

Can biomarkers advance the development of new TB vaccines?

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How can biomarkers help us develop a protective TB vaccine?

- Allow the demonstration of vaccine immunogenicity and potential efficacy at an early stage
- Facilitate the selection and prioritisation of candidate TB vaccines for human clinical efficacy testing
- Contribute to stage gates?
- Help reduce the protracted time scale, large size and expense of human efficacy trials
- Permit optimization of dose, vehicle, antigens and adjuvants, and immunization schedules of new candidate vaccines

The TBVAC2020 Work Package on Biomarkers aims to:

identify, test, evaluate and prioritize surrogate-endpoints of protection (“correlates of protection”) in human TB, and to develop further tests to measure these



Foundation to facilitate European efforts towards the global development of new TB vaccines

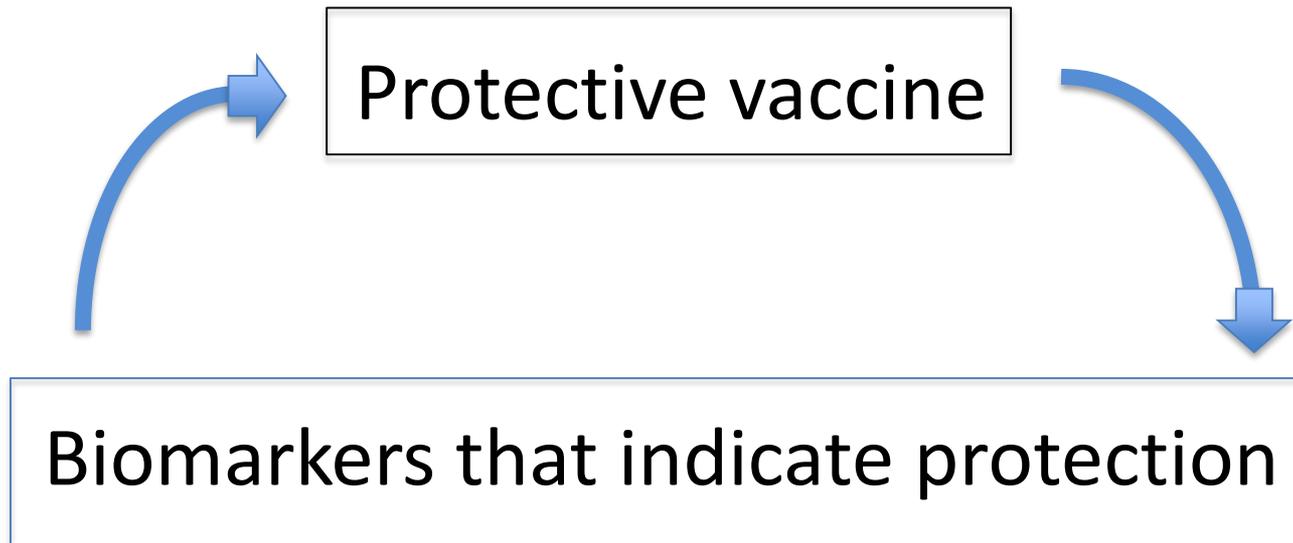
Identify best TB vaccine candidates for clinical trials

	Protective biosignature	Decision
VACCINE A	+++	Take forward
VACCINE B	-	Halt development
VACCINE C	+	Further improvement

But:

- Head-to-head testing of vaccine candidates is rare and mainly in animal models
- We need to identify protective biosignatures, and biomarkers may not be the same for all types of vaccines

However....



- We have a pipeline of promising candidates but no new effective TB vaccine as yet

Can we learn from other comparisons?

Those who do or do not develop TB disease in vaccine trials (CoP)

TB contacts who do or do not develop disease (CoR, incipient TB)

TB cases compared to Latent TB infection (LTBI)

Long term LTBI non-progressors

TB cases before and after TB treatment

Treated TB cases who do or do not relapse

CoP, Correlates of Protection; CoR, Correlates of Risk

- **Database of TBVAC2020 WP5 cohorts, including assays performed and samples available for study**

Which assays look most promising?

