BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Immune Correlates of Protection for BCG and M72 TB Vaccines

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CONFLICT OF INTEREST DISCLOSURE FORM

☒ I have no Conflict of Interest to report.

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Problem Statement

- 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

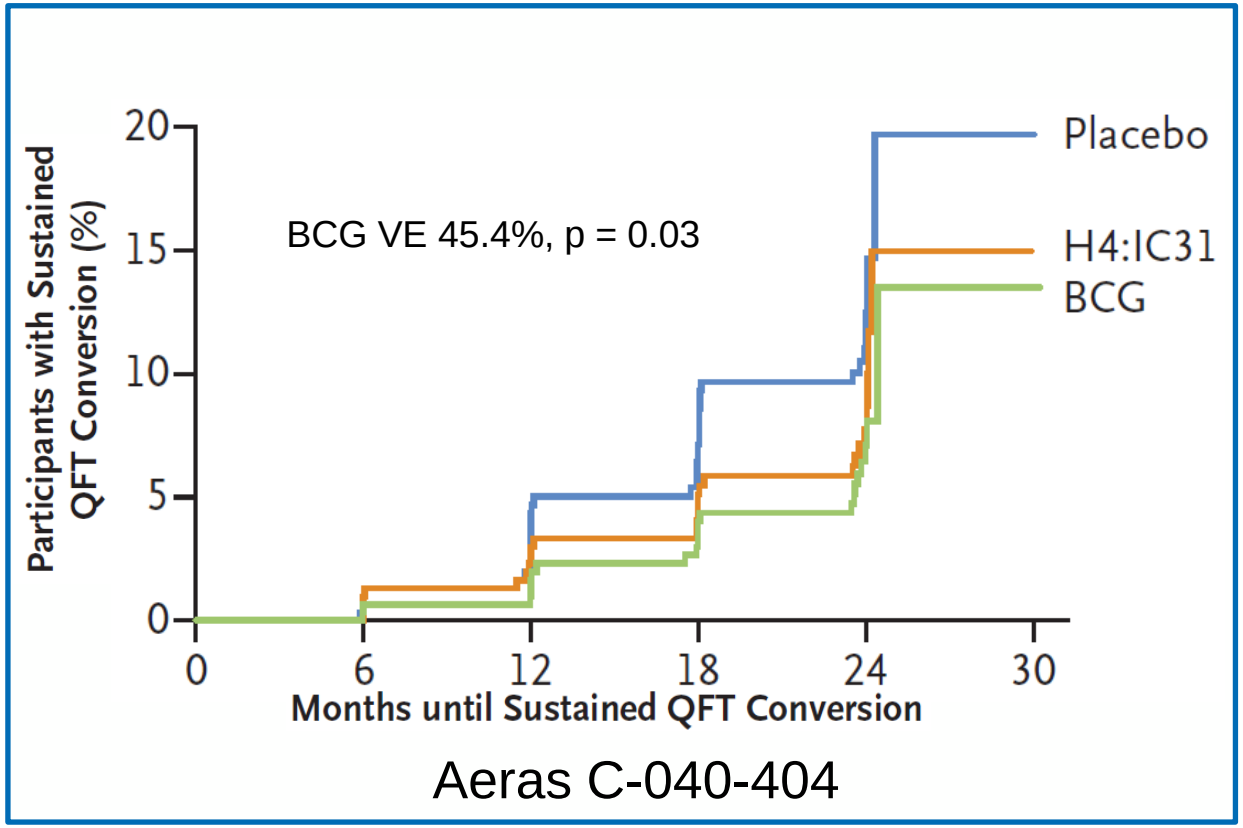
Correlates of Protection (CoP) for TB vaccines have not yet been identified, but

