CBER / FDA Workshop on Immune Correlates of Protection for Tuberculosis Vaccines

Dear Workshop Participants,

It is our pleasure to welcome you to the CBER / FDA Workshop on Immune Correlates of Protection for Tuberculosis Vaccines. Recently, a variety of new TB vaccines have entered clinical trials throughout the world. Many different types of laboratory assays are being used to measure vaccine immunogenicity, with the hope that a measurement also proves to correlate with protection. Some of these approaches are technically complex, and may not yet be standardized to the degree usually expected to support regulatory decisions regarding vaccine licensing. In this meeting, we will discuss approaches to advancing complex clinical assays, such as multiparameter flow cytometry and global profiling techniques, toward rigorous standardization and validation.

But the issues facing application of relevant assays to support regulatory decisions are embedded within a larger scientific problem: no predictive correlates of protection have yet been identified for tuberculosis, or any other intracellular pathogen. Further, to date no new vaccine candidate has provided clear clinical benefit over and above that offered by vaccination with BCG. Thus the overall path to detecting correlates of protective immunity for tuberculosis vaccines remains unclear. In this context, the meeting’s larger purpose is to provide a forum for focused, pragmatic discussion of strategies for deriving protective correlates. How can we translate what is known about protection to meaningful immunologic measures that might predict protection? Can we identify correlates of risk, and translate that to TB vaccines? What are the considerations and criteria in deciding on approaches? What are the gaps in knowledge and tools? In facilitating these conversations, we hope to identify additional opportunities that might be available in upcoming clinical trials, pinpoint roadblocks, suggest solutions, and create momentum for future progress.

To that end, the meeting’s format will be comprised of platform presentations with the most recent clinical and animal data on TB vaccine development; short presentations on focused aspects of assay development; and substantive discussion of specific questions. We invite you to thoughtfully consider the discussion questions provided with the meeting agenda, come prepared for active participation, and help this research community develop constructive answers that will guide future work and funding. Thanks for joining us!

We are most grateful to our generous meeting sponsors!

The Bill & Melinda Gates Foundation
Center for Biologics Evaluation and Research, U.S. FDA
The National Institute of Allergy and Infectious Diseases, NIH
Aeras
Correlates Workshop Schedule

Tuesday
September 10
Jeffersonian Room

12:00 Noon - 2:30 PM  Registration – Promenade, adjacent to Jeffersonian Room

2:30 PM - 6:00 PM  Joint Session: Vaccine-related biomarkers

2:30  *Peter Andersen, Chair, Statens Serum Institute
      TB subunit vaccines and immunological memory

3:00  JoAnne Flynn, University of Pittsburgh
      Variability is the rule in tuberculosis, in individual hosts and populations

3:30  Willem Hanekom, University of Cape Town
      Correlates of risk of TB in infants and adolescents

4:00 PM – 4:30 PM  Coffee Break

4:30  Stefan H.E. Kaufmann, Max Planck Institute for Infection Biology
      Transcriptomic and metabolomic markers in TB: From data generation to data analysis

5:00  Erik Jongert, GlaxoSmithKline Biologicals
      GSK’s assay strategies in the clinical development of M72/AS01E

5:30  Helen McShane, University of Oxford
      Update on MVA85A correlate studies

6:30 PM – 8:00 PM  Dinner – Palm Court
Wednesday
September 11
Jeffersonian Room

8:15 AM – 8:30 AM  Introduction: Overview and goals for the day

8:30 AM – 10:30 AM  Session: Functional assay approaches in TB vaccine trials
    Moderators: Helen Fletcher and Daniel Hoft

8:30  Thomas Scriba, South African Tuberculosis Vaccine Initiative
    Measuring immune responses to TB vaccines: Experience from MVA85A trials

8:50  Helen Fletcher, University of Oxford
    Functional assessment of BCG and MVA85A using a Bactec MGIT based assay

9:10  Daniel Hoft, St. Louis University
    Potential applications and advantages of different TB functional immunoassays

9:30  Stephen DeRosa, University of Washington
    Intracellular cytokine staining and cytokine multiplex bead array used for correlates analyses in HIV vaccine trial

9:50  Group Discussion

Questions:

- From a scientific perspective, what are the strengths and weaknesses of each type of assay approach, including practical considerations? Discuss selection process and criteria, with case studies as examples

- What advances can ultimately come from the use of mycobacterial growth inhibition assays?

