Advancing covalent ligand discovery beyond cysteine

Abstract:

One of the major challenges in drug discovery is targeting proteins that are considered intractable - those lacking clear binding pockets or having surfaces too shallow for traditional drugs to bind effectively. Covalent chemistry offers a powerful way to overcome this challenge by forming a lasting bond with specific sites on proteins. Using approaches such as activity-based protein profiling (ABPP) and mass spectrometry (LC-MS/MS), researchers have made progress in designing molecules that react with cysteine residues to access difficult-to-target proteins and modulate important biological pathways. However, because cysteines are relatively rare, expanding this strategy to target other amino acids, like tyrosine and lysine, could greatly broaden the scope of proteins that can be addressed. In this talk, I will discuss recent progress in developing covalent chemistry that go beyond cysteine, showcase examples of their application in biology, and highlight how these tools are advancing our ability to study and treat disease.