- 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/NEJMoa1714021



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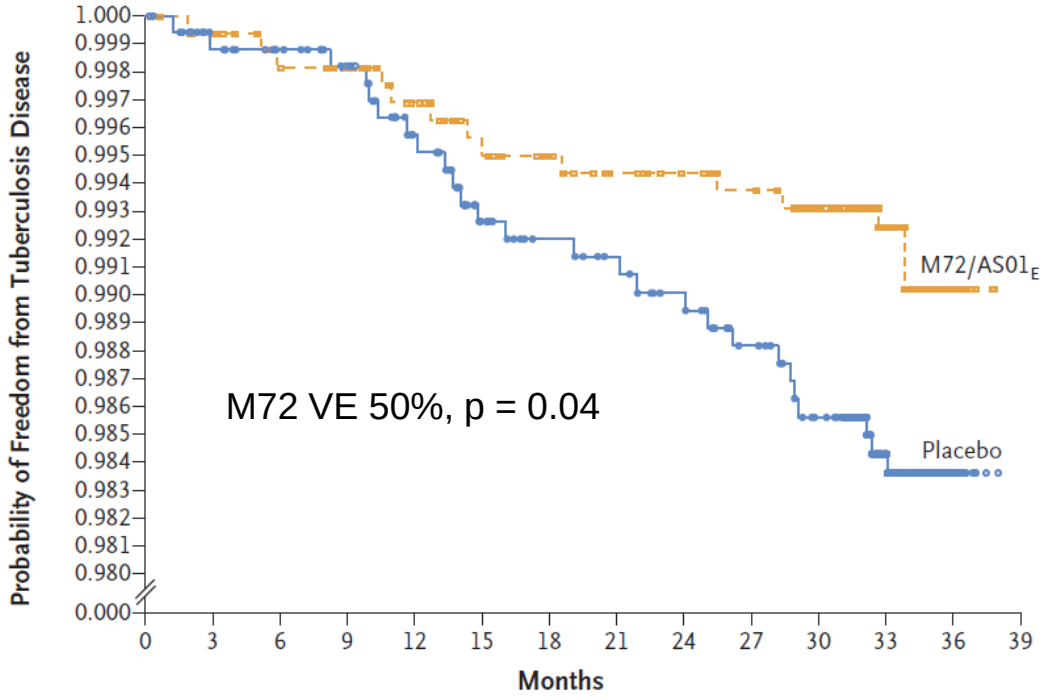
Tait *et al*, NEJM 2019, DOI: 10.1056/NEJMc2001364



