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Bioorganic, Synthetic Organic and Medicinal

My group's research interests reside at the interface between chemistry and biology where the vast arsenal of synthetic organic chemistry can be directed by biophysical insights taken from "Nature's notebook." Our primary goal is the development of therapeutic agents relevant to the prevention, detection, or treatment of cancer, neurodegenerative diseases, and environmental pathogens. In this regard, we apply traditional synthetic chemistry to the synthesis of natural products and analogs designed with the aid of molecular modeling. Solid phase synthetic techniques are also employed in the construction of small molecule and peptidomimetic libraries which allow the biochemistry of disease pathologies to be examined with molecular detail in high throughput formats.

The aberrant regulation of natural processes, including programmed cell death, is a hallmark of several human diseases including cancer and neurological disorders. In cancer, tumors acquire malignant phenotypes that allow them to evade cell death by ignoring or repressing pro-apoptotic signals, resulting in uncontrolled growth, drug resistance, and even metastasis. Our approach to chemotherapeutic development targets multiple pathways in the progression of cancer, including inhibition of oncogenic transcription factors responsible for drug resistance, activation of apoptosis by inhibition of histone deacetylases, as well as blockade of the metastatic cascade, ultimately re-activating apoptosis in tumors. In contrast to cancer, neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are characterized by unscheduled apoptosis leading to the loss of specific populations of neurons. Thus, our approach to the development of AD or PD therapeutics focuses on finding small molecules or combinations thereof able to halt premature cell death. Research in this area examines the role played by misfolded oligomeric proteins in generating mitochondrial and endoplasmic reticulum stress. The ability of these soluble oligomers to interact with intracellular proteins and initiate stress and ultimately apoptosis will be explored with the aim of developing peptidomimetic ligands capable of disrupting pathogenic protein-protein interactions.

Clearly, the success of small molecule strategies to activate or deactivate apoptosis requires efficient drug delivery vehicles, capable of directing small molecule therapeutics to specific cellular and intracellular addresses. Towards this end, pro-drug systems containing signal peptides will be applied to both cancer and neurodegenerative disease programs. Cancer pro-drug designs seek to employ cancer-specific proteases as a means to deliver multiple warheads to diseased tissues. Pro-drug strategies for neuroprotective species focuses on delivery agents capable of carrying small molecules across the blood brain barrier.

During their first semester of research, undergraduates are exposed to core synthetic techniques in organic chemistry. These techniques include solution phase organic synthesis, chromatography, and interpretation of NMR and mass spectra. Upon

mastering these fundamental operations, undergraduates are trained in the art of solid phase synthesis, including the use of an automated synthesizer and HPLC. Undergraduates who become proficient with the above synthetic techniques will then learn how to analyze the structure and function of their molecules. This process may involve spectroscopic techniques such as 2D NMR, LC-MS, circular dichroism, and fluorescence spectroscopy. Alternatively, *in vitro* biochemical assays might be performed. A strong background in organic chemistry and a working knowledge of biochemistry, though not required, are recommended for undergraduates interested in research in this group.