- From a scientific perspective, what do these assays tell us? Discuss link to clinical responses

10:30 AM – 11:00 AM  Coffee Break
11:00 AM – 1:00 PM  
Session: ‘Omic assay approaches in TB vaccine trials
Moderators: Thomas Scriba and Daniel Zak

11:00  
Rafick Sekaly, Vaccine and Gene Therapy Institute
*Predictors of vaccine efficacy and immunogenicity: a systems biology overview*

11:20  
Alessandro Sette, La Jolla Institute for Allergy and Immunology
*Definition of the targets of immune responses in LTBI*

11:40  
Daniel Zak, Seattle Biomedical Research Institute
*Systems-level analysis of vaccine trials to identify correlates and generate new mechanistic hypotheses*

12:00  
Robert Van den Berg, GlaxoSmithKline Biologicals
*GSK ‘omics approaches in TB*

12:20  
Group Discussion

Questions:

- What do we mean by omics-based “correlates of protection?” Does this relate to predictive biomarkers (to use for prediction/stratification), or mechanistic hypothesis generation, or both? The analysis strategy used will be different for each.

- How can we develop correlates of risk of TB, to achieve either a reduction in trial size by targeted enrollment of “at risk” persons, and/or to understand the biology underlying progression from infection to TB disease (e.g., the ACS, GC6 projects)?

- Can we measure the acute/early innate response to vaccination as a surrogate and predictor of immunogenicity (e.g., as for the Merck/Ad5 HIV vaccine; Zak *et al.*, PNAS 2012)?

- How can we use ‘omics to find “correlates of vaccine success,” and make better decisions about vaccine design and which vaccines to advance (e.g., Sette and colleagues, PLoS Path 2013)?

1:00 PM – 1:45 PM  
Lunch – Palm Court
1:45 PM – 3:30 PM

Session: Developing complex assays to support regulatory decisions
Moderators: Freyja Lynn and Thomas Evans

1:45 Freyja Lynn, Center for Biologics Evaluation and Research
Developing complex assay to support regulatory decisions: general principles

2:15 Sylvia Janetzki, ZellNet Consulting
Flow cytometry assay harmonization and the MIATA experience

2:35 J. Peyton Hobson
‘Omic assays in a regulatory context

2:55 Group Discussion

Questions:

Particularly for complex assays (e.g., flow cytometry, global profiling approaches), what are the considerations for validation, and for using data from such methods to support regulatory decisions? Specifically,

- How exactly are complex assays likely to be used?
  - Investigational tools (e.g., during early clinical development, as exploratory endpoints or for proof of concept, and scientific inquiries)?
  - Regulatory purposes (e.g., to support licensure/registration, or to support post-licensure decisions like changes to manufacturing, changes to dose/schedule, or new indications)?

- Will data from complex assays be compared across laboratories, or will all data be generated by a central site?

- What are the roadblocks to using complex assays to support regulatory decisions (e.g., practicality, cost, difficult to control)?

- What are the obstacles to control and formal validation of complex assays, and how can those obstacles be addressed (e.g., reference standards; control samples; formalizing methodology; routine control/assay stability)?

3:30 PM – 4:00 PM Coffee Break
4:00 PM – 6:00 PM  Session: Approaches to correlate development for TB vaccines
Moderators: Willem Hanekom and Barry Bloom

4:00  Jerome Kim, Walter Reed Army Institute of Research
*Insight from study of correlates in the RV144 HIV vaccine trial*

4:25  Barry Bloom, Harvard University
*In desperation: A challenging approach*

4:35  Willem Hanekom, University of Cape Town
*Critical issues in defining correlates of risk and of protection*

4:45  Group Discussion

Questions:

Correlates of risk and of protection:

- Correlates of risk studies are possible in the absence of an effective vaccine – how could these translate to TB vaccines, and particularly how could these guide defining correlates of protection against TB disease?
- How can we identify the multiple factors or conditions that are not only necessary, but also sufficient for protection?
- What are the considerations and criteria in deciding on an approach for identification of correlates of risk: Unbiased (hypothesis-generating), hypothesis-driven (RV144-like), combination?
- Should diversity of vaccines and populations influence correlate development, and how?
- How can this work be funded?

Correlates of vaccine take:

- Current approaches aim to measure a T cell response – should we aim for different markers, e.g., early gene expression markers of vaccine take?
- How would this be accomplished (including funding)?

5:45 PM – 6:00 PM  Summary and wrap up
# The Organizing Committee

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# Biomarkers for Tuberculosis: New Questions, New Tools and CBER / FDA Workshop on Immune Correlates of Protection for Tuberculosis Vaccines

**September 8 – 11, 2013**

## Combined Agenda at a Glance

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<td>“Late breaking” talks, from abstracts</td>
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