

An agenda for research on T-Cell Based Diagnosis of Latent Tuberculosis Infection

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Major thematic areas

- Basic science and assay development
- Test performance in high risk populations and poorly studied groups
- Risk prediction and modeling
- Reproducibility and serial testing
- Issues relating to treatment
- Epidemiology
- Health systems and economic issues

Basic science and assay development

- Identify and validate novel antigens that can increase sensitivity of T cell based assays without compromising their high specificity
- Identify and validate novel antigens that can distinguish between LTBI and active disease
- What is the association between bacterial burden and IFN-g response?
- What type of T cell responses are detected by short incubation IGRAs - effector or memory T cell responses?
- Validation of IGRA cut-points
- Simplification of tests for resource limited settings

Test performance in high risk populations

- Immunocompromised
 - HIV
 - Others (immunosuppressive meds, cancer, diabetes, renal failure, transplantation, etc.)
- Children
- Close contacts
- Healthcare workers

Risk prediction

- What is the predictive value of a positive IGRA test for development of active disease, relative to a positive TST?
 - Among IGRA positive individuals, are individuals with higher levels of IFN-g responses more or less likely to progress to active disease?
- What is the accuracy and role of IGRAs as a “rule out” test for active TB?

Reproducibility and serial testing

- What is the test-related variability in the T cell responses? (i.e. operators, labs, sample processing, incubation times, antigens (proteins vs peptides), formats (ELISA vs ELISPOT), etc.)
- What is the within-subject, biological variability of IFN-g responses over time, including day to day, week to week, and month to month variability of IFN-g levels?
- What is an IGRA conversion?
 - Which IFN-g threshold is optimal for distinguishing between true infection and non-specific, random variation?
 - Are those with dramatic increases in IFN-g more likely to develop active disease? Is the dramatic increase more likely to be seen in those with recent exposure?
- What is an IGRA reversion?
 - Which thresholds should be used for reversion, frequency of reversions, clinical/epidemiological significance of reversions, and factors associated with reversions (e.g. treatment, baseline IFN-g levels, variability around cut-points, etc).

Issues relating to treatment

- How do T cell responses change during and after treatment for latent TB infection?
 - What factors, including host, disease, and assay characteristics, influence variability in responses after treatment?
- How do T cell responses change during and after treatment for active TB?
 - What factors, including host, disease, and assay characteristics, influence variability in responses after treatment?
- Can T cell based assays play a useful role in monitoring response to latent and active TB treatment?
 - What is the ability of IGRAs to detect reinfection after treatment for both LTBI and TB disease?
 - What is the ability of IGRAs to predict treatment failures?

Epidemiology

- Can IGRAs be used in community surveys to estimate annual risk of TB infection, LTBI prevalence, etc?
 - Use IGRAs to re-appraise traditional estimates used in TB modeling and impact assessment: e.g. Styblo rule, 10% risk of progression from LTBI to active TB, one-third of the world's population infected, etc.
- What is the accuracy and utility of screening strategies that use combinations of TST and IGRAs: e.g. first screen with TST, and confirmation of positive results by IGRAs?
- How does IGRA performance vary between high and low TB incidence settings?
 - In high burden settings, what is the impact of immune modulators on IGRA performance: BCG, NTM, HIV, leprosy, malnutrition, parasitic infections (e.g. helminths), etc.
 - In high burden settings, which population subgroups are most likely to benefit from IGRAs?

Health systems & economics

- Economic and decision analyses comparing TST with IGRAs for various screening programs (e.g. immigrant screening, contact investigations, serial testing of HCWs, etc.)
- What is the impact of switching from TST to IGRA on laboratory/clinic work load, staff work load, program costs, patient convenience, compliance with testing and follow-up, etc.?
- What resources are needed to increase lab capacity in developing countries to enable implementation of new tools such as IGRAs?
- What is the expected impact of introduction of new LTBI tools on global TB burden?