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DEFENSE OF THE DOCTORAL

DISSERTATION

"Biomarkers of and Immune Mechanisms Underlying Distinct *Mycobacterium tuberculosis* Infection Outcomes"

by

Sarah Lundell

M.D./Ph.D. Program

BS, Chemistry and Philosophy, 2017, Fordham University, Bronx, NY

Thesis Advisors:

Padmini Salgame, Ph.D.

Professor
Division of Infectious Diseases
Department of Medicine

Friday, April 12th, 2024
10:00 A.M.
ICPH Auditorium C109

https://rutgers.zoom.us/j/91449325796?pwd=YlpEMTM1dVM0bWFEVEtTWnJNck1WUT09
Meeting ID: 914 4932 5796
Password: 752417

Abstract

Mycobacterium tuberculosis (Mtb) is an ancient pathogen that remains a major health threat in the modern world, infecting nearly a third of the world's population. The heterogeneity of Mtb infection trajectories and presentations complicates the prevention and diagnosis of tuberculosis (TB) disease. Of those infected, 5-10% progress from latent infection to active disease, and biomarkers to identify which individuals will progress are needed to allow targeted prophylactic treatment. Mechanistic understanding of the memory immune responses associated with progression or control of infection is needed to identify therapeutic targets and correlates of protection. Finally, pediatric tuberculosis presents a diagnostic challenge due to its paucibacillary nature, leading to missed cases; diagnostic biomarkers of pediatric TB are needed to close the detection gap. The goals of this dissertation were I) to validate transcriptomic biomarkers of progression in a household contact cohort, II) to evaluate diagnostic performance of adult-derived signatures in a pediatric TB cohort, and III) to identify mechanisms of protection from disease progression in reconsented household contacts (HHCs). The NanoString platform was used to quantify a panel of published TB gene signatures in household contacts at baseline, and several signatures were validated to predict progression to disease. Combinations of signatures lead to increased specificity and positive predictive value, meeting WHO target product profile levels. In the pediatric diagnostic cohort, several adult gene signatures were able to distinguish between confirmed TB and unlikely TB cases, and machine learning was used to derive new pediatric signatures. Performance was highly age-specific, with the lowest performance in the youngest age group. Lastly, single cell RNAseq was performed on Mtb-antigen stimulated and unstimulated peripheral blood mononuclear cells from reconsented HHCs with previous progression to disease or long-term latent infection, to identify correlates of protection. Distinct natural killer cell subsets were identified with differential frequency and gene expression in previous progressors and individuals with LTBI, as well as progression-specific gene expression in CD4+ and CD8+ memory cells. Together, these findings contribute to our understanding of protective immune responses to TB as well as the clinical need to derive diagnostic and prognostic biomarkers to combat this global health threat.