TB Immune Correlates of Protection Program

Nicole Frahm, PhD
Head of Biomarker Development

WHO mRNA Technology Transfer Programme
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Problem Statement

• BCG is the only commercially available TB vaccine, and while the vaccine protects infants & young children, it offers limited or no protection for adults
• New TB vaccines that 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 cheaper, 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 been identified yet

• 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

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Opportunity: 2018 was the year of TB vaccines

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

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

- **M72/AS01ₐ vaccination**
  / QFT-positive adults
  / Protection from pulmonary TB disease
    • Measured as microbiologically confirmed pulmonary TB in subjects with clinical symptoms
  / Defined vaccine consisting of 2 Mtb ORFs
    • Adjuvanted with AS01ₐ

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021
Tait et al, NEJM 2019, DOI: 10.1056/NEJMc2001364
TB Immune Correlates Program

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 PIs Study Team & the M72 Correlates PIs Study Team
Hypotheses

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 72 samples
- Samples: 24 BCG and 12 placebo recipients, before and after vaccination (Day 0 vs. Day 70)
- 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. Pre-vaccine variability may also be informative
  5. Readouts should occupy their own niche of immunologic space (low correlation)
  6. Low technical measurement error
Non-parametric statistics for readout evaluation

A: BCG vs. Placebo at Day 70
- Estimate AUROC for separation of BCG and Placebo samples at Day 70
- Wilcoxon rank-sum test for p-value

B: BCG vs. Placebo for (Day 70 – Day 0)
- Like A, except values at Day 70 are first adjusted by subtracting their value at baseline/Day 0.

C: BCG vs. Placebo at Day 0
- At baseline these two randomized groups should be indistinguishable (AUROC ≈ 0.5). If they are different, it suggests that if there is a vaccine effect, it may be a false discovery.

D: Day 70 vs. Day 0 among BCG group
- Can use Wilcoxon signed-rank test for p-value
- Developed ROC for paired-sample data: AUROC indicates separation of Day 70 and Day 0 samples, accounting for pairing of participants’ samples

E: Day 70 vs. Day 0 among Placebo group
- Like D, except among Placebo recipients. A readout with a scaled statistic near 0.5 is ideal, indicating no separation between Day 0 and Day 70.
Statistical Criteria for Assay Ranking

- Evaluate all readouts based on their ability to detect a vaccine response and demonstrate reproducible results
  - The BCG-induced effect (y-axis) is a composite value that takes into account statistics A, B and C
  - The readout reproducibility (x-axis) is a composite value based on statistics D and E
- Each dot is one assay readout
- Dots are colored by different antigens
- Readouts in shaded area are most promising biomarkers

*Reproducibility is scaled so that 1 is optimal*
BCG-induced effects vs. reproducibility - cellular

**Intracellular cytokine staining (ICS)**
Antigen-specific T and innate cells

**Differential leukocyte counting and immunophenotyping in cryopreserved ex vivo whole blood (DLC-ICE)**
Absolute cell counts

**Secreted cytokines following PBMC stimulation**
Trained and adaptive immunity

✓ ✓ ✓
BCG-induced effects vs. reproducibility - humoral

Binding antibody multiplex assay (BAMA)
(Ab subclass and FcR binding)

Bio Layer Interferometry (BLI)
(Avidity)

Phage Immuno-precipitation sequencing (PhIPseq)
(antibody mapping)
BCG-induced effects vs. reproducibility – single cell

**scRNAseq**
transcriptomics

**EpiToF**
Epigenetic marks by CyToF

**scATACseq**
Epigenetic modulation on gene level

- ✓
- ❌
- ✓

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Consensus for assays moving into 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
- scRNAseq
  / PI: Shalek, MIT
- scATACseq
  / 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 QFT-negative adolescents randomized 1:1 to receive BCG or placebo in South Africa
  - Primary endpoint: prevention of sustained QFT 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/AS01\textsubscript{E} (TBV02-301)**
  - Planned: 26,000 adolescents and adults randomized 1:1 to receive 2 doses of M72/AS01\textsubscript{E} or placebo
  - Primary endpoint: prevention of bacteriologically confirmed pulmonary TB
  - Biospecimen collection:
    - PBMC and plasma/serum 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
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Leadership Team
Cesar Boggiano
Margherita Coccia
Patricia D'Souza
Andrew Fiore-Gartland
Nicole Frahm
Peter Gilbert
Ann Ginsberg
Ollivier Hyrien
Caitlyn Linde
Karen Makar
M. Juliana McElrath
Elisa Nemes
Lakshmi Ramachandra
Alexander C. Schmidt
Lewis Schrager
Thomas J. Scriba
Michael Shaffer
Solmaz Shotorbani
Georgia Tomaras

Scientific Advisory Committee
Erica Andersen-Nissen
Alvaro Borges
Rhea Coler
Mark Davis
Tom Evans
Helen Fletcher
Sarah Fortune
Willem Hanekom
Anne Kasmar
Shabaana Khader
James Kublin
Sarah Mudrak
Bali Pulendran
Mario Roederer
Lew Schrager
Robert Seder
Divya Shah
Kevin Urdahl
Robert Wilkinson

Biospecimen Access Oversight Committees
Ann Ginsberg
Willem Hanekom
Mark Hatherill
Dominick Liddy
Morton Ruhwald
Alexander Schmidt
Lewis Schrager
Heather Siefers
Dereck Tait
Jim Tartaglia

BCG Correlates PIs
Galit Alter
Erica Andersen-Nissen
Luis Barreiro
S. Moses Dennison
One Dintwe
Andrew Fiore-Gartland
Ollivier Hyrien
Claire Imbratta
Babak Javid
Purvesh Khatri
Hadar Malca
Elisa Nemes
Gerlinde Obermoser
Jayant Rajan
Thomas Scriba
Alex K. Shalek
Georgia Tomaras
Nancy Tran
PJ Utz

M72 Correlates PIs
John Aitchison
Erica Andersen-Nissen
S. Moses Dennison
One Dintwe
Fergal Duffy
Joel Ernst
Andrew Fiore-Gartland
Sarah Fortune
Ollivier Hyrien
Claire Imbratta
Simone A. Joosten
Purvesh Khatri
Ofer Levy
David Lewinsohn
Holden Maecher
Hadar Malca
Musa Mhlanga
Munyadzi Musvosvi
Elisa Nemes
Mihai Netea
Gerlinde Obermoser
Tom H.M. Ottenhoff
Bali Pulendran
Thomas Scriba
Alex K. Shalek
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Lu Zhang
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Sheetal Sawant

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Bryan Mayer
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Abby Wall

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Steve De Rosa, MD
Valentin Voillet, PhD
Zelda Euler
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Sharon Khuzwayo
Sarah Everett

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Ryan McNamara
Sabian Taylor
Eddie Irvine
Jessica Shih-Lu Lee

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Meenakshi Jha
Ali Bond

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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

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Krista E van Meijgaarden