BCHM 421/422 – 2018/2019

Project #2 Outline: *Pseudomonas aeruginosa* is a Gram-negative pathogen that causes infectious disease and inflammation in humans. With the increasing incidence of antibiotic-resistant *P. aeruginosa* infections, the World Health Organization has recently deemed this bacterium a Priority 1 pathogen that is in urgent need of new antibiotics. Based on the structure of several complexes in Type 2 secretion system, we have shown that the structure-based peptides disruptin protein interaction, as well as small molecules (T2SS), have inhibitory effects on the bacterium. More importantly, the peptides also attenuated *P. aeruginosa* infection in an animal model using *Caenorhabditis elegans*. We will further characterize the function and structure of various components in T2SS, either individually and in complex forms. Meanwhile, using our established assays we will screen small molecules to find lead compounds for potential antibiotics development.

Supervisor: Zongchao Jia

Project Title: Structure-based disruption of Type 2 secretion system of *Pseudomonas aeruginosa* for development of antibiotics

Keywords (3-5):

1. **Pathogen**
2. **Antibiotics**
3. **Protein crystallography**
4. **Peptide design**
5. **Small molecule screening**

Project Goals: This project aims to determine structures of several other complexes, including those with protein toxins which are secreted by T2SS. In parallel, screening of small molecules will be carried out in order to find inhibitory compounds.

Experimental Approaches: Cloning, protein expression and purification, crystallization, computer docking, fluorescence assay, cell growth assay.

References:

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

Korotkov, K. V., Sandkvist, M., and Hol, W. G. J. (2012) The type II secretion system: biogenesis, molecular architecture and mechanism. *Nat. Rev. Microbiol.* 10.1038/nrmicro2762