Sample	Assays
PBMC	Flow cytometry and intracellular cytokine staining; Elispots, Mycobacterial growth inhibition
RNA	Ex vivo; stimulated and unstimulated PBMC (database)
Serum/plasma	Antibody ELISAs; multiplex cytokine/chemokine analysis

- Standardised harmonised SOPs (including stimuli) will enable comparison of results from different studies and trials
- Obtain as much non-overlapping information about the immune space as possible

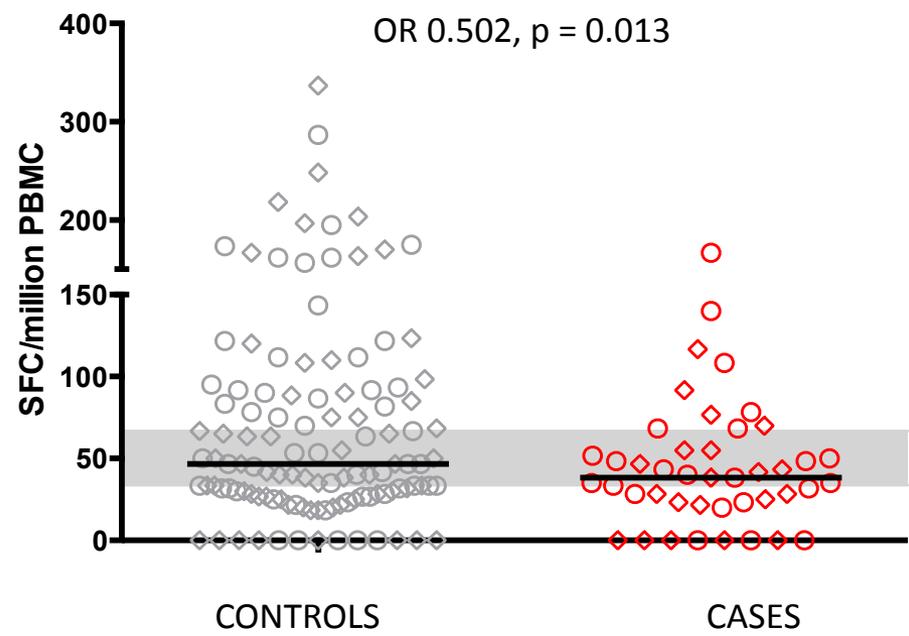
Infants with greater BCG-specific IFN γ ELISPOT responses show slower progression to TB

ARTICLE

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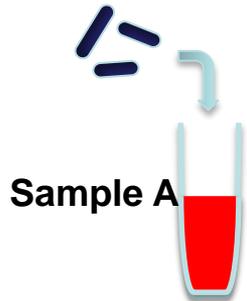
T-cell activation is an immune correlate of risk in BCG vaccinated infants



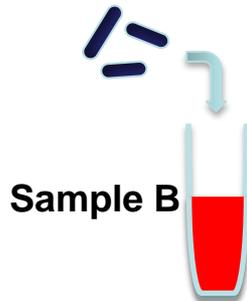
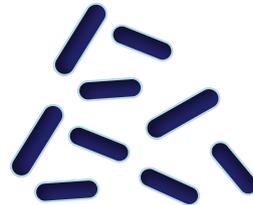
- Magnitude of IFN γ ELISPOT at day 0 associated with reduced risk of disease and slower progression to disease; this needs replication
- BCG-specific polyfunctional T cell cytokine responses were not associated with protection in a BCG-vaccinated cohort in South Africa

Mycobacterial growth inhibition as an unbiased measure of TB vaccine-induced immunity

Straight to MGIT reference tube



Incubate PBMC and mycobacteria for 4 days



Lyse cells, extract remaining mycobacteria and add to MGIT tube



Time to positivity (TTP) in days and hours

Mycobacterial Growth Inhibition Assay Optimisation: EURIPRED

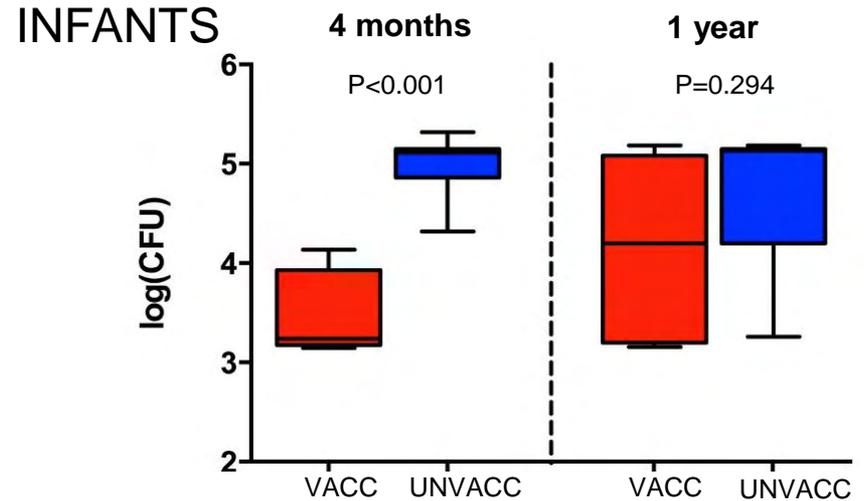
- Harmonised SOPs, shared stocks of BCG, and joint training have greatly improved the performance of assays such as the MGIA



