Abstract
Small-molecule ligands are powerful tools for modulating protein function, and in turn modulating cellular signaling pathways. For this reason, small molecules have found great utility as chemical probes to study cellular signaling, and as therapeutics for the treatment of human diseases. Unfortunately, developing new chemical matter capable of modulating a protein’s function is difficult and slow. To address this, we have utilized the power of protein engineering to rapidly generate protein/small-molecule interactions that allow for small-molecule control of protein and cellular function. I will present two stories highlighting this work. The first will focus on our use of disulfide-fragment tethering to identify a new allosteric site on the important drug target, protein tyrosine phosphatase 1B (PTP1B), and a covalent fragment capable of binding to and inhibiting PTP1B at this site. This new site and fragment may serve as the basis for the development of a new class of allosteric PTP1B inhibitors. The second story will describe our efforts to generate new chemically induced dimerizers (CIDs) from existing protein/small-molecule complexes and synthetic antibody libraries. We have applied our novel CIDs to regulating the activity of CAR T-cells, an exciting new class of cell-based cancer therapeutics. Together, these two stories demonstrate the incredible power of combining small molecules and protein engineering to generate ligand-based tools for manipulating biology.