

Internship Proposal

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Project Title:

Defining antimicrobial killing modulators in *Mycobacterium tuberculosis*

Level:

Master Student

Project Summary:

Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide. Although the treatment leads to cure, it is lengthy and encompasses the daily intake of multiple antibiotics. This compromises patients' adherence to the treatment regimen, leading to avoidable deaths and setting the breeding ground for the emergence of drug resistant strains. The need for long and multi-drug treatment is, in part, driven by the extraordinary capacity of *Mycobacterium tuberculosis* (Mtb) to survive antibiotic treatment or delay bactericidal effect, a phenotype designated by drug tolerance. The genetic basis of drug tolerance is poorly understood, thus understanding how Mtb survive or delay antibiotic killing opens the possibility of accelerating bactericidal effects and shorten treatment regimens. In our laboratory, we are optimizing a systems biology approach to identify Mtb genetic determinants of antibiotic tolerance mechanisms – antibiotic killing modulators - through a multi-omics approach combined with CRISPR interference technology. In the future, we will develop inhibitors for validated antimicrobial killing modulators and test if these compounds can accelerate infection eradication.

Work to be developed by the student:

Aim: The main goal of this MSc project is to identify Mtb antibiotic killing modulators for the anti-TB drug bedaquiline.

Main methodology: The project encompasses training in biosafety laboratory level-3, general microbiology and molecular biology techniques, bacterial genetic manipulation, and multi-omics (transcriptomics, proteomics and metabolomics) analysis.

References:

- Xu Y, Ehrh S, Schnappinger D, Beites T (2023) Synthetic lethality of Mycobacterium tuberculosis NADH dehydrogenases is due to impaired NADH oxidation. mBio <https://journals.asm.org/doi/10.1128/mbio.01045-23>



- Wong AI, Beites T, Planck KA, Li S, Poulton NC, Rhee K, Schnappinger D, Ehrh S, Rock JM. (2023) Cyclic-AMP is a critical mediator of intrinsic drug resistance and fatty acid metabolism in Mycobacterium tuberculosis. eLife <https://elifesciences.org/articles/81177>

- Schrader SM, Botella H, Vaubourgeix J (2023) Reframing antimicrobial resistance as a continuous spectrum of manifestations. Curr Opin Microbiol <https://doi.org/10.1016/j.mib.2022.102259>