SJSU | DEPARTMENT OF CHEMISTRY

CHEMISTRY Departmental Seminar

Spring 2022
CHEM 285/191 Schedule
Tuesdays at 4:30-5:45PM

January 27th, 2022

Dr. Arunika Ekanayake
University of Alberta

Creating Millions of Drug Leads in a Small Tube: Genetically Encoded Fragment-based Discovery (GE-FBD)

Genetically encoded fragment-based discovery (GE-FBD) is a promising approach for selection of ligands and drug leads from existing GE libraries displayed on phage, DNA, or mRNA. GE-FBD starts with a fragment that interacts with a known site of the target protein but often with low potency and specificity. Covalent incorporation of unnatural fragments or 'pharmacophores' into conventional peptide libraries expands the chemical space and facilitates the discovery of molecules with favorable properties not offered by the fragments alone. This strategy can be applied to both linear and cyclic peptide libraries, using pharmacophores that have covalent as well as non-covalent reactivities towards target proteins. Since cyclic peptides alleviate several caveats presented by linear peptides, macrocyclization strategies that enable the installation of pharmacophores or other chemical moieties are highly desirable. Traditionally, the generation of GE-FBD libraries employs "early-stage" incorporation of unnatural building blocks into the chemically or translationally produced macrocycles. This talk will describe a divergent late-stage modification approach to such libraries starting from readily available starting material: genetically encoded phage-displayed libraries of peptides. Converting these phage-displayed peptides to 1,3-diketone bearing macrocycles provides a shelf-stable precursor for further functionalization with hydrazine through a well-established Knorr-pyrazole synthesis reaction. Ligation of diverse hydrazine derivatives onto diketone macrocyclic peptide libraries displayed on a phage that carries silent DNA barcodes enables genetic encoding of these post-translational chemical modifications. These libraries can be applied against "undruggable" protein targets to discover ligands with improved affinity and specificity.

Zoom link: https://sjsu.zoom.us/j/84626719622

Please RSVP at https://forms.gle/QuLDzNBJcKNJXjwK6 if you're not enrolled in Chem 285 or Chem 191

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