BCHM 421/422 – 2019/2020

Project Outline: Multi-drug resistant bacteria continue to be encountered in the modern medical landscape. Their increasing prevalence poses a significant threat to human health. In several pathogens, virulence responses seem to implicate the biosynthesis of inorganic polyphosphate polymers (poly P). Interestingly, the enzyme responsible for poly P synthesis, polyphosphate kinase 1 (PPK1), is found highly conserved in many bacteria including but not limited to *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Helicobacter pylori*, and *Salmonella typhimurium*. Mutant strains unable to synthesize poly P are deficient in mobility, quorum sensing, toxin secretion, biofilm formation, antibiotic resistant-persistence, and stress induced survival. This research is concerned with examining the *in vivo* relevance of poly P biosynthesis with respect to virulence. As the first crucial step, we have already identified lead compounds capable of inhibiting PPK1 and stalling poly P accumulation in *P. aeruginosa*. In order to further characterize our inhibitory compounds, we plan to assess their potential effects on other kinases from both bacterial and mammalian systems. Furthermore, we will attempt to characterize the ability of our compounds to inhibit poly P biosynthesis in other pathogenic bacteria. With antibiotics having remained largely unchanged for decades, bacterial anti-virulence through inhibition of poly P biosynthesis highlights a promising new approach for developing anti-virulence drugs.

Supervisor: Zongchao Jia

Project Title: Polyphosphate biosynthesis as a virulence factor determinant in multi-drug resistant bacterial pathogens.

Project Goals: This project aims to investigate potential effects of our PPK1 inhibitors on other kinases from bacterial and mammalian systems. In addition to *P. aeruginosa*, we will characterize the ability of our compounds to inhibit poly P biosynthesis in other pathogenic bacteria for the treatment of infections caused by multi-drug resistant pathogens.

Experimental Approaches: Cloning, protein expression and purification, various assays including enzyme inhibition, mobility, quorum sensing, toxin secretion, biofilm formation, antibiotic resistant-persistence, and stress induced survival.

References:

WHO list of bacteria for which new antibiotics are urgently needed *World Health Organization*. http://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

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