Tanner, McShane, Meijgarden, Ottenhoff, Smith, Dockrell, unpub data

BCG vaccination induces greater mycobacterial growth inhibition

- MGIA performed on PBMC from UK BCG vaccinated or unvaccinated infants
- BCG-vaccinated infants show increased growth inhibition, but some lose this by 1 year
- Growth inhibition was associated with frequency of polyfunctional T cells
- BCG vaccinated adults also show more growth inhibition (Anwar, unpub data)



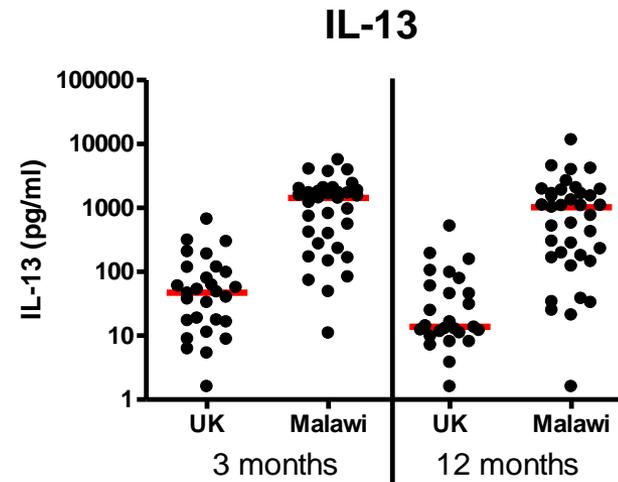
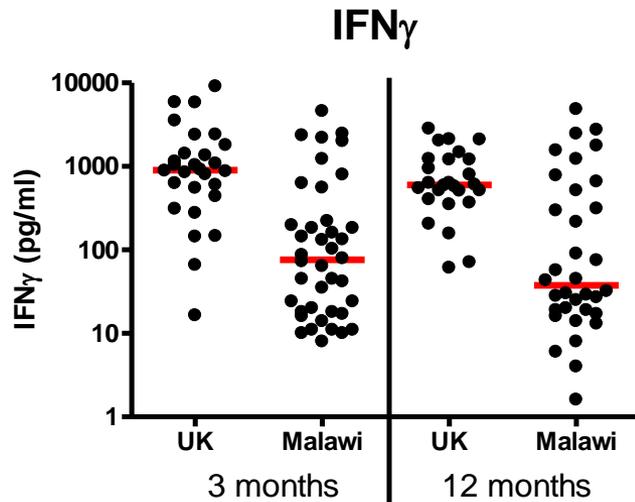
Progress towards useful biomarkers

- Valuable sets of samples available including serum/plasma, RNA, PBMC etc
- Cohorts that can give us insights until we have a protective vaccine
- Best assays selected with optimised standardised SOPs
- More cohorts and banked samples are needed though...

When we have useful biomarkers, we need to test them:

- Immune responses following vaccination can vary in different geographic settings
- Co-infection with HIV, CMV, helminths can induce immunosuppression
- Co-morbidity also modulates immunity and inflammation, for example, patients with type 2 diabetes are 2-3x more likely to develop TB
- ***We need to be sure biomarker signatures will work in different settings, with different co-infections and co-morbidities***

•Earlier studies in Malawi and the UK showed differences in how infants responded to BCG Danish vaccination



•Measured in PPD stimulated 6 day WB supernatants by 42 plex Luminex assay (n=28)

Further evidence that the infant immune system reacts differently to vaccination in different settings

- UK and Ugandan infants given BCG Danish at birth, bled at 10 and 52 weeks after BCG vaccination
- Differences in cytokine production in the two settings (Mawa, Hasso-Agopsowicz, Cose, Dockrell, Smith, unpub data)
- Factors could include maternal factors, epigenetic differences, nutritional differences, etc – at this age little or no exposure to environmental mycobacteria pre-vaccination

Protective vaccines should induce the correct biomarkers in all settings

Vaccination of adolescents and adults: Helminth infected patients exhibit poor BCG growth inhibition which improves after anthelmintic treatment

- Patients with latent TB infection and helminth infection show lower mycobacterial growth inhibition compared to those with LTBI alone
- Anthelmintic treatment is associated with an increase in CD4 T cell IFN γ production and a decrease in regulatory T cells (Toulza et al. Eur J Immunol. 2016; 46:752)
- Mycobacterial growth inhibition also increases (Anwar, Brown, Fletcher, Dockrell, unpub data)
- Most vaccine studies do not include testing for helminth infection which may be common in children, adolescents and adults

Therapeutic vaccination in adults: how might co-morbidity with type 2 diabetes affect biomarkers?

