TB Vaccine Development Status:
Review of Critical Issues and
Selected Candidates in
Phase 2 or Phase 3

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Outline

• Update of global tuberculosis (TB) burden, including drug-resistant TB
• Review of potential target patient populations and clinical endpoints for TB vaccines
• Review the status of four selected TB vaccine candidates in advanced (phase 2 – phase 3) clinical development
• WHO-IVR TB vaccine development workshop, Geneva, 24 May 2017: summary of key issues
TB: Key Statistics (2015)
WHO Global TB Report 2016

- **10.4 million incident TB cases**
  - 5.9 million (56%) men
  - 3.5 million (34%) women
  - 1 million (10%) children
- **1.8 million TB deaths**
  - Kills more people than any other single infectious agent
  - 400,000 TB deaths among HIV+’s (#1 opportunistic killer)
- **580,000 new drug-resistant (DR) TB cases**
  - 480,000 multi-drug-resistant (MDR-TB)
  - 100,000 rifampicin-resistant (RR-TB)
  - ~10% of MDR = extensively drug-resistant (XDR-TB)
  - 45% of DR-TB came from India, China, Russian Federation
  - Extremely expensive to treat
    - MDR: approximately 10x more expensive than drug sensitive cases
    - XDR: approximately 25-32x more expensive than drug sensitive cases
Projected acceleration of TB incidence decline to target levels (World Health Assembly 2014)

Current global trend: -1.5%/year

-10%/year by 2025

-5%/year

-17%/year

Optimize use of current & new tools emerging from pipeline, pursue universal health coverage and social protection

Introduce new tools: a vaccine, new drugs and shorter regimens for treatment of active TB and latent infection, a point-of-care test
Target Patient Populations: Adolescents and Adults

• The major source of *Mycobacterium tuberculosis* (Mtb) transmission
• Preventing pulmonary TB disease = the key to preventing Mtb transmission
  – Necessary to reach the End TB 2035 goals
  – The most effective strategy to prevent Mtb infection and disease in infants and children*

*Harris R, et. al., Human Vaccine Immuno 2016*
Target Patient Populations: Infants

• Not an important source of Mtb spread
• Efforts ongoing to improve upon BCG
  – Improving safety:
    • BCG contraindicated in immunosuppressed patients or persons with congenital or acquired immune deficiencies
  – Improving efficacy: defining appropriate endpoints = a complex undertaking
    • For new, unmodified BCG vaccines, demonstrating a “take” (TST conversion, local scarring) is sufficient
    • For novel BCG-replacement vaccines, need to demonstrate substantial, clinically significant benefit
    • How to deal with issue of possible non-specific benefits of BCG vaccination?
  – Policy issue: justifying the use of more costly BCG replacement vaccines
Major TB Vaccine Clinical Trial Endpoints (Adolescents, Adults)

1) Prevention of pulmonary TB disease: PoD

– Key public health goal; most widely acceptable TB vaccine registration endpoint

– Issues for phase 2b trials
  
  • Large, lengthy and costly, even in high TB burden areas
    – IGRA+/- 7000+ participants, 3 year follow-up
    – IGRA+ 3500 participants, 3 years follow-up
  
  • Vaccine ability to prevent disease among LTBI and non-LTBI vaccinees may differ (needs to be assessed in clinical trials)
Major TB Vaccine Clinical Trial Endpoints (Adolescents, Adults)

2) Prevention of sustained Mtb infection: PoI

- Endpoint utilized in phase 2 “proof of biological activity” trials in higher risk populations
  - “Biological activity” = evidence beyond immunogenicity
  - A strategy to reduce risk of phase 2b trials given lack of immunological correlate of protection, functional assay or human challenge
  - Not intended as the ultimate vaccine indication
- Mainly applicable to Mtb uninfected adolescents in TB endemic areas at high risk of acquiring Mtb
- Use as a licensable indication controversial
  - TB disease occurs in ~10% of Mtb-infected persons
  - Hypothetical concern: might PoI only occur in the 90% of Mtb-infected persons who never will develop TB disease?
3) Prevention of recurrent TB disease: PoR

- Goal: prevent recurrence of TB disease in persons after completing drug treatment
- Opportunity for a more efficient efficacy trial (smaller sample size and duration)
  - 3 to 5 fold higher incidence of future TB after completing treatment for initial case of TB
  - 70%-90% of recurrences occur during first year following treatment completion (efficient efficacy trial scenario)
- Potentially a phase 2 “proof of biological activity” endpoint leading to a phase 2b PoD trial
- Potentially a licensable indication in a formal phase 3 trial
Global Clinical Pipeline of TB Vaccine Candidates

