Immune Correlates of Protection for BCG and M72 TB Vaccines

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Union World Conference on Lung Health 2023
November 16th, 2023
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BCG is the only commercially available TB vaccine, and while the vaccine helps protect infants & young children, it offers limited or no protection for adults.

New TB vaccines that can protect adolescents and adults are urgently needed to accelerate the end of the TB epidemic.

TB vaccine development is challenging for many reasons:
- No animal model that predicts prevention of TB disease
- Poor understanding of the immune responses that confer protection from disease
- Only 1 in 20 *Mtb*-infected progress to TB disease and there is no marker of recent infection
- Incidence rates are highly heterogeneous and relatively low, thus large clinical endpoint trials are needed to demonstrate vaccine efficacy

There is limited interest in industry to invest in TB vaccine R&D because programs cannot be de-risked prior to spending hundreds of millions on a Phase 3 program.

If a CoP for prevention of TB disease were identified, confirmed, and accepted by health authorities for licensure of novel TB vaccines, Phase 3 trials could be much smaller and less costly, thus more attractive for developers to engage in TB vaccine R&D.
Assumptions regarding mechanisms of protection

Correlates of Protection (CoP) for TB vaccines have not yet been identified, but

• There is consensus that TB-specific T cells likely play a major role in protection from TB disease
  / Mouse and human data point to IFN-γ as a major mediator of protective immunity
  / Data from the investigational MVA85A vaccine trial suggest IFN-γ may be necessary but not sufficient for protection

• Immune responses beyond IFN-γ-expressing T cells likely contribute to protection
  / Antibody responses may contribute to protection based on new data in humans and NHP
  / IV BCG vaccination points to IL-17 as critical
  / BCG is known to induce epigenetic modifications that afford some level of protection beyond TB
  / Non-classical T cells may also play a role

A comprehensive assessment of immune responses induced by vaccination and their association with protection in human clinical trials would be valuable to provide guidance for vaccine development
Opportunity: 2018 was the year of TB vaccines

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMo1714021

Tait et al, NEJM 2019, DOI: 10.1056/NEJMc2001364

Two vaccine trials with ~50% efficacy and established sample repositories allowed for the creation of the TB Immune Correlates Program
Caveat: CoP are defined for a specific “P” and are often vaccine platform-dependent

- **BCG revaccination**
  - IGRA-negative adolescents
  - Protection from sustained infection
    - Measured as sustained QFT conversion
  - Complex vaccine with ~4000 ORFs
    - Intrinsically adjuvanted

- **M72/AS01$_{E}$ vaccination**
  - IGRA-positive adults
  - Protection from pulmonary TB disease
    - Measured as microbiologically confirmed pulmonary TB in participants with clinical symptoms
  - Defined vaccine consisting of 2 Mtb ORFs
    - Adjuvanted with AS01$_{E}$

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

Tait et al, NEJM 2019, DOI: 10.1056/NEJMc2001364
TB Immune Correlates Program

VACCINE INSIGHTS
PRECLINICAL & CLINICAL DEVELOPMENT

EXPERT INSIGHT
The quest for vaccine-induced immune correlates of protection against tuberculosis

Elisa Nemes, Andrew Fiore-Gartland, Cesar Boggiano, Margherita Coccia, Patricia D’Souza, Peter Gilbert, Ann Ginsberg, Ollivier Hyrien, Dominick Laddy, Karen Makar, M. Juliana McElrath, Lakshmi Ramachandra, Alexander C. Schmidt, Solmaz Shotorbani, Justine Sunshine, Georgia Tomaras, Wen-Han Yu, Thomas J. Scriba, Nicole Frahm; the BCG Correlates Pls Study Team & the M72 Correlates Pls Study Team

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Nemes and Fiore-Gartland, “The quest for vaccine-induced immune correlates of protection against tuberculosis”. Vaccine Insights. 2022
Nemes and Fiore-Gartland, “The quest for vaccine-induced immune correlates of protection against tuberculosis”. Vaccine Insights. 2022
Criteria for prioritization of assays and primary markers