GSK TB-018

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

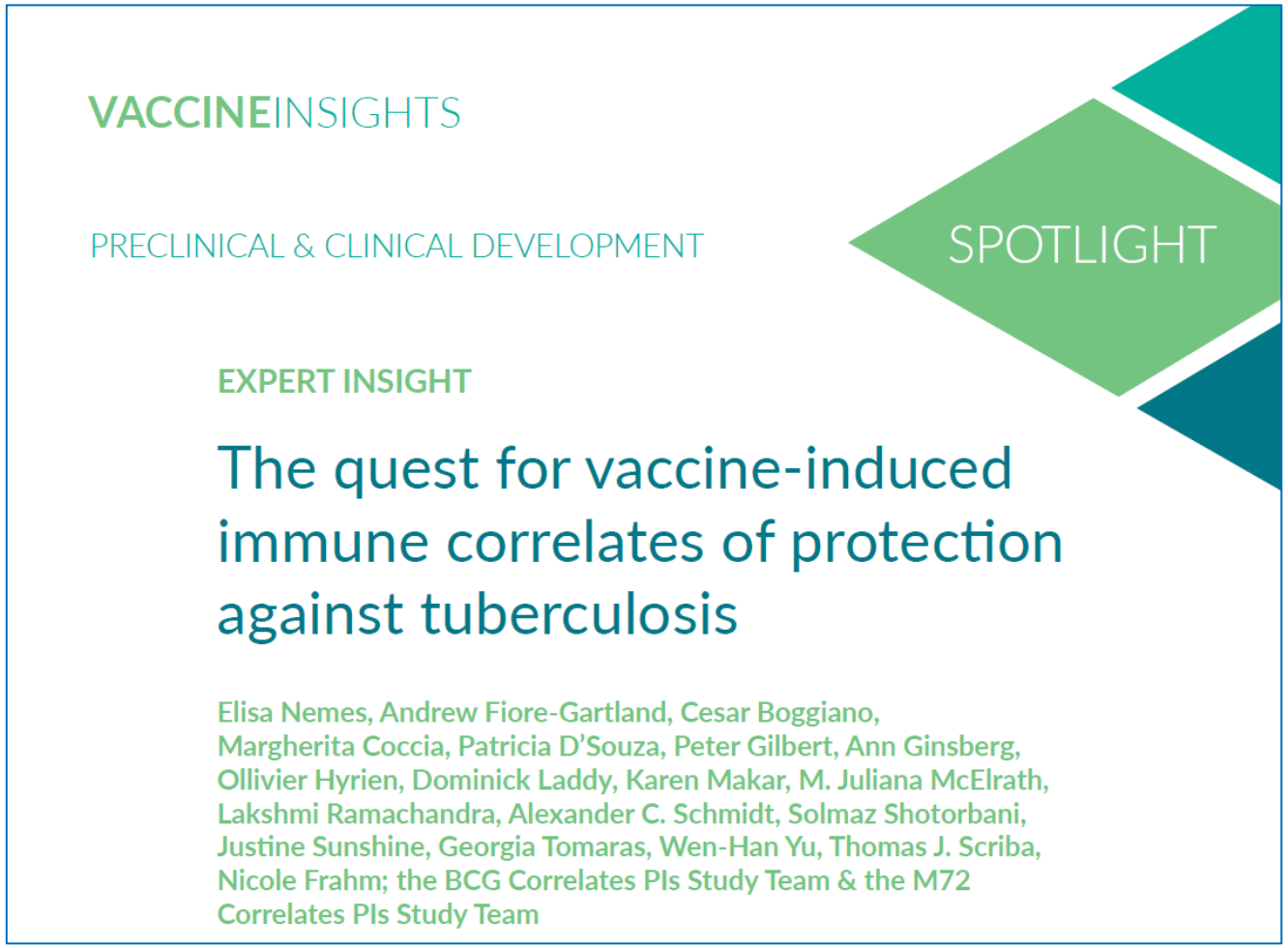
- BCG revaccination
  - IGRA-negative adolescents
  - Protection from sustained infection
    - Measured as sustained QFT conversion
  - Complex vaccine with ~4000 ORFs
    - Intrinsically adjuvanted

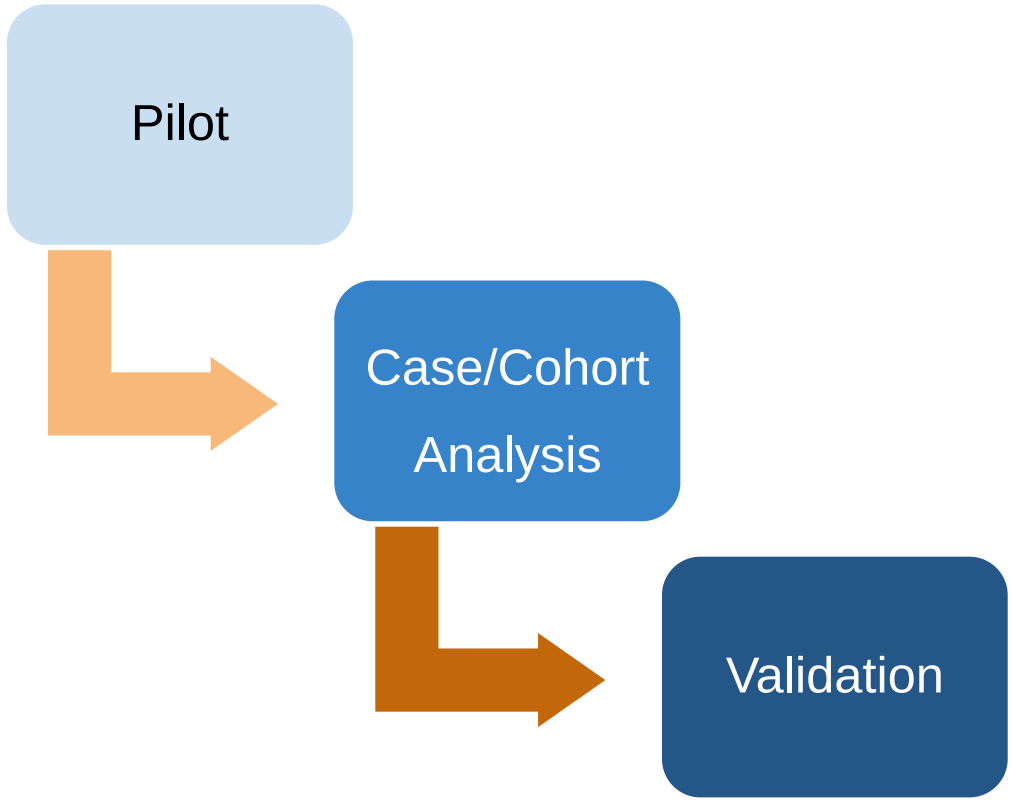
Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