**Phase 1**
- MTBVAC
  - Biofabri, TBVI, Zaragosa
- Ad5 Ag85A
  - McMaster, CanSino
- ChAdOx1.85A/MVA85A
  - Oxford, Birmingham
- MVA85A/MVA85A (ID, Aerosol)
  - Oxford
- TB/FLU-04L
  - RIBSP

**Phase 2a**
- RUTI
  - Archivel Farma, S.L
- H1/H56: IC31
  - SSI, Valneva, Aeras
- H4: IC31
  - Sanofi Pasteur, SSI, Aeras
- ID93 + GLA-SE
  - IDRI, Wellcome Trust

**Phase 2b**
- DAR-901
  - Dartmouth
- VPM 1002
  - SII, Max Planck, VPM, TBVI
- M72 + AS01E
  - GSK, Aeras

**Phase 3**
- Vaccae™
  - Anhui Zhifei Longcom

**Viral Vector**
- Protein / Adjuvant
- Mycobacterial – Whole Cell or Extract

Revised on February 2, 2017
Please note: Information is self-reported by vaccine sponsors

Courtesy of Aeras
TB Vaccine Candidate in Phase 3: 
Vaccae™ (*M. vaccae*)

**Background**
- Chinese-developed product: Anhui Zhifei Longcom
- Registered in China as adjunct immunotherapeutic for active TB disease (6 doses required)

**Description**
- Heat-killed *M. vaccae*
- High pressure homogenized lysate
Vaccae™: Development Status

• Currently in Phase 3 trial in China in TST+ participants
  – Endpoint: prevention of active pulmonary TB disease
    • Clinical endpoint determination
    • Symptoms + CXR
    • Sputum assessment (GeneXpert) obtained non-systematically (not part of endpoint definition)
  – Enrollment: 10,000 TST(+), aged 15-65 years
  – Dosing: 6 doses
• Data initially expected in late 2016
• Plan for data release currently not clear
• Registration intentions outside of China unclear
  – Will require additional Phase 3 efficacy studies
  – Will require reduction in number of doses from the current 6
TB Vaccine Candidates in Advanced Phase 2: DAR-901

• Background
  – Developed at Geisel School of Medicine, Dartmouth U. (Ford von Reyn)

• Description
  – Heat-inactivated *M. obuense*
  – DAR-901 represents broth-grown, scalable variant of SRL172 (agar-grown)
  – SRL172: only TB vaccine to have data reported from a phase 3 trial (2001-2008)
SRL172: Phase 3 Study Review (1)


- Endpoints
  - Primary: prevention of disseminated TB
  - Secondary
    - Prevention of definite TB (including disseminated and pulmonary)
    - Prevention of probable TB (including disseminated and pulmonary)

- Study description
  - 2,013 subjects, 1:1 randomization
  - 5 ID doses over 12 months
  - Followed every 3 months, median 3.3 years
SRL172: Phase 3 Study Review (2)

• Results
  – Safe, immunogenic
  – Hazard ratios for endpoints
    • Disseminated TB: 0.52 (95% CI 0.21-1.34); 7 (vaccine) to 13 (placebo) cases (p = 0.16)
    • **Definite (culture-confirmed) TB**: 0.61 (95% CI 0.39-0.96); 33 (v) to 52 (p) cases (p = 0.03)
    • Probable TB: 1.17 (95% CI 0.76-1.80); 48 (v) to 40 (p) cases (p = 0.46)

• Study terminated after 7 years by data safety monitoring board
  – Significant protection vs. definite TB (39% reduction in culture-confirmed TB)
  – Primary endpoint: 50% reduction (underpowered to reach statistical significance; 70 cases needed)

• SRL172 development terminated due to non-scalability
DAR-901

• Development status
  – Safe, immunogenic in phase 1 dose-escalation study (3 dose ID regimen)
  – Phase 2b study for prevention of Mtb infection (PoI) in BCG-vaccinated, IGRA-negative Tanzanian adolescents
    • N = 650; ages 13-15
    • Powering assumptions
      – Reduction of new Mtb infection (IGRA- to IGRA+) by 50%
      – 7% new Mtb infections/year
      – 80% power, Type 1 error 5%
    • 3 doses (0, 2, 4 months)
    • Status: initiated March 2016 (fully enrolled); fully vaccinated (February 2017); estimated completion December 2018
    • Funding: Global Health Innovative Technology (GHIT) Fund, Japan
      – Ultimate intended indication: PoD (adolescents, adults)

• Development plan
  – PoI phase 2b study completion: 2018
  – Initiate 5 year phase 3 PoD trial: 2019 (seeking pharma partner +- GHIT, for funding)
  – Licensure and subsequent WHO prequalification: 2025
VPM 1002

