SJSU | DEPARTMENT OF CHEMISTRY

CHEMISTRY Departmental Seminar

Spring 2022
CHEM 285/191 Schedule
Tuesday at 4:30-5:45PM
Duncan Hall 250
March 22nd, 2022

Ms. Lucero Sandoval
San José State University (Miller Conrad Lab)

Targeting Pseudomonas aeruginosa*: Exploration of an antipyocyanin compound and Characterization of the C-terminal domain of* Pseudomonas aeruginosa *ArnA*

Pseudomonas aeruginosa, a gram-negative opportunistic pathogen, is classified as a critical priority by The World Health Organization for its threat to human health, and antibiotic-resistant strains are increasingly encountered.[1,2] Therefore, there is an urgent need for the development of new therapies to combat multidrug-resistant infections of the pathogen.

One way to develop new treatment strategies is to target virulence. *P. aeruginosa* contains a complex phenazine biosynthetic pathway consisting of *phz*A1-G1 and *phz*A2-G2, which are responsible for the synthesis of phenazine-1-carboxylic acid (PCA). PCA is then converted to pyocyanin, an important virulence factor, by PhzM and PhzS.[3] To understand the molecular target of an antipyocyanin compound, our lab assessed whether it could inhibit one of the biosynthetic enzymes required to synthesize PCA. In addition, we developed a photoaffinity analog of the antipyocyanin compound to cast a wider net to identify the molecular target.

The top hit from the photoaffinity studies was ArnA, an enzyme involved in resistance to cationic antimicrobial peptides (CAPs), not phenazine regulation. CAPs like colistin are unable to treat infections with resistant strains of *P. aeruginosa* due to the upregulation the *arnBCADTEF* pathway, which modifies lipid A in the outer membrane.4 The lipid A modification reduces the net negative charge of the outer membrane, removing the favorable electrostatic interactions with the positively charged CAPs, preventing the disruption of the outer membrane and subsequent cell death by the antibiotics. To enable treatment of colistin-resistant strains, we hypothesized that inhibition of the C-terminal domain of ArnA, the first committed step encoded by the *arnBCADTEF* pathway, will prevent outer membrane modification and render the bacteria susceptible to CAPs like colistin in a combination therapy. While the ultimate goal is to develop inhibitors of the enzyme, it is crucial to first characterize the kinetics of the enzyme, which we tracked by NADH formation at 340 nm.[5] Both projects have contributed to our goal to develop new treatment strategies for *P. aeruginosa*.

1. WHO (2017) Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics, World Health Organization, Geneva.
2. Lee, J.; Park, K. Y.; Chung, S. E.; Na Y. I.; Ko, S. K. *Sci. Rep.* **2016,** *6,* 25543-25555.
3. Zhang Z.; Ortega D.; Rush A., Blankenship L. R.; Cheng Z. J.; Moore R. E.; Tran M. L. N.; Sandoval L. G.; Aboulhosn K.; Watanabe S.; Cortez K. S.; Perlman D. H.; Semmelhack M. F.; Miller Conrad L. C. *ACS Infectious Diseases*, **2021**, 7, 535–543.
4. Kline, T.; Trent, M. S.; Stead, C. M.; Lee, M. S.; Sousa, M. C.; Felise, H. B.; Nguyen, H. V.; Miller, S. I. *Bioorg. Med. Chem. Lett*. **2007**, *18*, 1507-1520.
5. Williams, G. J.; Breazeale, S. D.; Raetz, C. R.; Naismith, J. H. *J. Biol. Chem*. **2005**, *280*, 23000-23008.

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