May 1, 2018

DAR-901 – A TB Booster Vaccine for the World

Tuberculosis (TB) is the leading infectious disease cause of death worldwide, including in persons with HIV infection. Drug-resistant TB, an increasingly global epidemic, requires prolonged treatment with toxic, expensive drugs. BCG, the only vaccine currently in use for prevention of TB, is very effective for the first few years of life, but loses efficacy after 10-15 years. Booster immunization of adolescents or adults with a repeat dose of live BCG does not increase protection (presumably because the immunity induced by a priming dose of BCG reduces replication of a booster dose). Therefore, development of an effective booster TB vaccine for the world is a major international health priority and will be required to meet the global target of tuberculosis elimination by 2035.

Pauci-antigenic **subunit vaccines** have shown promise in animal models but the only two candidates to have completed Ph2 trials have been ineffective (MVA85A, H4:IC131). An emerging consensus favors polyantigenic **whole cell vaccines** as the optimal approach for inducing immunity in the complex human model. The only new vaccine to have shown efficacy in humans in a fully-powered Phase 3 trial is the booster vaccine being developed by investigators at Dartmouth College. The DarDar Trial, a 7-year, 2,000-subject rigorously designed trial conducted in Tanzania and sponsored by the National Institutes of Health ($8 million) showed that SRL172, an inactivated, whole cell vaccine prepared from an environmental mycobacteria, was safe and effective in persons with HIV infection (von Reyn et al AIDS 2010; 24: 675-685).

In 2013, Dartmouth College obtained from Immodulon (London) an exclusive, transferable, worldwide license for the seed strain of SRL 172 for TB prevention. A new, scalable method of manufacture was developed by Aeras (Rockville, MD) and an initial batch of GMP vaccine prepared. An IND was filed with FDA (15838, von Reyn). The vaccine product, now designated DAR-901, is the most advanced and promising candidate in the global portfolio. Pre-clinical studies include a tuberculosis challenge study indicating DAR-901 is superior to BCG booster (Lahey et al, PLoS One, 2016).

DAR-901

- Target product profile: A whole cell, inactivated booster TB vaccine for all adolescents and adults in the world who received BCG at birth (est >2 billion)
- A TB vaccine booster will be used throughout the world in all Low and Middle Income Countries (LMICs). Minimum estimated annual revenue $100 million.

Development team

- Lead: Ford von Reyn MD, Principal Investigator. Harvard Medical School, cum laude ’71; Professor of Medicine at Geisel School of Medicine; Lifetime Achievement Award from the International Union against Tuberculosis (2013); DSc (Hon) from Dartmouth College (2017)
- Collaborators:
    - Robert Arbeit MD, Tufts University School of Medicine, academic research experience in mycobacterial disease, long term collaborator on Dartmouth TB vaccine trials, and extensive drug development experience in biologics
    - C. Robert Horsburgh MD, Boston University School of Public Health, President-Elect, NAR, International Union Against Tuberculosis, PI on MDR-TB clinical trials
    - Ajit Lalvani MD, Chair, Infectious Disease, Imperial College London; Founding Director, Tuberculosis Research Centre; global authority on tuberculosis disease

Phase 1 trial (MDES, US)

- Three-injection Phase 1 dose escalation trial in 59 BCG-primed HIV-negative and HIV-positive adult subjects conducted at Dartmouth under FDA IND (support: Dartmouth College, Aeras)
- Trial completion in February 2016. Excellent tolerability and safety.
- Safety profile: Injection site reactions, mild and comparable to SRL-172; no other treatment-related AEs; no serious adverse events.
- 1 mg dose selected by expert Dose Review Committee (same dose as SRL-172 Phase 3)
- Immune assays confirm both cellular and humoral response to vaccine antigen
- CSR on file with FDA; trial results published April 2017 (PLoS 2016; 12(5))

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Phase 2b trial (PIAT, Tanzania)

- GCP Prevention of Infection (POI) trial funded by GHIT-Japan for $2 million
- POI design represents new paradigm for proof-of-concept; TB infection 10x more common than TB disease and permits smaller sample size and shorter duration of follow-up.
- Design: 650 BCG-primed adolescents, randomized (1:1) three doses DAR-901 vs. Placebo, follow-up 2 years
- Interferon gamma release assay (IGRA) used to detect TB infection endpoint
- Submitted to US IND and approved by Tanzanian Food and Drugs Authority.
- Enrollment complete October 2016, immunization complete February 2017
- Blinded data confirm that immunization is safe and well-tolerated, no related SAEs
- Study completion 2019.

Phase 3 -- Concept

- Trial start 2019 by or with support of future commercial partner
- CBER has indicated EoPh2 meeting can now be scheduled based on SLR172 Ph3 and DAR-901 Ph1 and 2b after commercial partner identified for production of GMP vaccine for Ph3
- Study design: 4-8,000 adolescents and young adults; placebo-controlled RCT; 5-year follow-up.
- Primary endpoint: Prevention of Disease; Secondary endpoint: Prevention of Infection.
- To be conducted at two to four sites in highly endemic regions (e.g., India, Tanzania, South Africa)
- Estimated cost: $50-75 million for standard prevention of disease trial; study team has full trial infrastructure in Tanzania; adaptive design trials also possible at lower cost.
- Target registration: 2025 and subsequent WHO pre-qualification

Manufacturing and vaccine supply

- Robust, broth-based manufacturing process developed by Aeras for Dartmouth
- Cost: filled vial containing 1 mg dose = $1.50
- Bulk drug substance (BDS) representing 150,000 doses stored at IDT Biologika (Rockville MD)
- Master Cell Bank (200 vials) in storage at two separate Fisher BioServices facilities
- Dartmouth has full, transferable rights to manufacturing process

Pharma or investment partner

- Opportunity to acquire license on a TB vaccine already in advanced stages of development, substantially de-risked with extensive safety data, proof-of-concept in humans and opportunity for a priority review voucher (PRV) with the US FDA
- Potential for orphan vaccine indication to prevent pulmonary NTM infection in cystic fibrosis (CF) and chronic lung disease (developed countries); Ph1 study in CF now being planned.

Implications for global health

- Potential to be the first new TB vaccine licensed in the world
- An effective new TB booster vaccine would save millions of lives world-wide and is essential for achieving global TB elimination by 2035
- Full information and on-site presentations are available from Dr. Ford von Reyn

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