• Background
  – Originally developed by Stefan Kaufmann, Max Planck Institute
  – Now being developed by Vakzine Projekt Management (VPM), Hannover, Germany and Serum Institute of India (SII), Pune, India

• Description:
  – Recombinant BCG
  – Listeriolysin gene inserted
    • Enhances BCG immunogenicity
    • Mechanism debated: induction of apoptosis and autophagy, leading to better immune presentation, hypothesized
  – Urease gene inactivated (lowers pH in macrophage, optimizing listeriolysin activity)
VPM 1002: Development Status

• In Phase 2b trial vs. BCG in HIV+ and HIV- infants <12 days old (South Africa)
  – Endpoints: safety; immunogenicity
  – N = 416
  – Primary data analysis: Sept 2017; completion date December 2017

• Phase 2b-Phase 3 trial for prevention of TB disease recurrence (PoR) in adults planned for India
  – Initiation date: July 2017
  – Double blind, randomized, placebo controlled
  – N = 2,000 persons completing TB treatment (1,000 persons per arm)
  – Powering assumptions (Phase 3 trial)
    • 50% reduction in recurrence during the 12 months after vaccination
    • 5% recurrence in placebo arm in 12 months after treatment completion
    • 80% power at 5% significance level
  – Potential for transition to phase 3 trial after safety assessment of first 200 enrollees

• Funded by Serum Institute of India
VPM 1002 - Key Issues

• Potential for most rapid licensure of a new TB vaccine
  – If phase 3 trial initiated for PoR in 2017-2018, could have potential licensure submission by 2020 – 2021
  – Licensure pathway for VPM 1002 BCG replacement indication in infants is under discussion
    • WHO communicated to VPM-SII that evidence of “take”, as per WHO requirement for an unmodified BCG vaccine, would not be sufficient for this new, recombinant vaccine
    • Further discussion required re:
      – Safety, efficacy criteria supporting licensure
      – Defining claims of improved safety, efficacy over BCG
      – Value assessment, justifying use despite increased cost over BCG

• Also being developed as a replacement for BCG treatment of bladder cancer

• Liquid culture manufacture more scalable; potential to reduce concerns over future BCG shortages
H4:IC31

• Background
  – Sanofi Pasteur product
  – Developed in collaboration with Aeras, Statens Serum Institute (SSI)

• Description
  – Fusion protein
    • Ag85B (mycolyl transferase; necessary for maintaining cell wall integrity)
    • TB 10.4 (virulence factor; member of ESAT-6 protein family)
  – IC31 adjuvant (Valneva)
    • T-cell stimulator (TLR9 agonist)
H4:IC31 – Development Status

• In phase 2 “proof of biological activity” trial
• Endpoint: Pol (QFT conversion) in high risk, IGRA- South African adolescents
• BCG revaccination and placebo comparator arms
• Fully enrolled (n=990, 330/arm)
• Power assumptions
  – 50% reduction in Mtb infection (QFT-GIT conversion)/yr. among vaccinated (H4; BCG) compared to placebo
  – 10% incidence of primary Mtb infection/yr.
  – Power 80%; 10% Type 1 error rate (1 sided)
• Primary analysis (64 conversions and 15 month median follow-up): 3Q2016
  – Study continued
  – Results remain blinded
• Final analysis: Q4 2017/Q1 2018
H4:IC31 - Key Issues

• If PoI endpoint targets reached, would open door to a possible phase 2b trial for a PoD indication

• BCG comparator arm included
  – Will provide data on effect of BCG revaccination on preventing Mtb infection in high risk, IGRA-adolescents in Cape Town
WHO-IVR TB Vaccine Workshop
24 May 2017

• WHO-IVR intention to increase activity in TB vaccine arena due to pressing need
  – Define preferred product characteristic (PPC) criteria for TB vaccines
  – Essential to advocate for increased TB vaccine research funding

• Emphasis on necessity for TB vaccine development to meet END TB 2035 goals
  – Decrease from current 100 cases/100K population to 10 cases/100k population
  – PoD indication represents fastest way to impact the TB epidemic
• Recognition of a sluggish TB vaccine pipeline (2010-present)
  – Need new tools, new approaches (e.g., human challenge model)
  – Need to diversify vaccine strategies (e.g., persistent vaccines; aerosol delivery)
  – Need to identify, advance and learn from promising new approaches (e.g., rCMV vaccine in preclinical development)

• Important to manage expectations
  – PoD vaccine efficacy as low as 20% could be cost effective if targeted at adolescents and adults
  – Advanced clinical trials of lower efficacy vaccines will be costly

• Importance of vaccine as a counter to spread of DR-TB strains
  – Need to explore potential drug-vaccine integrated approaches against drug-resistant TB

• WHO role: serve as “honest broker” to help coordinate the field
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