was found to negatively impact efficacy in the NHPs. Andersen also presented results from human phase 1 and 2a trials of H56:IC31 and its predecessor H1:IC31, demonstrating that these vaccines are well tolerated and generate an immune profile with sustained IL-2 and TNF-alpha double positive central memory T-cells [12].

6. Vaccination of adolescents in a TB endemic setting with M72/AS01_E

Dr. Adam Penn-Nicholson (SATVI, University of Cape Town, South Africa) described results from a phase 2 safety and immunogenicity trial of M72/AS01_E recently conducted at SATVI in HIV-, healthy adolescents [13]. Two doses of vaccine (n = 40) or placebo (n = 20) were administered one month apart. Approximately 50% of participants were QuantiFERON (QFT)+. M72/AS01_E demonstrated an acceptable safety profile with no serious adverse events (SAEs) reported. A marked increase in CD4⁺ antigen-specific T-cell responses was seen seven days after each vaccination; responses were sustained above background throughout the study with magnitudes among the highest from any TB vaccine seen at SATVI. The immune response was dominated by IFN-gamma, TNF-alpha, IL-2 triple positive cells and IFN-gamma, TNF-alpha double positive cells. Of interest, the IL-2⁺TNF-alpha⁺ antigen-specific CD4⁺ T-cells increased relatively late compared to other T-cell populations identified. CD8⁺ T-cell responses were generally detectable but low in vaccine recipients. The importance of conducting trials in TB endemic areas was highlighted by the finding that 3 of 20 placebo recipients had significantly higher than background responses to M72. Also, QFT+ individuals demonstrated rapid and sustained antigen-specific CD4⁺ T-cell and antibody responses following the first vaccination while QFT- individuals required the second vaccination to produce similar magnitude responses. These results suggest natural infection may prime the immune response to M72. M72/AS01_E is being further evaluated in an ongoing multicenter phase 2b safety, immunogenicity and efficacy trial in approximately 3500 QFT+, HIV-adults across Africa [3].

7. DAR-901 inactivated whole cell mycobacterial booster vaccine: phase I dose escalation study

Dr. Ford von Reyn (Geisel School of Medicine, Dartmouth College, USA) presented the heat-inactivated, whole cell mycobacterial vaccine candidate, DAR-901, which at the time of the Forum was undergoing a first-in-human, phase 1 dose escalation study in the United States in collaboration with Aeras [14]. DAR-901 represents a scalable, broth grown manufacturing method for agar-grown SRL172 and is being developed as a booster for adolescents and adults [15]. SRL172 was evaluated in Tanzania in a phase 3 trial of 2013 HIV+, BCG + adults who each received five vaccinations (at 0, 2, 4, 6 and 12 months). The vaccine demonstrated an acceptable safety and tolerability profile and 39% efficacy against the secondary endpoint of preventing “definite TB” (≥ 1 positive culture or ≥ 2 positive sputum smears). Both cellular and humoral responses were detected in this trial [16]. Von Reyn commented that a study in the 1930s of five doses of inactivated *Mycobacterium bovis*, delivered intradermally, demonstrated 42% efficacy against TB disease ($p < 0.1$) [17].

The first-in-human DAR-901 phase 1 trial enrolled HIV- (n = 54) and + (n = 5) adults who had received BCG in the past. The double-blind dose escalation stage of the trial administered vaccine intradermally x3 at 0, 2 and 4 months versus saline placebo x3 or active control (saline x2, BCG x1). Participants are followed up to 10 months. The study is designed with dose escalation cohorts starting at 0.1 mg and escalation to 0.3 mg and 1 mg. von Reyn reported that the preliminary safety data show the vaccine has an acceptable safety profile, is well tolerated and has injection site reactions comparable to those observed in the SRL-172 trial. Immunology data are pending.

8. AdHu5Ag85A vaccine for aerosol delivery

Dr. Fiona Smaill (McMaster University, Canada) reported on the development of an Ad5-vectored Ag85A vaccine. From the recombinant Ad5 vector, E1 and E3 have been genetically deleted, and the expression of the Ag85A insert is driven by a CMV promoter. This vaccine has been evaluated in several animal models including mice, guinea pigs, goats, cattle and NHP; a first-in-human study has also been conducted [18]. The vaccine induced antigen specific polyfunctional CD4⁺ and CD8⁺ T-cells (as measured by intracellular cytokine staining) and demonstrated an acceptable safety profile.

To support aerosol vaccination of Ad5Ag85A in humans, Smaill and colleagues evaluated the characteristics of aerosol generated by the Aeroneb™ Solo Single Patient Use Vibrating Mesh Nebulizer. They found that a loading volume of 0.5 mL could be delivered within 2 min with about 50% of the dose available at the mouth and 85% of droplets less than 5.39 µm in size, which should enhance delivery to airways below the larynx. Vaccine viability was estimated at 17.4%. This nebulizer system will now be used in a planned phase 1 study of aerosol Ad5Ag85A in 36 BCG+ healthy adults [19]. Dose escalation based on safety will be conducted using, 10⁶, 10⁷, and 10⁸ pfu by aerosol with the highest dose also delivered to a cohort intramuscularly for comparison of immune responses in whole blood, PBMCs, and BAL (by ICS and ELISpot, and for Ag85A antibodies). Induced sputum will also be evaluated for comparison with BAL. All participants will have normal pulmonary function at baseline; anyone with a history of smoking or lung disease will be excluded from the study. Participants will be monitored for development of pulmonary symptoms and changes in routine lung function tests.

Dr. Rhea Coler (Infectious Disease Research Institute - IDRI, USA) was unable to present during the Forum but her planned presentation of the adjuvanted subunit vaccine candidate, ID93, can be viewed online through 2017 by visiting www.tbvaccines2015.org and selecting the link to “Forum presentations”.

9. Conclusion

Despite progress in developing clinical TB vaccine candidates, the current global portfolio requires greater diversity in immunologic mechanisms to increase the likelihood of eventual success. The present candidates represent rather limited immunologic diversity—most being focused on inducing conventional CD4⁺ and/or CD8⁺ T-cells, and/or a limited repertoire of target antigens. Discovery efforts are now re-focusing on generating candidates that induce a more diverse set of immune mechanisms. Other areas of focus needed to ensure high probability of success for TB vaccine development include standardized animal models that model natural transmission and use clinical isolates, the development of predefined endpoints and clear criteria to define “protection”, discovery and validation of correlates of protection and risk of disease, new innovative trial designs such as prevention of infection and prevention of TB recurrence trials, and a safe and sensitive human challenge model. Each of these, once validated as predictive with human efficacy data, would transform the process of future TB vaccine development.

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Competing interest: MR is employed by Statens Serum Institute, a governmental not for profit organization holding IP rights to the vaccine H56; MR has no personal ownership of said IP. AMG, HM, HMCs have no conflicts of interest to declare.

Ethical approval: Not required.

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