BIOCHEMISTRY SEMINAR

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"From Peanuts to Peptide Cyclization"

Abstract : Macrocyclic peptides are an increasingly used scaffold in drug discovery. Peptide cyclization often increases resistance to proteolysis compared to linear peptides, leading to longer half-life in the body, and improves the likelihood of binding to a specific biological target. Cyclic peptides can be generated in bacteria, fungi, and plants as Ribosomally synthesized and Post-translationally modified Peptides (RiPPs). RiPPs that form macrocycles through unactivated C(sp3) or C(sp2) positions during late-stage bond-forming steps are often challenging to synthesize using conventional methods. By studying the enzyme mechanisms of proteins that catalyze peptide macrocyclization, we expand the range of cyclic peptides available for drug discovery and can engineer these proteins to make new-to-nature compounds. The recent discovery of plant copper-dependent proteins, BURP domain proteins, are a new source of bioactive cyclic peptides, yet their enzyme mechanism and protein structures are largely unexplored.

BURP domain proteins are named after their four founding members (BNM2, USP, RD22, PG1Beta) and form C-C, C-N, and C-O crosslinks between the aromatic side chains of tyrosine and tryptophan and unactivated amino acid carbons in the presence of O2 and copper. Often, the substrate peptide is within the same polypeptide chain as the catalytic BURP domain protein. We present the first experimentally determined structure of a BURP domain protein from the peanut plant, AhyBURP. AhyBURP contains a new protein fold and copper site compared to other known metalloproteins based on X-ray crystallography. Functional studies illustrate how AhyBURP cyclizes a linear 8 amino acid substrate within the BURP domain to both a monocyclic and bicyclic peptide in a sequential mechanism. We also provide evidence that the peptide cyclization occurs by an intramolecular reaction, contrary to the dogma of intermolecular RiPP biosynthesis. Our study is the starting point for investigating the mechanism of BURP domain proteins and intramolecular reactions in RiPP natural product biosynthesis.

BURP domain proteins are one of the main projects in the Mydy lab, where we also study other plant metalloenzymes, their role in unique bond formations, and exploring applications of their natural products.

Bio: Lisa Mydy is from Milwaukee, Wisconsin, and initially had no interest in the sciences when she enrolled in college at University of Wisconsin-Milwaukee. Nonetheless, she quickly found her passion for Chemistry, and graduated with a Bachelor's degree. Undergraduate research motivated her to go to graduate school, also at the University of Wisconsin-Milwaukee in the Department of Chemistry and Biochemistry, studying the protein structure and function of bacterial natural products for her Ph.D. in Nick Silvaggi's lab. Afterwards, she joined Andy Gulick's lab at the University at Buffalo-SUNY for her first postdoc, diving into protein structure and enzyme kinetics of proteins in bacterial pathogens. Lisa then worked in the pharmaceutical industry as a Senior Scientist at Abbott Laboratories, in research and development in the Diagnostic and Diabetes Care Divisions. During this time, she realized she wanted to be a professor. Lisa then joined Roland Kersten's lab at the University of Michigan, co-mentored with Janet Smith in structural biology, for a second postdoc. Here, she used her passion for X-ray crystallography and enzyme kinetics with bioinformatics and mass spectrometry to pioneer the structure and function studies of a conserved plant-specific protein, that she will talk about today.

During her time at Michigan, she earned the NIH F32 NRSA Fellowship and won the 2022 Journal of Biological Chemistry Poster Award at the Enzyme Mechanisms Conference. Lisa is also passionate about communicating her research and science to broader audiences. While at Michigan, she also initiated a weekly STEM course and taught with a small group of postdocs for discussion-led classes at a correctional facility. Lisa is now in the Department of Biochemistry at Purdue, beginning in August 2025, and her lab is quickly growing to study plant protein structure, function, and their roles in natural product biosynthesis.