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Keynote Forum
September 20, 2017

Tuberculosis 2017



Global summit on

TUBERCULOSIS AND LUNG DISEASE

September 20-21, 2017 Philadelphia, USA

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Emory University, USA

Identifying patients at high risk of tuberculosis recurrence

Several studies have been done in relation to recurrence of tuberculosis (TB) following completion of treatment. However, recurrence of TB is still a major problem from a public health perspective in high-burden countries, where no special attention is being given to this issue. Disease recurrence is an important indicator of the efficacy of antituberculosis treatment. The rate of recurrence is highly variable and has been estimated to range from 4.9% to 25%. This variability is not only a reflection of regional epidemiology of recurrence but differences in the definitions used by the TB control programs. In addition to treatment failure related to medication adherence, there are several key host factors that are associated with high rates of recurrence. The widely recognized host factors independent of treatment program that predispose to TB recurrence include: malnutrition; human immunodeficiency virus; substance abuse including tobacco use; comorbidity such as diabetes, renal failure and systemic diseases, especially immunosuppressive states; and environmental exposure such as silicosis. With improved understanding of the human genome, proteome, and metabolome, additional host-specific factors that predispose to recurrence are being discovered. Information on temporal and geographical trends of TB cases as well as genotyping might provide further information to enable us to fully understand TB recurrence and discriminate between reactivation and new infection. The recently launched World Health Organization End TB Strategy emphasizes the importance of integrated, patient-centered TB care. Continued improvement in diagnosis, treatment approaches, and defining host-specific factors are needed to fully understand the clinical epidemiological and social determinants of TB recurrence.

Speaker Biography

Ruxana T Sadikot is a Professor of Medicine at the Emory University in Atlanta and serves as the Section Chief of Pulmonary and Critical Care Medicine at the Atlanta VA Medical Center. Her research career has focused on defining the lung immune response and mechanism of lung injury. In particular her research is focused on defining the role of transcription factors, lipid mediators (prostaglandins) and super immunoglobulin receptor TREM-1 in macrophages in resistant infections. Her clinical research focus is bronchiectasis and infections including tuberculous and non-tuberculous mycobacteria and P. aeruginosa. She has published extensively on these topics in high impact peer reviewed journals and book chapters. She serves on the Editorial Board Member of Clinical Respiratory Medicine, Biomedical Research International and Annals of American Thoracic Society. She has mentored several graduate students, residents, post-doctoral fellows and junior faculty through her career.

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Seyed Ehtesham Hasnain

Jamia Hamdard University, India

Newer molecular targets and therapeutic strategies for intervention against *Mycobacterium tuberculosis*

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*M. tb*), takes one human life every 15-20 seconds globally. We have been focusing on the functional biology of this pathogen with a view to design innovative interventions against TB. We identified and characterized several virulent proteins of *M. tb* that help in intracellular survival by modifying host cellular machinery. Phylogenetic analysis of *M. tb* methyltransferases (MTases) pointed to an evolutionary relationship of *M. tb* with halotolerant organisms, notably in the context of their ability to withstand the host osmotic stress, thus highlighting their likely role in pathogenesis, virulence and niche adaptation. Some of the MTases exhibit antigenic patches and regulate transmembrane transport proteins. Another class of proteins, the sigma factors and their target genes, has been shown to move from non-pathogenic to pathogenic Mycobacteria. The *M. tb* PE_PGRS subfamily has unusually high levels of disordered stretches compared to any other family in the proteome and was highly enriched in average number of anchor binding sites, eukaryotic linear motifs (ELMs) and has highly biased amino acid composition rich in disorder promoting alanine and glycine residues and play roles in molecular mimicry. One member of this protein family causes activation of Unfolded Protein Response as evident from increased expression of GRP78/GRP94 and CHOP/ATF4, leading to disruption of intracellular Ca2+ homeostasis and increased NO and ROS production. The consequent activation of effector caspase-8, resulted in apoptosis of macrophages. In other series of investigations, comparative proteomic and genomic analyses revealed the exclusive presence of 'Signature sequences' in *M. tb* genome, some of which have potential utility in TB diagnosis based on limited clinical validation. Hypothetical proteins coded by one such 'Signature sequences' was found to be a functional S-adenosyl dependent DNA methyltransferase and binds DNA non-specifically and protects DNA from oxidative stress by scavenging iron thereby, preventing generation of free radicals and by physically binding DNA and providing a physical barrier. Using drug re-purposing strategies we also identified existing US FDA approved drugs that inhibit *M. tb* by disrupting the pathogen's biofilm forming ability and thus have the potential to act as a new TB drug and to reduce the duration of treatment. My presentation will cover some of these findings from our group.

Speaker Biography

Seyed Ehtesham Hasnain is a Professor and the Head of Jamia Hamdard-Institute of Molecular Medicine and Invited Professor at Indian Institute of Technology, Delhi. He has received his PhD from JNU (1980), Post-doctoral training in Canada/USA, and was a Staff Scientist at National Institute of Immunology, New Delhi and the Vice Chancellor (President) of Jamia Hamdard. He is associated with editorial boards of national/international journals and has authored more than 250 publications/patents and recipient of many national and international awards including S S Bhatnagar Prize, Ranbaxy Research Award, J C Bose National Fellow, Humboldt Research Prize and Robert Koch Fellow (Berlin). He is an Elected Fellow of German Academy of Sciences, Leopoldina and American Academy of Microbiology, etc. He has received Germany's highest recognition DasVerdienstkreuz, 1. Klasse in 2014. His research area includes functional molecular epidemiology and biology, *Mycobacterium tuberculosis*, transcriptional regulation of gene expression, genetic hyper-variability, molecular pathogenesis and disease intervention.

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