TANDEM

Concurrent tuberculosis and diabetes mellitus: unravelling the causal link & improving care

“The TANDEM Consortium brings together partners with complementary skills in clinical studies, epidemiology, health economics, human genetics and immunology.”



- Gene expression analysis using RNA-Seq using samples from TB, diabetes and TB-diabetes patients from South Africa, Peru, Romania and Indonesia
- Gene expression profiles in TB patients with diabetes are different from those with either TB or diabetes (Eckold, Cliff, unpub data)

Global Clinical Pipeline of TB Vaccine Candidates

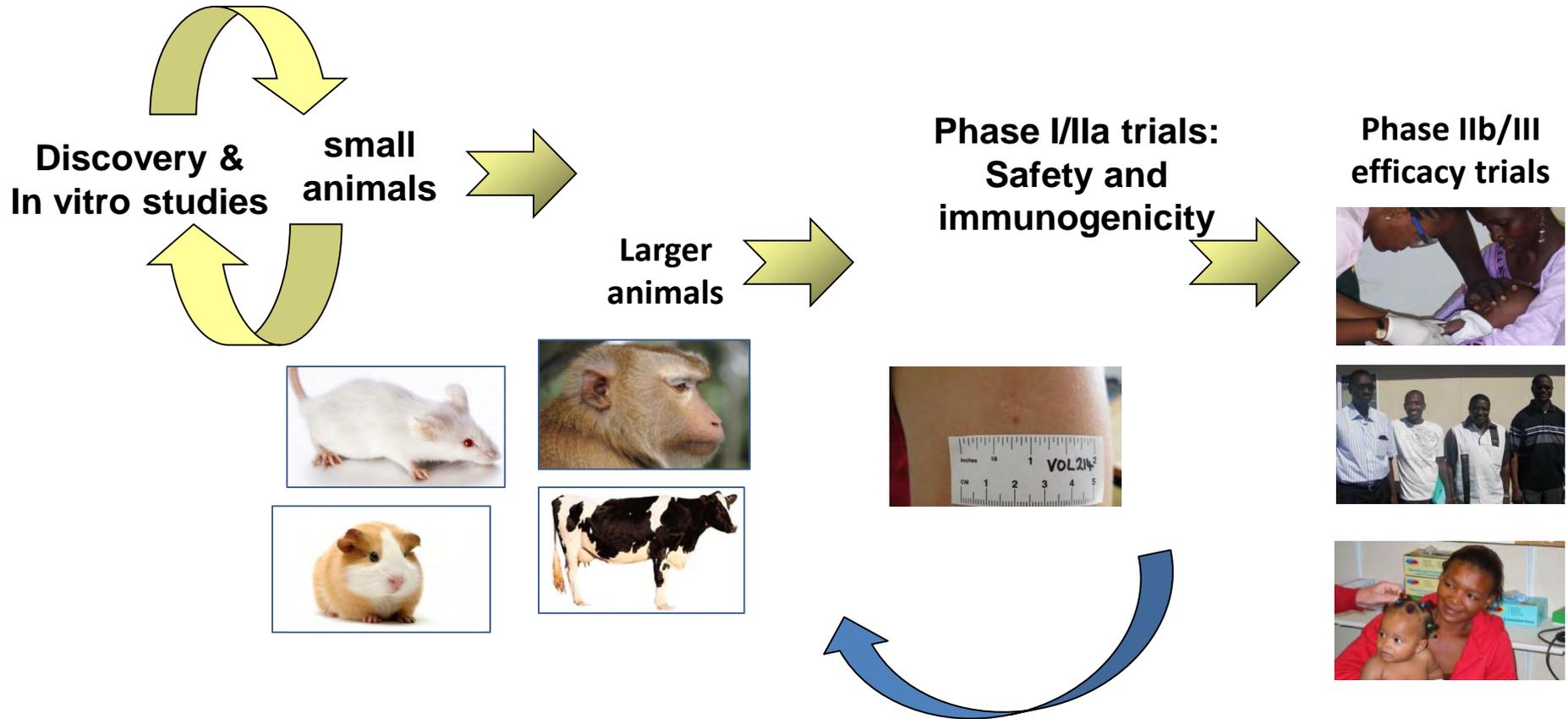


Revised on 9/26/17

Please note: Information is self-reported by vaccine sponsors

- Biomarkers can help us identify those candidates with the greatest potential for protective efficacy

Pathway for Human Vaccine Development



We can learn from the biomarker signatures in clinical trials

We should continue to invest in biomarker research; biomarkers can help us develop a protective TB vaccine

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- Steven Smith, Mateusz Hasso-Agopsowicz, Michael Brown and Shaheda Anwar at LSHTM (EC TBVAC2020, IDEA, MRC)
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