

WORKSHOP

Tuberculosis Meningitis: Advancing Immunopathogenesis, Diagnosis, and Treatment

Sponsored by

National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver National Institute of Child Health and Human Development

May 22-23, 2017
5601 Fishers Lane, Room 1D13
Rockville, Maryland

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AGENDA

May 22 (Monday), 2017

- 7:30-8:00 **Registration**
- 8:00-8:15 **Welcome and Opening Remarks**
Richard Hafner (National Institute of Allergy and Infectious Diseases)
Rohan Hazra (Eunice Kennedy Shriver National Institute of Child Health and Human Development)
- 8:15-8:35 **Keynote Speaker: TBM Clinical Research Agenda**
Guy Thwaites (University of Oxford)
- 8:35-8:55 **Keynote Speaker: Basic Science Review of Bacterial Meningitis**
Nemani Prasadarao (Children's Hospital Los Angeles)
- 8:55-9:10 **Break**

9:10-10:30 Session 1: Diagnostics and Biomarkers

Co-Chairs: Omar Siddiqi (Beth Israel Deaconess Medical Center)
Dima Hammoud (National Institutes of Health Clinical Center)

Session Overview:

This session will discuss the current state of TBM diagnostics while highlighting the gaps that exist as well as emerging diagnostic tools. The session will also discuss the potential role of neuroimaging and diagnostic biomarkers to improve future testing.

9:10-9:30 Current and Future Ultra Diagnostics in TB Meningitis

David Boulware (University of Minnesota)

9:30-9:50 Diagnostic and Prognostic Potential of Neuroimaging and Neurotissue Markers in Tuberculous Meningitis

Ursula Rohlwink (University of Cape Town)

9:50-10:10 Potential Diagnostic Biomarkers

Keertan Dheda (University of Cape Town)

10:10-10:30 Group Discussion for Session 1**10:30-10:45 Break****10:45-12:15 Session 2, Part 1: Immunopathogenesis**

Co-Chairs: Reinout van Crevel (Radboud University Medical Center)
Zsuzsanna Fabry (University of Wisconsin-Madison)

Session Overview:

This session aims to summarize what is known regarding host immune response and immunopathology in TBM patients, integrating clinical and laboratory phenotyping data, in order to identify relevant biomarkers or possible targets for host-directed therapy.

10:45-10:50 Session Introduction

Reinout van Crevel (Radboud University Medical Center)

10:50-11:10 Stroke in TB Meningitis: Path-Physiology, Clinical and Management Issues

Usha Kant Misra (Sanjay Gandhi Postgraduate Institute of Medical Sciences)

11:10-11:30 **Host Genotypes, Inflammatory Response and Outcome of TBM; Vietnam Cohort**
Nguyen Thuy Thuong Thuong (Oxford University Research Unit, Ho Chi Minh City)

11:30-11:50 **Host Inflammatory Phenotype and Outcome TBM Indonesia**
Arjan van Laarhoven (Radboud University Medical Center)

11:50-12:50 **Lunch**

12:50-1:10 **Phosphodiesterase and DAMP Inhibitors as Adjunctive Agents**
William Bishai (Johns Hopkins University)

1:10-1:50 **Group Discussion for Session 2, Part 1**

1:50-4:00 **Session 2, Part 2: Modeling**

Co-Chairs: *Sanjay K. Jain (Johns Hopkins University)*
David Tobin (Duke University)

Session Overview:

This session will provide an overview of preclinical models (in vitro blood-brain barrier and animal models) for central nervous system (CNS) tuberculosis (TB) including those relevant to pediatric disease. Animal models that simulate the natural course of infection as well as those utilizing direct inoculation into CSF/cerebellum and their use in studying microbial virulence factors, disease pathogenesis, unique vaccine targets and drug treatment will be discussed. We will also discuss real-time imaging techniques to study pathogenesis and to monitor disease. Finally, we would like to identify knowledge gaps in the current understanding of CNS TB and how models can help to bridge these gaps.