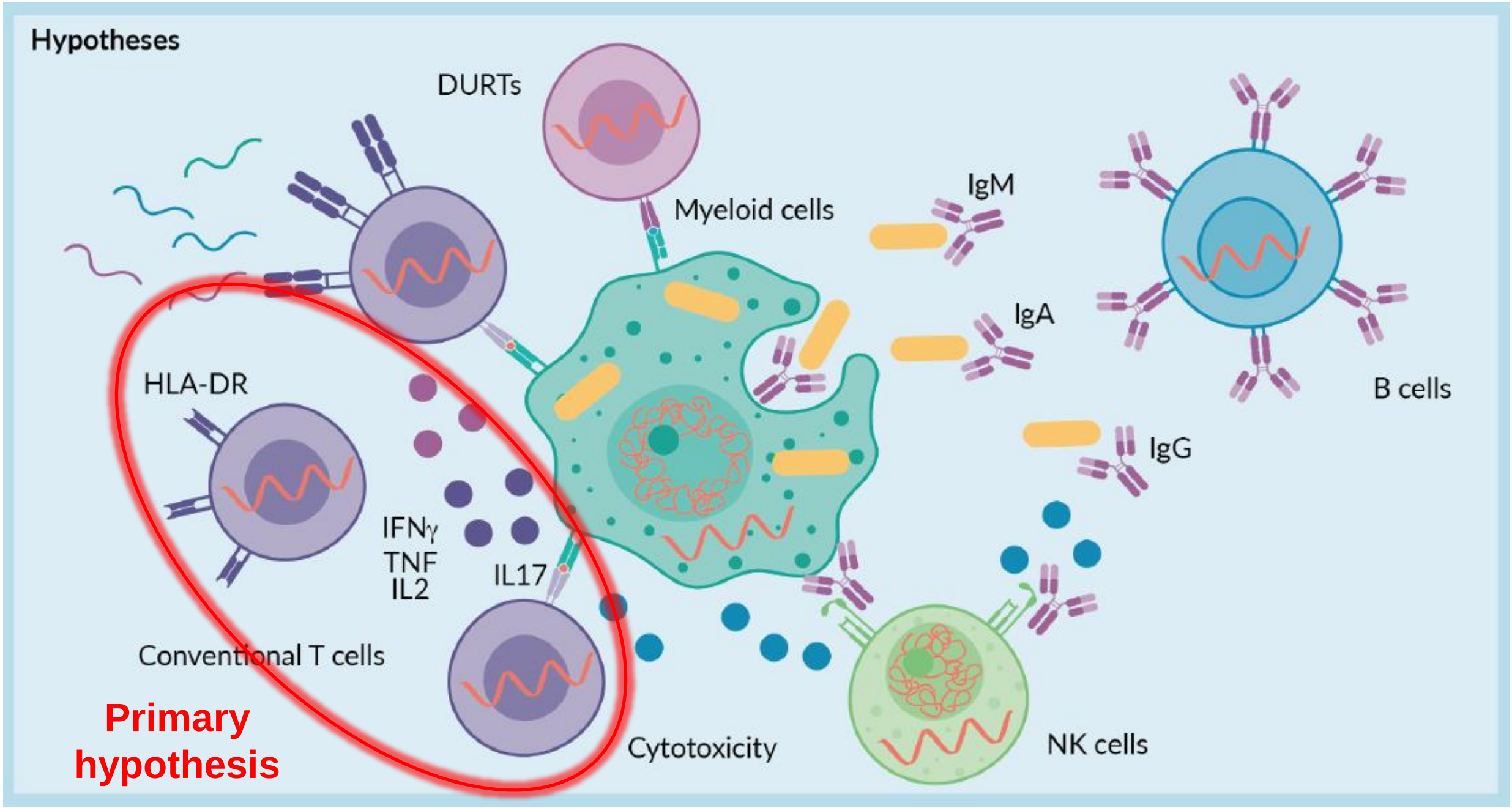
- M72/AS01$_E$ vaccination
  - IGRA-positive adults
  - Protection from pulmonary TB disease
    - Measured as microbiologically confirmed pulmonary TB in participants with clinical symptoms
  - Defined vaccine consisting of 2 *Mtb* ORFs
    - Adjuvanted with AS01$_E$

