PReDiCTR-TB Consortium JHU-mouse Laboratory:

Tuberculosis (TB) remains the world's deadliest infectious disease and still requires 4–6 months of combination chemotherapy to cure most patients. Although successive advances have shortened treatment, current therapies remain constrained by long duration, toxicity, drug–drug interactions, and the growing threat of resistance. At the same time, TB drug discovery has produced an unprecedented pipeline of new compounds. This creates a central challenge for the field: how to efficiently determine which drug combinations are most likely to succeed as shorter, safer, and more effective regimens. Mouse models are essential to meeting this challenge. Because TB treatment is prolonged and early clinical biomarkers do not reliably predict cure, preclinical mouse efficacy studies play a critical role in prioritizing regimens for clinical trials. Mice are tractable, cost-effective, and uniquely validated by decades of experience showing that major treatment-shortening advances were first predicted in mouse models. From the contributions of rifampin and pyrazinamide, to the benefits of rifapentine and moxifloxacin, to the development of BPaL and BPaLM, mouse efficacy studies have consistently anticipated clinical outcomes.

The JHU Mouse TB Laboratory, led by Dr. Eric Nuermberger, has more than 20 years of experience conducting mouse efficacy studies that directly informed landmark clinical regimens, including HPZM for drug-susceptible TB and BPaL/BPaLM for rifamycin-resistant TB. A major strength of the JHU lab is its combined expertise in two highly validated and complementary mouse models. The first is the refined **BALB/c Relapsing Mouse Model (RMM)**, optimized to predict treatment-shortening potential. The second is the **C3HeB/FeJ model**, which uniquely develops caseous necrotic lung lesions that mimic cavitary human TB. Across these models, the lab maintains extensive comparative datasets linking CFU decline, relapse, and regimen performance. **A) BALB/c Relapsing Mouse Model (RMM)**: Accurately predicted key clinical outcomes, including: (1) sterilizing roles of rifampin and pyrazinamide in HRZE, (2) the modest treatment-shortening effect of moxifloxacin seen in REMox-TB, (3) exposure-dependent benefits of high-dose rifamycins, and (4) regimen rank ordering that led to HPZM and BPa-based successes. Uses mixed-effects and simulation modeling to translate relapse data into quantitative clinical predictions while reducing animal use. **B) C3HeB/FeJ Caseating Lesion Model** Replicates hard-to-treat TB features such as high bacterial burden, caseous necrosis, and lesion heterogeneity. Reveals how drug penetration and activity differ across lesion compartments and better reflects outcomes in cavitary disease. Provided more accurate representation of moxifloxacin's limited impact, HPZM superiority over HPZE in high-risk patients, and rifampin–rifapentine differences driven by lesion distribution, guiding smarter regimen design. The lab integrates rigorous outcome measures within a pharmacometric framework that links early readouts to long-term outcomes. Standard measures include (1) lung CFU counts, (2) relapse ≥12 weeks post-treatment as the gold standard for sterilizing activity, and (3) the RS ratio as a rapid pharmacodynamic biomarker. These are used together to strengthen translational relevance and reduce reliance on lengthy relapse studies when possible.

Advanced PK/PD capabilities further distinguish the platform. The lab has established methods to quantify drug penetration into lung lesions and lesion sub-compartments using laser capture microdissection and integrates plasma and lesion pharmacokinetic data for both approved TB drugs and next-generation candidates. In parallel, the lab employs in vivo target-validation tools, including doxycycline-inducible depletion systems and CRISPRi approaches, in collaboration with omics and systems biology groups to test mechanistic hypotheses during combination therapy. Together, these capabilities make the JHU Mouse TB Laboratory one of the most clinically validated and translationally powerful preclinical TB regimen platforms in the world, uniquely positioned to prioritize drug combinations and targets with the highest likelihood of success in human TB trials.