Special Seminar in Chemical Biology and Bioorganic Chemistry

Changing the Drug Discovery Perspective

Tuesday, Februart 14th – 12:20 PM
Room: Chapman 125

Dr. Eli Chapman
Assistant Professor
College of Pharmacy

The University of Arizona

The number of new molecular entities submitted to the FDA for approval is down from its peak, but the amount of money needed for a drug to reach the clinic is on the rise. Two predominant strategies are generally employed in drug discovery. In natural products chemistry, a molecule-centric perspective, an extract from an organism is added to cells and a cellular response is measured. The extract is then fractionated and the active principle isolated. Many years can then be spent to understand how the molecule exerts its biological effect. We illustrated the challenges of this strategy through elucidation of the mode of action of ritterostatin. In large-scale screening campaigns, an assay-centric perspective, compound libraries are screened using biochemical or cellular assays and robotic equipment. Once hits obtain, they are analyzed and optimized through medicinal chemistry campaigns. We have employed this strategy to uncover potential antibiotics targeting the chaperonin, GroEL. However, in an effort to change this perspective, our laboratory has embarked on evaluating a target-centric perspective to drug discovery that operates through a simple resin-based strategy, called functional chromatography, that enriches for potential lead molecules based on binding interactions with a protein of interest. We have used this procedure to isolate p97 modulators and more recently compounds that bind selectively to the KRAS oncogenic variant, G12D. Finally, we have used collections of highly conserved isoforms of proteins to run parallel biochemical screens to discover isoform-selective inhibitors. This is illustrated with two cases, the protein tyrosine phosphatase, PTP1B, and the DEAD box RNA helicase, eIF4A.