Title: Covalent inhibitors - from discovery to function

Abstract:

Inhibitors and drugs that are able to form a covalent bond with their protein target has several advantages over traditional binders. They are attracting significant interest as underscored by FDA approvals of several rationally designed covalent drugs, such as Ibrutinib and Afatinib. My research team is focused on covalent ligand discovery and has developed methods including covalent virtual screening, covalent fragment screening, and computational redesign of reversible binders. We have now transitioned from discovery of covalent binders to their functionalization as for instance reversible covalent targeted degraders (PROTACs), and most recently the discovery of a new class of electrophiles that allows covalent binding triggered release of a specific cargo. I will share two stories: one on the discovery of a Pin1 covalent inhibitor, starting from a covalent fragment screen and going all the way to in vivo efficacy in various cancer models. And another on our recently discovered covalent ligand directed release (CoLDR) chemistry that allows the functionalization of covalent binders.