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

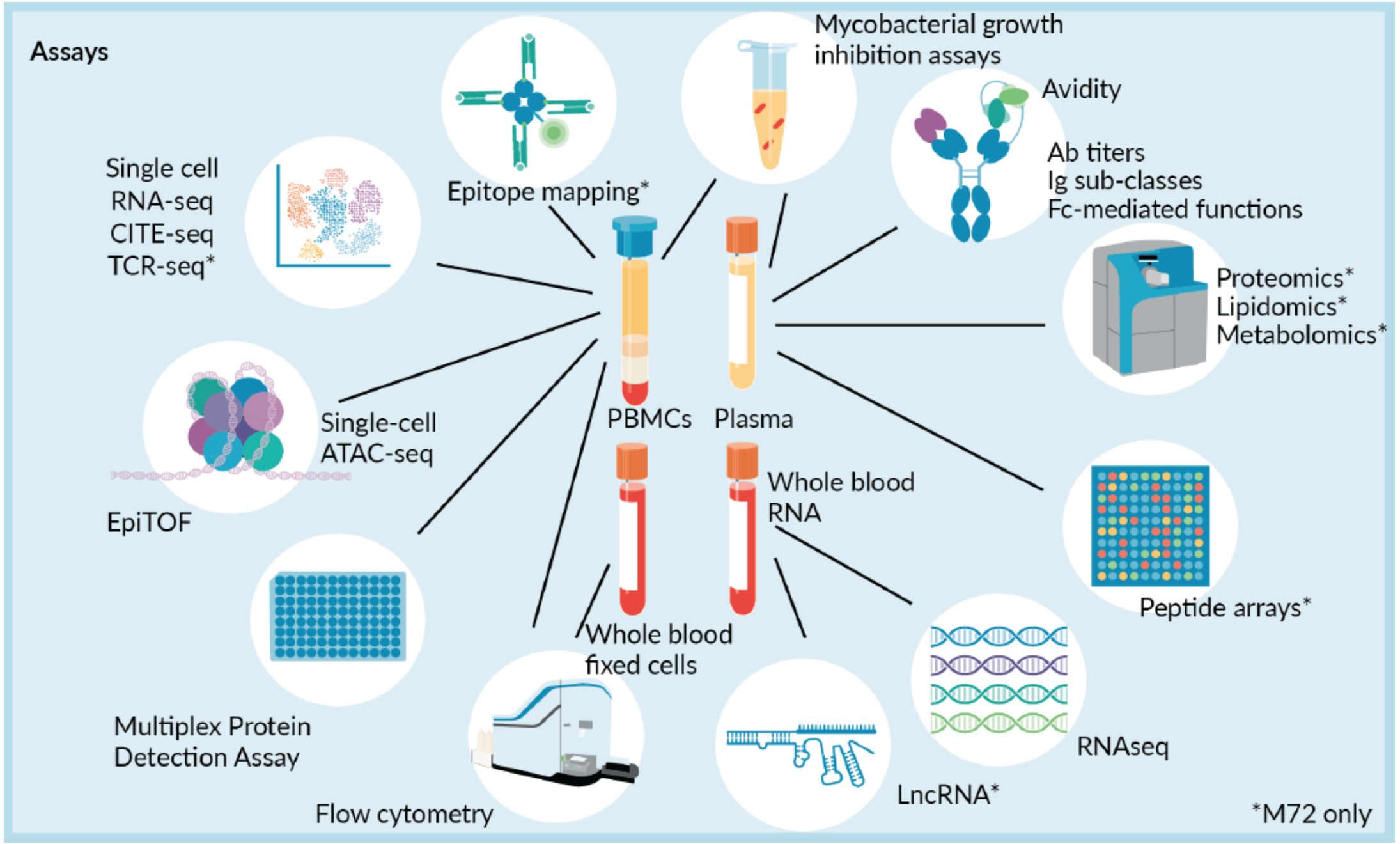
TB Immune Correlates Program







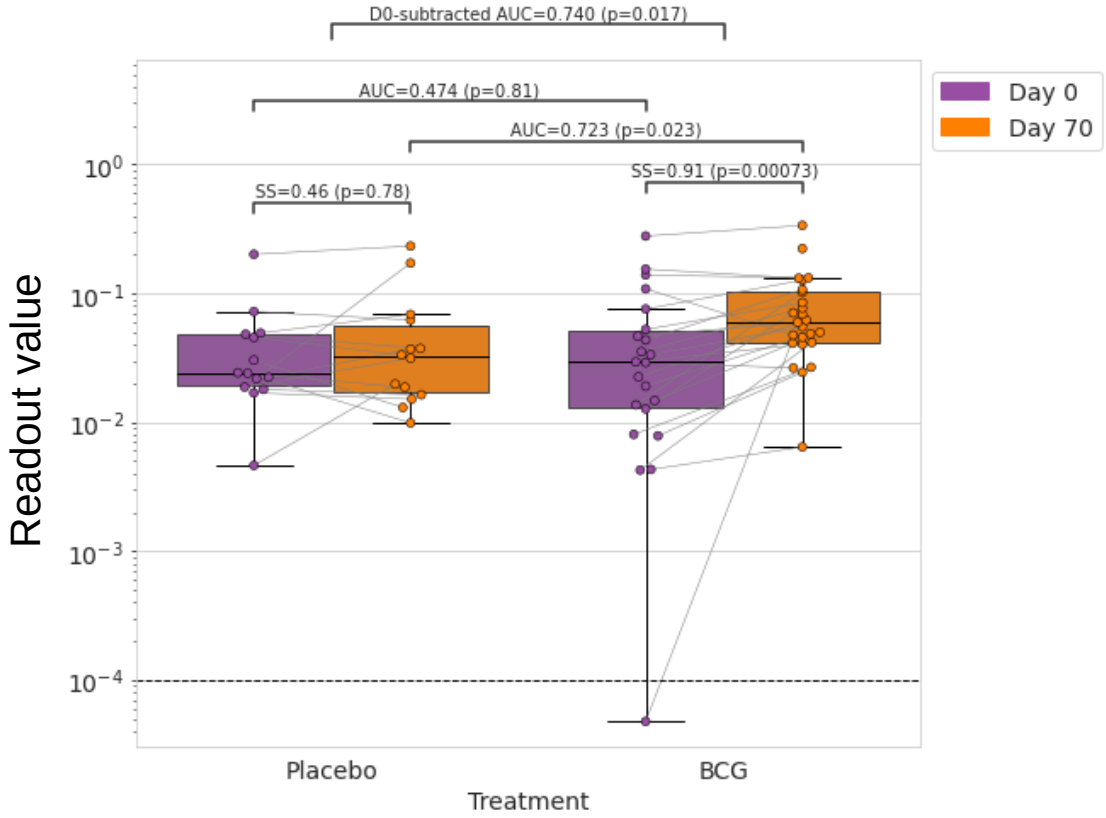
Nemes and Fiore-Gartland, "*The quest for vaccine-induced immune correlates of protection against tuberculosis*". Vaccine Insights. 2022



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/AS01$_E$ (TBV02-301)
  - Planned: 26,000 adolescents and adults randomized 1:1 to receive 2 doses of M72/AS01$_E$ 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

*PAXgene® trademarked by PreAnalytiX GmBH

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