“Drugging ‘Undruggable’ Targets with Macrocyclic Peptides “

ORGANIC SEMINAR

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Friday, September 22nd,

9:00am

Hutchison Hall 473

University of Rochester

Department of Chemistry

Abstract

The majority (~80%) of disease-relevant human proteins, including most of those involved in intracellular protein-protein interactions (PPIs), are undruggable by the current drug modalities, namely small molecules (MW<500) and biologics (MW>5000). I will discuss our efforts on developing molecules in the "middle space" (MW 500-2000; e.g., macrocyclic peptides) to target intracellular proteins. We first developed a combinatorial library technology to discover macrocyclic peptidyl ligands that bind to a protein target of interest with antibody-like affinity and specificity. We next discovered a family of small, amphipathic cyclic peptides as a novel class of exceptionally active cell-penetrating peptides and elucidated their mechanism of action. Finally, by integrating the two platform technologies, we have designed potent, selective, cell-permeable, and metabolically stable macrocyclic peptidyl inhibitors against a wide variety of intracellular enzymes (e.g., Pin1 and PTP1B) and PPIs (e.g., calcineurin-NFAT, CFTR-associated ligand-CFTR, Ras-Raf, and NEMO-IKK interactions).

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