School of Molecular Sciences
Arizona State University

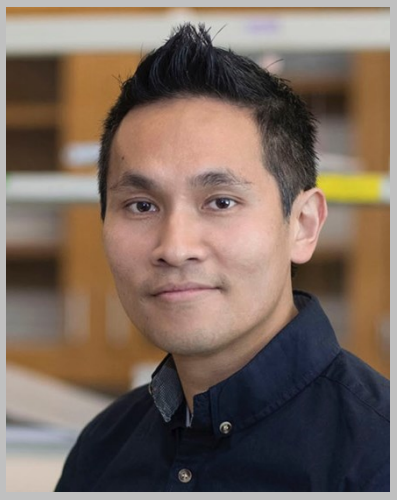
SMS Fall 2023 Seminar Series

Friday Sept 29 | 3pm | Biodesign Auditorium

SuTEx chemistry: applications for chemical biology and protein ligand discovery

Covalent drugs disrupt protein function by forming a specific bond between the drug and an amino acid residue on a target protein. Several important medicines in cancer produce a therapeutic response through a covalent mechanism of action (MOA). The renewed excitement for covalent drugs is motivated by distinct features of this class including high biochemical efficiency from non-equilibrium blockade of a target, pharmacological activity that can outlast drug pharmacokinetics, and access to challenging binding pockets on 'undruggable' protein targets. Our group developed sulfonyl-triazoles as a covalent binder of tyrosines to enable ligand discovery of catalytic and non-catalytic sites on proteins through sulfur-triazole exchange (SuTEx) chemistry. I will discuss efforts from my group and the field to advance the capabilities of SuTEx for covalent ligand discovery by (i) facilitating the global discovery of actionable (i.e. high propensity for covalent binding) tyrosines in the human proteome using tandem liquid chromatography-mass spectrometry (LC-MS/MS) quantitative chemical proteomics, (ii) establishing a prioritization strategy to identify functional tyrosine sites based on reactive/structural features, (iii) demonstrating capabilities for tuning the reactivity and selectivity of sulfonyl-triazoles for a tyrosine site of interest using medicinal chemistry, (iv) providing a facile means for target identification in cell lysate and phenotypic screening formats, and (v) late stage functionalization of inhibitor compounds with a SuTEx reactive group for developing targeted covalent inhibitors.

Ku-Lung (Ken) Hsu
Associate Professor, University of Virginia



Ken earned his PhD in Chemistry and Biochemistry from the University of Texas at Austin where he trained with Prof. Lara Mahal to pioneer the development of protein microarrays for global profiling of complex glycosylation on bacterial and tumor cells. He pursued further training in chemical biology with Prof. Benjamin Cravatt at The Scripps Research Institute (TSRI) as a Hewitt Foundation for Medical Research Postdoctoral Fellow. At TSRI, Ken gained expertise in activity-based protein profiling (ABPP) and mass spectrometry-based lipidomics to discover and functionally annotate lipid-signaling pathways in macrophages.

Ken launched his independent career as an Assistant Professor in the Department of Chemistry at the University of Virginia (UVA) in 2015. At UVA, Ken has built two major, high-impact research programs – 1) chemistry and chemical biology approaches to decipher the biological roles of proteins involved in the metabolism of lipids; and 2) chemical proteomic strategies to expand the druggable proteome through the discovery of sulfonyl-triazoles as covalent binders of tyrosines enabled by sulfur-triazole exchange (SuTEx) chemistry. Ken received early promotion to Associate Professor with tenure in 2020 and his research program has been recognized by several awards including the highly competitive NIH K99/R00 Pathway to Independence Award, Department of Defense CDMRP Career Development Award, Melanoma Research Alliance Young Investigator Award, the NSF CAREER Award, and the Emerging Leader Award from The Mark Foundation for Cancer Research.

In 2022, Ken was recruited to the Department of Chemistry at the University of Texas (UT) at Austin as a Cancer Prevention and Research Institute of Texas (CPRIT) Scholar Rising Star and the Stephen F. and Fay Evans Martin Endowed Associate Professor. At UT Austin, Ken will apply his innovative research program in chemical biology to gain basic insights and develop new pharmacological approaches for cancer and immunology.

**ZOOM option available: https://asu.zoom.us/j/81517529537*