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**3rd year Medicinal Chemistry Student Seminar**

**Title:** Plant Transcriptome Mining of Macrocyclic Peptides for *In Silico* Drug Discovery

**Abstract:**

The discovery of bioactive plant natural products by lab-based approaches is challenging and laborious due to plant chemical complexity and rediscovery. Therefore, an effective strategy that enables *in silico* prediction of new structures and their bioactivity is needed. Given increasing plant genetic data and structural biology models of drug targets, this project aims to develop a computational pipeline that identifies bioactive compounds from plants by (a) prediction of biosynthetically feasible molecules from plant genes in diverse genetic databases and (b) generation and evaluation of an *in silico* library of predicted plant natural products in targeting proteins relevant to human diseases. Ribosomally-synthesized and post-translationally modified peptides (RiPPs) are synthesized as precursor peptides encoded by a structural gene containing a core peptide region that is modified and released as the mature peptide. The target compound class for this project are burpitides, side-chain-macrocyclic plant RiPPs derived from BURP-domain peptide cyclases, which enables (a) chemical structure prediction from precursor gene sequences and (b) *in silico* macrocyclic sampling and screening due to medicinal chemistry profiles bordering Lipinski’s rule of 5. As a proof-of-concept experiment, BURP-domain peptide cyclase genes encoding cyclic peptide motifs were queried from transcriptomes of >2400 plant species, and 3D structures of corresponding burpitide macrocycles were predicted, curated into a library, and screened against lipoprotein signal peptidase II (LspA), a cyclic peptide antimicrobial target in Methicillin-resistant *S. aureus* (MRSA), via molecular docking. Cyclic peptides with promising *in silico* interactions with LspA are produced via transient gene expression in tobacco and will be tested for *in vitro* bioactivity. This work expands known plant peptide chemistry and its application in rational drug design.

Zoom Link: <https://umich.zoom.us/j/91557753414>

Meeting ID: 915 5775 3414

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