

## BCHM 421/422 – 2020/2021

**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 kinases (PPK), is found highly conserved in many bacteria such as *A. baumannii* and *K. pneumoniae*. 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 PPKs and stalling poly P accumulation in bacterial cells. In order to further characterize our inhibitory compounds, we plan to assess their inhibitory effects on PPKs from a variety of bacteria, including some of the most pathogenic strains. 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 inhibitory effects of our PPK inhibitors on PPKs from various bacterial strains. We will characterize the ability of our compounds to inhibit poly P biosynthesis and also characterize the bacterial strains using gene knockout approaches.

**Experimental Approaches:** Cloning, protein expression and purification, various assays including enzyme inhibition, mobility, quorum sensing, toxin secretion, biofilm formation, antibiotic resistant-persistence, gene knockout 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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