

Seminar

4 p.m. Friday, March 29, 2013 • 331 Smith Hall



Assistant Professor
Erin Carlson
Department of Chemistry
Indiana University

Chemical Strategies to Promote Discovery of Antibacterial Agents

Research interests: development and application of advanced chemical biology and systems biology technologies to both define the mechanisms of bacterial pathogenesis and identify potential therapeutic agents.
Website: <http://carlson.chem.indiana.edu/>

Abstract

Given the dearth of new antibacterial drugs and the facile evolution of microbial resistance, some fear that we have entered the post-antibiotic era. Our research focuses on both the development and application of new technologies to explore the mechanisms of bacterial growth and pathogenesis and the identification of potential therapeutic agents. We are particularly interested in generating tools for the study of two-component signal transduction systems (TCSs), which are commonly used by bacteria to couple environmental stimuli to adaptive responses through gene regulation. They contribute to many critical bacterial functions, including virulence, resistance mechanisms, and survival, making the TCS proteins potential drug targets. TCSs are composed of two proteins, a histidine kinase (HK) and a response regulator. The prototypical HK has an extracellular sensory domain and a catalytic and ATPase domain, which binds to ATP and transfers the γ -phosphate to a conserved histidine, initiating the signaling cascade. HK activity has been historically difficult to study because this phosphorylated intermediate is extremely fleeting, making detection problematic. We are working to design novel strategies to read-out histidine kinase activity and identify potential inhibitors of histidine kinase function and two-component signaling in bacteria. Progress toward these goals will be discussed.

Despite the urgent need for the development of antibiotics, only three new classes of drugs have been introduced in the last four decades. To facilitate the discovery of antibacterial agents, such as TCS inhibitors, we are also devising new strategies for natural products isolation. Despite recent advances, the identification of novel natural products remains challenging as the use of traditional isolation methods often results in rediscovery of known compounds and/or the loss of bioactivity. Current enrichment strategies employed in natural products discovery still rely on relatively crude extraction and/or chromatographic separation techniques. To produce an enrichment strategy that provides a significant improvement over these techniques, a method that employs enrichment principles that are independent of the physicochemical properties of the compounds must be devised. We are creating a toolkit of functional group-specific tags to facilitate compound isolation and advance the exploration of natural product chemical space. To accomplish this goal, we employ controllably reversible reactions to immobilize the targeted functional group class onto solid support. Enriched natural products are then released using "traceless" conditions for direct characterization. Development and application of tagging strategies that facilitate the chemoselective enrichment of hydroxyl-, phenol-, and carboxylic acid-containing natural products will be discussed. Together, the described studies will lead to a more comprehensive understanding of bacterial pathogenesis and may provide novel therapeutic targets and lead structures.

Host: William Tolman Refreshments will be served prior to the seminar.