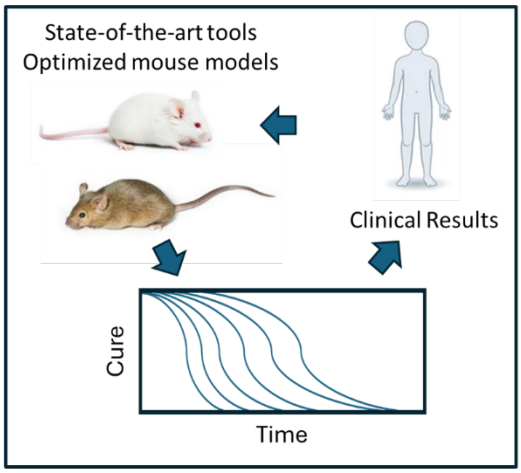
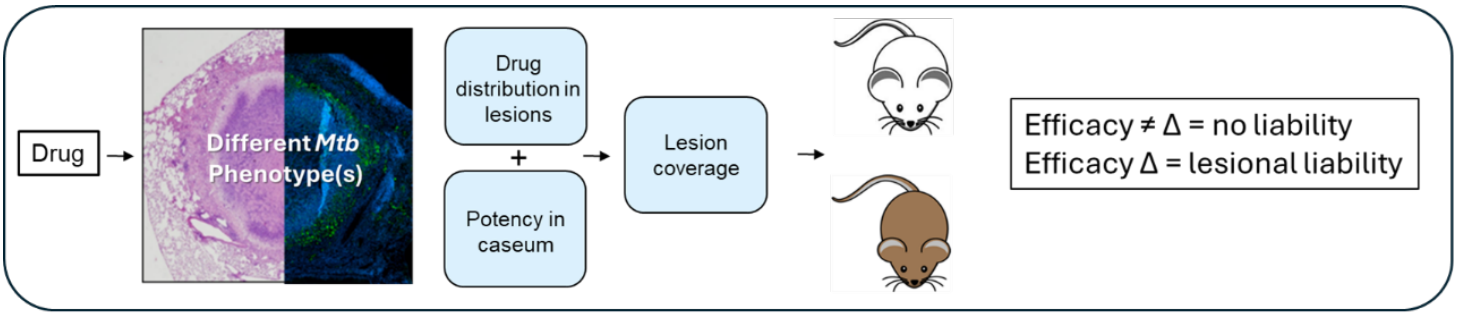
PReDiCTR-TB Consortium CSU Mouse Preclinical Laboratory

Murine models in TB antibiotic development. Since the pioneering work of Florey and Chain, mouse models have been central to antibiotic development, including tuberculosis (TB). Although several species are susceptible to *Mycobacterium tuberculosis* (Mtb), mice remain the most widely used model for TB drug and regimen development. Mouse models support all stages of the development pipeline, from early safety, tolerability, and mechanism-of-action studies to efficacy, pharmacokinetics (including lesion distribution), resistance risk, and late-stage regimen selection and optimization. Working as part of the **PReDiCTR-TB Consortium**, the **CSU Mouse Preclinical Laboratory** integrates state-of-the-art preclinical tools and deploys optimized mouse models to "back translate" human studies to mice, we then use these data to help make quantitative predictions to improve the likelihood of future regimen success for TB antibiotic development.



Optimized use of mouse models. Back-translate human studies to mice to improve and optimize models and understand limitations. Develop quantitative predictions of new regimen performance to improve clinical success.

Impact of granulomas on TB treatment. TB lesions in humans are heterogeneous and dynamic, varying in pathological, microbiological, and immunological features over time, often before clinical symptoms arise. As discrete, multifocal immunopathological units, granulomas form independent microenvironments within the lung, each capable of containing, eliminating, or failing to control *Mtb*. This heterogeneity creates diverse niches that shape bacterial replication, metabolism, population density, and intrinsic drug susceptibility while variable lesion architecture further influences antibiotic efficacy by producing lesion- and drug-specific pharmacokinetic effects. A loss of drug efficacy attributable to inadequate penetration and accumulation (PK) and/or due to limited activity against caseum phenotypes (PD) has been termed a "lesional liability" and is associated with poor clinical outcome. The **CSU Mouse Preclinical Laboratory** has capitalized on this knowledge to help de-risk **PReDiCTR-TB Consortium** new drug regimens for "lesional liabilities" by contrasting performance in two mouse models that develop markedly different forms of disease: the "easy-to-treat" BALB/c subacute TB infection model and the "hard-to-treat" C3HeB/FeJ chronic infection model of granulomatous disease.



Stepwise regimen evaluation pathway with a focus on lesional liability. Quantify potency against caseum-resident Mtb phenotypes with lesional PK to estimate steady state lesion coverage in caseating lesions. Assess lesional liability empirically *in vivo* via head-to-head comparison of the easy-to-treat BALB/c and hard-to-treat C3HeB/FeJ mouse models.