

YOU ARE INVITED TO ATTEND THE  
DEFENSE OF THE DOCTORAL  
DISSERTATION

**“HOST RESPONSES TO LOW-BURDEN MYCOBACTERIUM  
TUBERCULOSIS ACROSS DISTINCT BIOLOGICAL CONTEXTS:  
BIOMARKER DISCOVERY IN PAUCIBACILLARY TUBERCULOSIS  
AND MEMORY T-CELL REPROGRAMMING FOLLOWING  
PREVENTIVE THERAPY”**

by

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Tuesday, October 27, 2026  
10:00 AM

Join in person: ICPH Auditorium C109

**Join Zoom presentation**

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**Password: 143842**

## ABSTRACT

Tuberculosis (TB) remains a leading cause of mortality worldwide, presenting an ongoing public health challenge. A major barrier to TB elimination is the persistence of low-burden *Mtb* states across the infection spectrum. One challenge is detecting paucibacillary TB disease, where bacterial numbers fall below the limits of available diagnostics. Another is understanding whether eliminating low-level *Mtb* infection through preventive therapy does more than kill bacteria by reshaping memory T-cell responses and promoting durable protective immunity. This thesis addresses these challenges using transcriptomic, computational and immunological approaches in well-characterized cohorts from high-TB burden settings. We developed and internally validated TRACE4, a four-gene blood-based host signature intended as a reflex test to identify culture-confirmed paucibacillary TB among symptomatic individuals with Xpert MTB/RIF Ultra very low or trace results. TRACE4 demonstrated greater discriminatory performance than previously published TB signatures evaluated in the same cohort and identified culture-positive individuals who remained undiagnosed at early clinical follow-up. We further investigated memory T-cell reprogramming following three months of weekly isoniazid and rifapentine (3HP) using longitudinal samples from the Correlate of Risk Targeted Intervention Study (CORTIS) trial. Single-cell RNA sequencing and multiparameter flow cytometry revealed sustained, lineage- and differentiation-dependent immunometabolic differences at month 12 (post treatment completion). Following 3HP, CD4<sup>+</sup> stem-like memory T cells exhibited TCA-cycle and fatty acid oxidation-associated responses and a significant early *Mycobacterium tuberculosis* (*Mtb*)-induced IL-2 response, whereas untreated participants showed greater glucose uptake, glycolytic response and exhaustion-associated transcriptional signatures. Furthermore, CD8<sup>+</sup> stem-like memory T cells exhibited greater early glycolytic response and broader engagement of glycolytic and oxidative programs during later recall in untreated participants. Across differentiated memory subsets, 3HP was associated with greater engagement of oxidative metabolic programs while maintaining *Mtb*-responsive cytokine production. Together, these findings provide complementary insights into the biology of low-burden *Mtb* infection, advancing blood-based host biomarker development for paucibacillary TB while defining sustained immunometabolic reprogramming following preventive therapy. These studies lay the groundwork for improved diagnosis and uncovering underlying mechanisms that support durable immunity after clearance of low-level infection.