

YOU ARE INVITED TO ATTEND THE
DEFENSE OF THE DOCTORAL
DISSERTATION

**“Prescient Drug Resistance:
Characterization and functional significance of
Mycobacterium tuberculosis resistance to modern TB drugs
in the absence of prior drug exposure”**

by
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Tuesday, July 27th, 2021
12:00 P.M.

<https://rutgers.zoom.us/j/94981792855?pwd=WUxjMDdSMIB2Sk12NXJHQit1bThTZz09>

Meeting number (access code): 949 8179 2855

Meeting password: graduate7@

ABSTRACT

More than 500,000 new cases of drug resistant Tuberculosis (TB) are diagnosed each year. Delayed treatment is significantly associated with TB mortality. A universal 'pan-TB' regimen consisting of multiple totally new drugs is a proposed solution that would simplify treatment, remove time extensive phenotypic testing, and thus improve clinical outcomes. Mycobacterium tuberculosis (Mtb) is traditionally thought to develop step-wise resistance following exposure to TB drugs. Our results challenge this paradigm. Using a population of archival Mtb strains, we identified resistance to modern TB drugs introduced into clinical use over a decade after strain isolation. We demonstrate pre-existing drug resistance independent of drug exposure, which we term prescience. Prescient Mtb demonstrate significant survival advantages across multiple TB drugs. Multi-prescient strains are characterized by increased survival, altered growth and differential response to efflux inhibition. Prescience was also linked to strain lineage, and therefore demonstrates a critical risk to future Pan-TB regimens. Our results contradict drug resistance stepwise evolution following exposure to drug, and directly challenge current drug development pipeline design. This work emphasizes the continual need for phenotypic testing in the age of modern genetics. Testing future therapeutics against a larger spectrum of drug resistant and drug sensitive pathogens will be critical to prevent selective expansion of prescient Mtb and to curb the evolution of total drug resistance.