1:50-2:20 **Overview of Models of CNS TB and TB Meningitis**
Sanjay K. Jain (Johns Hopkins University)

2:20-2:40 **A Zebrafish Model of TB Meningitis**
Cressida Madigan (UCLA School of Medicine)

2:40-3:00 **CNS Barriers and Anti-microbial Immunity**
Zsuzsanna Fabry (University of Wisconsin-Madison)

3:00-3:15 **Break**

- 3:15-3:35 **Rabbit Model of TB Meningitis in Children**
Liz Tucker (Johns Hopkins University)
- 3:35-3:55 **Insights from Animal Models of Chemotherapy for Cryptococcal Meningitis**
John Perfect (Duke University)
- 3:55-4:15 **Molecular Imaging for Infections**
Alvaro Ordoñez (Johns Hopkins University)
- 4:15-5:30 **Group Discussion for Session 2, Parts 1 and 2**
- 5:30 **Adjourn**

May 23 (Tuesday), 2017

8:30-11:45 Session 2, Part 3: Host Directed Therapy

Co-Chairs: *Vishwanath Venketaraman (Western University of Health Sciences)*
Guy Thwaites (University of Oxford)

Session Overview:

Ever since the advent of anti-tuberculosis drugs in the late 1940s, it has been recognized that the host intracerebral inflammatory response is an important determinant of outcome from TBM. In the 1950's, adjunctive anti-inflammatory treatment with corticosteroids were found to speed recovery, but it took a further 50 years, and many clinical trials, to prove that they increased survival from TBM. Corticosteroids, however, have pleotropic effects, including some that are harmful; and novel, targeted, and potentially safer and more effective therapies are being sought. This session will provide overviews on host-directed therapy landscape for both meningeal and non-meningeal TB. Recent findings from preclinical and clinical studies using thalidomide, glutathione, and aspirin will be presented in this session.

- 8:30-9:00 **Overview of the HDT Landscape for Non-Meningeal TB**
Robert Wallis (Aurum Institute)
- 9:00-9:30 **Insights into the Host Response and the Potential for HDT from Studies of HIV-TB Associated TBM IRIS**
Robert Wilkinson (University of Cape Town, Imperial College London, Francis Crick Institute)

9:30-10:00 **Use of Thalidomide in Childhood TB Meningitis**
Johan Schoeman (Stellenbosch University)

10:00-10:15 **Break**

10:15-10:40 **Glutathione as an Immunoadjuvant**
Vishwanath Venketaraman (Western University of Health Sciences)

10:40-11:00 **Aspirin**
Guy Thwaites (University of Oxford)

11:00-12:00 Group Discussion for Session 2, Part 3

12:00-1:00 **Lunch**

1:00-3:15 Session 3: Optimized Tubercular Therapy

Co-Chairs: *Kelly Dooley (Johns Hopkins University)*
Rovina Ruslami (Universitas Padjadjaran)

Session Overview [Suggested topics – Session Chairs to finalize]:

In this session, we will explore potential therapeutic interventions for TBM, learn about the science and evaluation of drug delivery to the brain and meninges, and review state-of-the-art tools to inform neurosurgical and supportive management of TBM. Specific attention will be paid to pediatrics, HIV co-infection, and drug-resistance, with the goal of identifying knowledge gaps for optimizing TBM antimicrobial treatment for all, including special populations.

1:00-1:20 **Drug Delivery to Meninges/CNS – PBPk, PK-PD**
William Elmquist (University of Minnesota)

1:20-1:40 **Evaluation and Optimization of Existing and New TB drugs for TBM**
Rob Aarnoutse (Radboud University Medical Center)

1:40-2:00 **Linezolid for TBM**
Wenhong Zhang (Fudan University)

2:00-2:20 **Antimicrobial Management of Pediatric TBM**
Kelly Dooley (Johns Hopkins University)

2:20-2:35 **Break**

2:35-2:55 **Knowledge Gaps in HIV-TBM**
Suzaan Marais (Inkosi Albert Luthuli Central Hospital)

2:55-3:15 **Neurosurgical and Supportive Management of TBM: Insights and Opportunities using Modern Tools**
Tony Figaji (University of Cape Town)

3:15-4:15 Group Discussion for Session 3

4:15-4:30 **Wrap-up and Next Steps**
Richard Hafner (National Institute of Allergy and Infectious Diseases)
Rohan Hazra (Eunice Kennedy Shriver National Institute of Child Health and Human Development)

4:30 **Adjourn**