Progress towards vaccines against TB

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The problem

- Estimated 1/3 of world population infected
- 10% will develop TB
- 10.4 million cases and 1.4 million deaths in 2016
- WHO End TB strategy: 90% reduction in incidence by 2035
TB and AMR

- Better TB drugs becoming available
- Correlation between antibiotic use and resistance
- Vaccines reduce antibiotic use, reduce AMR
- Need for a TB vaccine as part of the global emergency response to AMR
BCG, the world’s most widely used vaccine

- Used in many national immunization programs with high coverage
- Different strains used for routine vaccination
- Efficacious against disseminated TB in children
- Estimated 117,132 deaths prevented per birth cohort during first 15 years of life
- Protection against leprosy
- Other non-specific (immuno-modulatory) effects suspected

- Variable protection from infection or pulmonary TB
- Inconsistent protection in adolescence
- Safety considerations in HIV-infected infants and children

- The BCG vaccine has not stopped the epidemic
Tb incidence per age group

Target populations and goals

• WHO draft Preferred Product Characteristics (soon final)

• Prevention of active pulmonary disease in adolescents and adults
  • Individual benefit
  • Reduction in transmission

• Prevention of TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children
  • Maintain and expand benefits of BCG (replace or boost)

http://www.who.int/immunization/research/ppc-tpp/WHO_new_TB_vaccine_PPC_20180116.pdf?ua=1
Key areas of focus and opportunities

• Rational investment decisions and portfolio management
  • Stage gating criteria
Stages and Gates for a TB vaccine

- **Stage A:** Discovery
- **Stage B:** POC studies

**Preclinical Development, CMC and animal studies**
- **Stage C:** Preclinical evaluations
- **Stage D:** Prepare FIH/Ph 1

**Clinical studies, CMC: scale up and validation**
- **Stage E:** Prepare FIH/Ph 1
- **Stage F:** Ph2
- **Stage G:** Ph 2b
- **Stage H:** Ph 3

**Registration**

Legend:
- Stage (period during which one conducts the activities described in the relevant stage)
- Gate (point at which one applies Gating criteria to decide whether move to next stage)
- Critical investment Gate
Stage gate process

• Criteria were initially defined in 2012 and now revised by Aeras and TBVI and validated through broad external stakeholder consultations

• Stage Gates are a versatile tool to accelerate TB vaccine candidates development

• Facilitate global TB vaccine portfolio management

• An offer to researchers, developers, funders and other decision-makers

• Will go online in summer of 2018
Pre-Clinical TB Vaccine Pipeline

- MTBVAC + (Inactivated) Biofabri, TBVI, Univ. Zaragosa
- rBCG-zmp1 Univ. of Zurich, TBVI, Aeras
- Therapeutic MVA Transgene , TBVI
- ChAdOx1.85A/PPE15 Univ. of Oxford, TBVI
- H64+CAF01 SSI, TBVI
- CMV-6Ag Aeras, Vir Biotech, OHSU
- ChAd3/MVA-5Ag(AE) Aeras, GSK, Transgene

Legend:
- Viral Vector
- Protein / Adjuvant
- Mycobacterial – Whole Cell or Extract
Key areas of focus and opportunities

- Rational investment decisions and pipeline management
  - Stage gating criteria
- Discovery research to feed the early pipeline
  - Technology platforms and antigens
  - Host-directed therapies
  - Alternative immunization routes
- Preclinical models to prioritize candidates
  - Pertinent models to answer scientific questions (i.v. BCG)
  - Supportive evidence for evaluation of novel candidates in clinical trials
  - Ultimate validation from a clinical efficacy signal
- Immune correlates and biomarkers to predict vaccine efficacy
  - Exploit the signal from BCG revaccination
  - Biobanks from clinical trials
  - Novel assays (microbial growth inhibition)
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• Clinical trials to progress towards new efficacious TB vaccines
  • Experimental medicine (aerosol) and controlled human challenge model
  • Alternative clinical endpoints
Clinical efficacy trial endpoints

- Prevention of Infection (POI), Disease (POD), Recurrence/re-infection (POR)
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  • Late stage trials
How to do TB vaccine efficacy trials

• Diagnostics and treatment insights
• Normal lab ranges in African infants
• Immunological mechanisms and correlates
Immune correlates of risk analysis – MVA85A efficacy trial

T-cell activation is an immune correlate of risk in BCG vaccinated infants

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Blood samples collected from healthy infants up to 3 years before they developed TB disease

Result significant if Conditional Logistic Regression P<0.05 and FDR<2
Shaded bar indicates medium third of immune response level

OR 1.828, p = 0.002
Antibodies correlate with reduced risk of TB disease

Estimated odds ratio 0.62, \( p = 0.019 \)

Are they directly involved in protection or correlating with another immune parameter?

Fletcher HA et al, Nature Communications, 2016
Priority areas and recommendations

• Maintain a healthy pipeline from discovery to late stage to launch and invest wisely

• Sustain discovery research
  • Novel antigens and technology platforms
  • Immune mechanisms of pathogenesis
  • Alternative delivery routes

• Continue to identify correlates of vaccine protection (and TB risk)
  • Novel in vitro assays
  • Relevant animal models
  • Controlled human challenge model
  • Learnings from late stage trials and cohort studies

• De-risk clinical development
  • Correlates of protection
  • Controlled human challenge model
  • Experimental medicine studies
  • Alternative clinical endpoints (infection, recurrence)

• Conduct late stage clinical trials
Acknowledgements and references

• Progress and challenges in TB vaccine development
  • [https://f1000research.com/articles/7-199/v1](https://f1000research.com/articles/7-199/v1)

• Global report on tuberculosis vaccines 2018

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