QCB Evenings

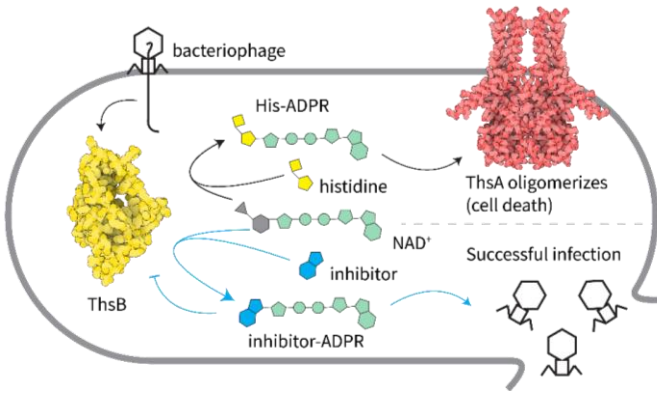
Friday, October 11th • 5:00 – 6:00 PM • SI001

Unveiling the Regulatory Mechanism of IreB in Peptidoglycan Synthesis in *Streptococcus pneumoniae* | Dr. Merrin Joseph, Winkler Lab

Peptidoglycan (PG) synthesis is essential for bacterial cell wall integrity, protecting against osmotic stress and serving as a structural scaffold. In Gram-positive pathogens like Streptococcus pneumoniae, PG synthesis is tightly controlled by complex regulatory networks involving protein-protein interactions and post-translational modifications. This study focuses on the regulation of MurZ enzymatic activity, a key enzyme in the first committed step of PG synthesis, through its interactions with the IreB protein. Previous research revealed that protein phosphorylation by Ser/Thr protein kinase StkP and the GpsB regulatory protein are critical for PG precursor synthesis. We also showed that genetic mutations in IreB can suppress the essentiality of *gpsB*. Here, we investigate the role of IreB phosphorylation, particularly the unphosphorylated form, in regulating MurZ activity. Our findings show that StkP phosphorylates IreB at a single Thr residue in ≈90% of WT cells. Through co-immunoprecipitation and bacterial two-hybrid assays, we show that unphosphorylated IreB interacts with MurZ and MurA, inhibiting their enzymatic functions and blocking the downstream synthesis of the lipid II precursor. Phosphomimetic changes in IreB prevent this interaction, restoring cell viability, while phosphoablative changes lead to lethality in a Δ*gpsB* background. Enzyme assays further confirm that IreB directly inhibits MurZ activity in vitro. These findings highlight the critical balance of IreB phosphorylation in regulating MurZ and MurA and offer new insights into the complex regulatory mechanisms underlying PG synthesis in *S. pneumoniae*.

Chemical inhibition of a bacterial immune system promotes bactericidal effects of bacteriophages | Zhiyu Zang, Gerdt Lab

The rise of antibiotic resistance motivates a revived interest in phage therapy. However, bacteria possess dozens of anti-bacteriophage immune systems that can preclude the success of phage-based interventions. Chemical inhibitors of these anti-phage immune systems could be useful as therapeutic adjuvants in phage therapy. Here, we report that anti-phage systems can be selectively inhibited by small molecules. We discovered a class of chemical inhibitors that inhibit the type II Thoeris anti-phage immune system. These inhibitors function by blocking the biosynthesis of a histidine-ADPR intracellular 'alarm' signal by ThsB, thereby preventing the activation of ThsA from arresting phage replication. We found that these inhibitors can promiscuously inhibit type II Thoeris systems from three diverse bacteria, including *Bacillus subtilis* and the opportunistic human pathogens *Pseudomonas aeruginosa* and *Enterococcus faecalis*. Since these inhibitors sensitize phage-resistant pathogens to phage lysis, they have potential as adjuvants in phage therapy. Furthermore, these inhibitors may be employed as chemical tools to dissect the importance of the Thoeris defense system in shaping microbial communities.



Free pizza and drinks! **All students and postdocs are welcome!**