PURDUE UNIVERSITY | Department of Chemistry

Special Analytical Seminar

Monday, November 15, 2021

9:30 – 10:30 am

BRWN 4102

"Chemical and Analytical Approaches for Understanding and Combating Human Disease"

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Abstract:

Antimicrobial resistance is on the rise at the same time the development of new antibiotics slows. This threat is particularly acute for Gram-negative bacterial infections as they are intrinsically resistant to most antibiotics due to the low permeability of their cellular envelope. In order to discover drug design principles that would enable penetrance, the accumulation of a diverse collection of molecules was measured in *E. coli* with a tag-free mass spectrometry-based assay. Cheminformatic analysis of high-accumulators revealed that the presence of an ionizable nitrogen, low flexibility, and low three-dimensionality all favor accumulation. Applying these eNTRy rules, we successfully transformed several Gram-positive-only agents into broad-spectrum antibiotics.

Signaling pathways have evolved to adapt to a wide array of input signals and respond with complex gene transcription programs. This complexity is mediated by combinations of post-translation modification of proteins within the pathway. Using targeted top-down proteomics, proteoforms within the MAPK and p53 pathways were directly measured. For particularly low-abundance and complex species, individual ion mass spectrometry greatly improves sensitivity and depth of coverage. This platform for targeted individual ion MS serves as an excellent launching point for studying proteins that are regulated by modification permutations.