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My research interests aim to investigate and target mechanisms of protein-protein interactions in cell death and cell survival signaling, which are deregulated in cancer and other diseases. In this effort we develop novel pharmacological strategies and chemical probes that can be used for target validation and serve as the basis for novel therapeutics. By operating at the interface of chemistry and biology, and developing innovative approaches, our goal is to advance understanding of the biological processes and provide new opportunities for drug discovery.

Since I started my lab we have made progress with elucidating biochemical mechanisms and discovery of chemical probes. We identified the first small-molecule activator of pro-apoptotic BAX and demonstrated a new paradigm for pharmacologic induction of apoptosis. We characterized the first small molecules that activate chaperone-mediated autophagy and protect cells from oxidative stress and proteotoxicity. We have contributed in the area of BCL-2 family inhibitors with investigating stapled peptides and small molecules broadly targeting the anti-apoptotic proteins or selectively the MCL-1 protein, an important target for overcoming apoptotic resistance in many tumors.

We elucidated novel mechanisms that regulate inhibition of cytosolic and mitochondrial BAX in BAX-induced apoptosis. Specifically, we identified a novel auto-regulatory mechanism of pro-apoptotic BAX induced by dimerization that inhibits BAX activation and regulates sensitivity to apoptosis induction. We solved the first crystal structure of full-length BAX and used NMR approaches to identify a novel binding-pocket to BAX that mediates repression by the BCL-2 protein at the mitochondria. Using phage display screens, we identified synthetic antibody fragments that bind to BAX at the N-terminal activation site, which can potently block BAX activation at an early step before its mitochondrial translocation. These studies provided novel pharmacologic opportunities to modulate BAX within the mitochondrial cell death pathway.

A recent line of research in the lab focuses on the ERK signaling pathway in cancer. We applied a structural and chemical biology approach to elucidate a major mechanism for RAF inhibitor-mediated resistance due to RAF dimerization and RAS-dependent BRAF activation. We have devised an integrated model that predicts activity of RAF inhibitors in different BRAF signaling contexts and tumors. We have pursued structure-based drug design using this conceptual understanding for novel inhibitor development.

References:

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