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Knottins are biologically-active small peptides isolated from animal venoms. They are an increasingly important class of natural products due to their structural diversity and broad-reaching drug targeting potential. They are small disulfide-rich peptides characterized by a "disulfide through disulfide knot", which is achieved when one disulfide bridge crosses the macrocycle formed by the two other disulfides and the interconnecting backbone. Owing to this distinct structural feature, knottin peptides display reduced metabolic liability, which makes them an attractive scaffold for drug design. The pharmacological characterization of knottins has demonstrated their ability to modulate a great diversity of targets, including targets in the central nervous system. However, one of the biggest challenges in obtaining knottins is their significantly challenging chemical synthesis.

Thus, we wish to develop a general bio-synthetic route for knottin biosynthesis. To achieve this goal, we will take advantage of synthetic biology tools and approaches to explore and generate a universal enzyme-catalyzed disulfide linkage strategy. More specifically, we will genetically engineer bacterial strains by designing and building de novo enzymatic pathways to promote disulfide bridge formation. We will also use customized cell-free expression systems with enhanced disulfide bridge formation ability, which allows for a rapid high-throughput expression and detection of disulfide bridged. Beyond this, our lab works as part of a cross-functional team with diverse backgrounds to identify structural requirements necessary to produce cell/brain permeable knottins with good pharmacokinetic properties and bioavailability.

Selected Publications

Chemical tailoring of teicoplanin with site-selective reactions.
Pathak TP, Miller SJ.

J Am Chem Soc. 2013 Jun 5;135(22):8415-22.

Palladium(II)-catalyzed enantio- and diastereoselective synthesis of pyrrolidine derivatives.
Jana R, Pathak TP, Jensen KH, Sigman MS.
Org Lett. 2012 Aug 17;14(16):4074-7.

Site-selective bromination of vancomycin.
Pathak TP, Miller SJ.
J Am Chem Soc. 2012 Apr 11;134(14):6120-3.

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