Yale *Chemical Biology Institute*

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Chemical tools to expand the ligandable proteome

Covalent inhibitors, often distinguished by their promise of potency and selectivity, have reemerged as attractive tools for perturbing protein function and can even serve as leads for new medications. In this seminar, I will describe our development of two complementary chemical proteomics platforms that enable quantitative analysis of cysteine- and lysine-reactive fragment electrophiles screened in parallel against thousands of proteins in proteomes and cells. We identify covalent ligands for >700 cysteines and >150 lysines found in both canonically druggable proteins (e.g., enzymes) and proteins lacking chemical probes, including transcription factors, adaptor/scaffolding proteins and uncharacterized proteins. Among the atypical cysteine-ligand interactions uncovered, we identified compounds that react preferentially with pro- (inactive) over active caspases and applied these ligands to characterize extrinsic apoptosis pathways in human cell lines and primary human T-cells. Expanding beyond cysteine-reactive small molecules, we show that reactive lysine residues are also amenable to activity-based protein profiling (ABPP) and can be selectively targeted by lysine-reactive compounds. Proteome-wide covalent ligand discovery provides an expanded portrait of the ligandable proteome and yields compounds that can illuminate protein functions in native biological systems.

Thursday, March 2
4:00 p.m.
15 Prospect St., Becton Seminar Room

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