BCHM 421/422 – 2020/2021

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 enzyme polyphosphate kinases (PPK) are 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 an attractive therapeutic target. In collaboration with 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* biofilm formation *in vivo*. This project will use a combination of X-ray crystallography, inhibition and kinetic studies, and analogue compound synthesis. This 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. This work will pave the way towards a much-needed novel class of antimicrobials to treat multidrug-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 determine structures of PPKs in complex with our lead compounds. In parallel, screening of small molecules will be carried out in order to find inhibitory compounds with high potency and selectivity.

Experimental Approaches: X-ray crystallography, in vitro and in vivo inhibition and kinetic studies.

References:

Gellatly, S. L., and Hancock, R. E. W. (2013) *Pseudomonas aeruginosa*: new insights into pathogenesis and host defenses. *Pathog. Dis.* **67**, 159-173.

Rashid, M. H., Rumbaugh, K., Passador, L., Davies, D. G., Hamood, A. N., Iglewski, B. H., and Kornberg, A. (2000) Polyphosphate kinase is essential for biofilm development, quorum sensing, and virulence of Pseudomonas aeruginosa. *PNAS*. **97**, 9636-9641.