

## A closer look at the Omics Group

**Who we are:** We are a group of scientists with expertise in mycobacterial genetics, genomics, metabolomics, and chemical biology, led by Drs. Sabine Ehrt, Kyu Rhee, Jeremy Rock, and Dirk Schnappinger. Our team combines complementary strengths to perform mechanistic analyses of TB drug regimens and their constituents, leveraging cutting-edge chemical genomics and metabolomics platforms to understand how drugs work individually and in combination.

**Our goals:** We aim to define in vitro biomarkers and mechanistic principles that predict the efficacy of TB drug regimens. By analyzing both successful and less effective drug combinations, we seek to identify which bacterial pathways are engaged by individual drugs and how these pathways change in drug combinations. Our work focuses on enabling early preclinical in vitro evaluation of novel combination therapies to shorten treatment duration.

**Our approach:** We apply chemical genomics using CRISPR interference (CRISPRi) technology to identify genes that affect drug activity, revealing both targets and potential resistance mechanisms. In parallel, we use mass spectrometry-based metabolomics to measure intrabacterial drug levels and their effects on bacterial metabolism - a paradigm referred to as intrabacterial pharmacology. We perform back-translation of clinically tested regimens, such as those from Study 31/A5349, to understand if and how trial outcomes could have been predicted early in development. These learnings then inform forward predictions for novel regimens, creating a systematic framework to evaluate candidate drugs in combination.

**Our history:** Our collaborative team has a strong track record with over 60 co-authored publications and numerous innovations. These include the first genome-wide quantification of gene vulnerability in *Mycobacterium tuberculosis* (Mtb), development of the most widely used regulated expression systems for mycobacteria, and creation of the first metabolomics platform for Mtb. As founding members of the Gates Foundation-funded TB Drug Accelerator, we have profiled hundreds of hit and lead compounds, establishing validated methodologies that are now broadly utilized by pharmaceutical partners. Our innovations in CRISPR interference for high-throughput gene silencing in Mtb and activity-based metabolomic profiling have enabled several novel insights into drug mechanisms of action and bacterial physiology.