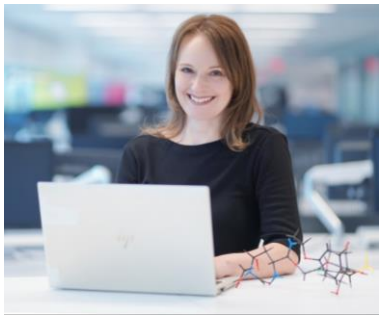

2024-2025 POCC Lecture Series

Nov 21, 2024, 7:30 PM

Dr. Beth Knapp-Reed

GSK

The Messy Business of Lead Discovery: Chemistry's Role & Challenges in Early Discovery

IN PERSON @:

Carolyn Hoff Lynch Lecture Hall Chemistry Building,
University of Pennsylvania
6:30 Reception in the Nobel Hall
Food and drinks to be provided!

The Philadelphia Organic Chemist's Club

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Abstract: SMYD3 target (in)validation from a medicinal chemistry perspective: Smyd3 is a SET-domain containing lysine methyltransferase that methylates both histone and non-histone proteins. Smyd3 methylation at MEKK2 lysine 260 (K260) has been reported to disrupt the interaction of MEKK2 with the inhibitory PP2A phosphatase, resulting in elevated phospho-ERK1/2 and phospho-ERK5. Additionally, Smyd3 is overexpressed in several tumor cell lines including colorectal carcinoma, breast cancer cells, and hepatocellular carcinoma. Lowering Smyd3 expression through treatment with small interfering RNA duplexes results in significantly suppressed growth in several cancer cell lines, suggesting that Smyd3 plays an important role in tumor proliferation. A three-pronged screening approach which included an HTS campaign, ELT screen, and a fragment screen, followed by lead optimization delivered multiple chemical series for key target validation studies. Several compounds exhibited excellent potency in the biochemical and cellular assays and demonstrated target engagement, however, failed to show anti-proliferative activity or changes in downstream pERK signaling.

Fragment-Based Approach Toward Lactate Dehydrogenase A (LDHA) Inhibitors: A fragment based approach was used to identify a unique series of LDHA inhibitors with good ligand efficiencies. Subsequent optimization delivered a novel lead series with LDHA cellular activity of 10 μM, selectivity against LDHB, and good physicochemical properties. The overall strategy of identification and optimization, lessons learned, and some guiding principles of the FBDD effort will be presented in the context of the discovery of a fragment-derived lead series for the inhibition of LDHA.

Bio: Beth Knapp-Reed has 18 years of experience in the pharmaceutical industry at GSK where she has coupled expertise in medicinal chemistry and matrix leadership with a passion for people development to deliver value to the GSK pipeline in all phases of drug discovery. In addition to leading chemistry teams across multiple therapeutic areas she has also helped build capability platforms in the areas of Fragment Based Drug Discovery and heterobivalent molecules, delivering multiple pre-clinical candidates from the latter platform. She currently leads a medicinal chemistry team focused on small molecule portfolio delivery. Beth completed her B.S. in Chemistry at Alma College in Michigan. She then moved to the University of Michigan in Ann Arbor to earn her Ph.D. in the labs of Bill Roush (polyketide natural product total synthesis) before completing a postdoc with John Montgomery (nickel-catalyzed synthetic methodology). As a Michigan native and long suffering Detroit Lions fan, Beth has high hopes for this year's NFL season. When she's not watching football, she enjoys

As a Michigan native and long suffering Detroit Lions fan, Beth has high hopes for this year's NFL season. When she's not watching football, she enjoys watching her 12 and 16 year old daughters play lacrosse, which has become a year round commitment.