BCHM421/422 - Jia Lab Project #1

Project Outline: *Pseudomonas aeruginosa* is an opportunistic Gram-negative bacterium known for its severe pathogenicity, particularly in immune-compromised patients and those with cystic fibrosis. The increasing incidence of multidrug-resistant *P. aeruginosa* infections has led the World Health Organization to deem this bacterium a Priority 1 pathogen that is in urgent need of new antibiotics. It has been documented that the polyphosphate kinase (PPK) family of enzymes is essential for *P. aeruginosa* virulence in a mouse model of infection, and *ppk* gene knockout strains feature multiple functional defects. PPKs have thus been lauded as attractive therapeutic targets. In collaboration with the pharmaceutical industry, the Jia lab recently discovered a family of small molecules that inhibit PPK *in vitro* with low-micromolar affinity and attenuate *P. aeruginosa* virulence phenotypes *in vivo*. To improve our PPK inhibitors, this project will use a combination of X-ray crystallography, inhibition kinetic studies, and analogue compound synthesis. These techniques will inform the development of a structure-activity relationship (SAR) to guide the rational modification of our lead compounds to optimize potency and specificity for PPK enzymes. This work will pave the way towards a much-needed novel class of antimicrobial drugs to treat resistant *P. aeruginosa* infections.

Supervisor: Zongchao Jia

Project Title: Structure-guided inhibition of polyphosphate kinases in *P. aeruginosa* as a novel antivirulence approach

Project Goals: This project aims to design new antimicrobial drugs via structure-guided chemical synthesis. These drug candidates will then be validated for activity against *P. aeruginosa*.

Experimental Approaches: X-ray crystallography, *in vitro* inhibition and kinetic studies, *P. aeruginosa* virulence phenotype assays (e.g. biofilm, pyoverdine, motility), *Caenorhabditis elegans* infection modelling.

References:

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