School of Molecular Sciences
Arizona State University

SMS Spring 2022 Seminar Series

Friday March 25 | 2:30pm | Biodesign Auditorium

Novel Chemotypes of Kinase Inhibitors for the Potential Treatment of Recurrent Cancers

Therapeutic resistance remains a critical issue in cancer treatment. While cancer patients who harbor dysregulated protein kinases benefit from the use of kinase inhibitors (KIs), many fail therapy and almost all patients become resistant to treatment, indicating a critical unmet need to prevent treatment failure.

Thus far (as of December 2021), the FDA has approved 69 protein kinase inhibitors and several others are also in various stages of clinical trials. Although many compounds that inhibit protein kinases have been described in the literature, only a small region of the chemical space has been explored for protein kinase inhibition and the majority of FDA approved kinase inhibitors contain only a handful of core moieties, such as indazole, quinoline, isoquinoline, quinazoline, pyrazole and pyrimidine. To belabor this point, about ~20% of FDA-approved protein kinases contain the pyrimidine moiety while six drugs contain quinazoline and eight drugs contain pyrazole. In other words, about 50% of approved protein kinase inhibitors contain one of pyrimidine, pyrazole or quinazoline, highlighting the lack of progress in using other regions of the chemical space to drug protein kinases. The Sintim group, integrating computational and experimental workflows, has identified a few novel chemotypes that inhibit disease-associated protein kinases (such as FLT3, RET, CDKs, Haspin) with sub-nanomolar IC_{50} values. Some of these new KI are long residence time (hours) inhibitors and have shown impressive efficacies in animal models of various cancers. Two of such compounds are currently undergoing toxicology studies to determine safe dosing regimens for potential phase 1 clinical trials against drug-resistant FLT3 (F691L and D835V/Y)-driven AML and RET (solvent front mutations)-driven lung cancers.

Herman O. Sintim, PhD

Professor, Purdue University

Dr. Herman O. Sintim is the Drug Discovery Professor of Chemistry at Purdue University. Prior to relocating to Purdue, he was at the University of Maryland, College Park, where he was Assistant (2006 to 2012), Associate (2012 to 2015) and then Full (2015) Professor. He studied medicinal chemistry at University College London (BSc), Organic Chemistry (DPhil) at the University of Oxford, and performed postdoctoral work in organic chemistry and chemical biology at Oxford and Stanford Universities respectively. Herman served on the editorial advisory board of RSC Molecular BioSystems (now Molecular Omics) and currently serves on the editorial advisory board of ACS Medicinal Chemistry Letters.

Some of Herman's awards include NSF Career award, Camille Dreyfus Teacher-Scholar, Sigma Xi Distinguish Lecturer, NOBCChE lectureship at UPenn and Purdue's Most Distinguished Faculty for Research in 2019 (voted by Residence Hall students).

The Sintim Group is funded by various external grants, including NIH RO1s, SBIRs, NSF, and Cohen Foundation. Herman is a co-founder of KinaRx Inc., a start-up focused on oncology. From August 2020, Herman also serves as a Program Director at the National Science Foundation, Chemistry Division. He enjoys walking and watching soccer.

**ZOOM option available: https://asu.zoom.us/j/87081218152*