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# Molecular analysis of *Mycobacterium tuberculosis* intracellular growth – from disease progression to drug development

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**Statement of the Problem:** *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis (TB) infects, survives, and replicates in the phagosomes of host alveolar macrophages. Mtb interacts with macrophage proteins to subvert the host antimicrobial mechanisms and thus evade the immune response. For instance, our lab has shown that PtpA, a tyrosine phosphatase secreted by Mtb, is able to block phagosome acidification, phagosome-lysosome fusion, and apoptosis in the macrophage by interfering with the host proteins V-ATPase, VPS33B, and GSK3α. Furthermore, while hiding within the phagosome, Mtb is isolated from many antibiotics used for treatment of infection, thus creating a challenge for anti-TB drug discovery. Therefore, novel approaches that consider the intracellular nature of Mtb and its interactions with the host are a promising new avenue for drug discovery.

**Methodology:** Given PtpA's key role during infection, we targeted PtpA-mediated growth of Mtb in host macrophages as an approach for novel drug development. First, we used a protein fragment complementation assay to analyze the interaction of PtpA with selected host targets, including the protein GSK3β, which control key cellular antimicrobial processes. Then, we took a host directed therapeutic approach, and targeted GSK3β in Mtb-infected macrophages to determine whether the disruption of the host protein restricts the growth of Mtb. To achieve this, we used an intracellular high-throughput screening (HTS) to test GSK3β inhibitor compounds for their ability to kill Mtb in the macrophage.

**Findings & Conclusions:** We discovered a new interaction in-vivo between PtpA and the host protein GSK3β, suggesting that PtpA modulates this protein during macrophage infection to promote Mtb's survival. Additionally, the HTS allowed us to identify new compounds that specifically target the host and can kill intracellular Mtb.

**Significance:** Our data highlights the importance of the macrophage for the growth and infectivity of Mtb and holds a promising strategy for the identification of potential anti-TB drugs with a new mechanism of action.

## Biography

Sandra Peña-Díaz is a PhD Candidate of Av-Gay lab at the University of British Columbia. She studies host-pathogen interactions during *M. tuberculosis* infection of the human macrophage, and performs high-throughput screenings of compounds for anti-TB drug discovery.

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