- Every readout is measured from the same samples
- Samples: pre- and post-vaccination
  - 24 BCG and 12 placebo recipients, Day 0 vs. Day 70
  - 40 M72 and 10 placebo recipients, Day 0 vs. Day 37
- We devised statistical criteria for identifying biomarkers that have high potential to be detected as a CoP
  1. Robust vaccine-induced effect
  2. Broad, biologically-relevant dynamic range among vaccine recipients after vaccination
  3. Low temporal variability (among placebo recipients)
  4. Some pre-vaccine variability expected
  5. Readouts should occupy their own niche of immunologic space (low correlation)
  6. Low technical measurement error

Cytokine producing CD4 T cells by ICS
Andersen-Nissen/McElrath, CHIL
Consensus for assays moving into BCG case/control phase

- Intracellular cytokine staining (T cells and innate cells)
  PI: Andersen-Nissen, Cape Town HVTN Immunology Laboratory
- Proteomics of antigen-specific and non-specific stimulations
  PI: Maecker, Stanford University
- Antibody subtype and FcR binding
  PI: Tomaras, Duke University
- Single-cell RNAseq
  PI: Shalek, MIT
- Single-cell ATACseq
  PI: Barreiro, University of Chicago
- Absolute cell counts in whole blood
  PI: Nemes, University of Cape Town
Potential confirmation of candidate CoP

Gates MRI clinical trials to confirm efficacy

• BCG Revaccination (TBV01-201)
  / 1800 IGRA-negative adolescents randomized 1:1 to receive BCG or placebo in South Africa
  / Primary endpoint: prevention of sustained IGRA conversion
  / Biospecimen collection:
    • PBMC and plasma at d1, 71, m6 and every 6 months through m48
    • Serum and PAXgene®* tubes at above timepoints plus d8, 29
    • Frozen whole blood for phenotyping
  / Clinicaltrials.gov NCT 04152161

• M72/AS01E (TBV02-301)
  / Planned: 26,000 adolescents and adults randomized 1:1 to receive 2 doses of M72/AS01E or placebo
  / Primary endpoint: prevention of bacteriologically confirmed pulmonary TB
  / Biospecimen collection:
    • PBMC and plasma at d1, 29, 36, 57, m7, 13, 37 and 61 (PBMC in ~50% of participants)
    • PAXgene® tubes at above timepoints
    • Frozen whole blood for phenotyping

*PAXgene® trademarked by PreAnalytiX GmbH
Acknowledgments

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PJ Utz
Angela Yee

Funders

National Institute of Allergy and Infectious Diseases

BILL & MELINDA GATES foundation
Acknowledgements (cont’d)

BCG and M72 teams

**UCT**
- Kelvin Addicott
- Stanley Kimbung
- Denis Awany
- Monika Looney

**Duke**
- Kelly Seaton
- Sarah Mudrak
- Jack Heptinstall
- Shyam Sutariya
- Kelvin Chiong
- Saman Baral
- Lu Zhang
- Angelina Sharak
- Sheetal Sawant

**VISC**
- Erica Beatman
- Lindsay Mwoga
- Bryan Mayer
- Drienna Holman
- Abby Wall

**Fred Hutch/CHIL**
- Steve De Rosa, MD
- Valentin Voillet, PhD
- Zelda Euler
- Lamar Fleming
- Sharon Khuzwayo
- Sarah Everett

**MGH**
- Ryan McNamara
- Sabian Taylor
- Eddie Irvine
- Jessica Shih-Lu Lee

**Boston Childrens Hospital**
- Meenakshi Jha
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**OHSU / PNNL**
- Thomas Metz
- Bobbie-Jo Webb-Robertson
- Jennifer Kyle
- Christina Stevenson

**ADI**
- Xiaowu Liang
- Arlo Randall
- Joseph J. Campo

**Radboud**
- Marion Bussmakers
- Mumin Ozturk
- Maaike Duijts

**Stanford**
- Sharon Dickow
- Natasha Haulman

**LUMC**
- Krista E van Meijgaarden

**Seattle Childrens Hospital**
- Johannes Nemeth