Poster Title: The development of membrane-permeable α/β-peptide foldamers for the inhibition of protein-protein interactions

Abstract: In the event of extensive cellular damage, proteins belonging to the Bcl-2 family play an important role in the initiation of apoptosis. Cytotoxic signals are transduced through a number of protein-protein interactions among pro- and anti-apoptotic Bcl-2 family members. Problems in the regulation of these interactions can result in a failure to initiate apoptosis in unwanted or damaged cells. Inhibitors of protein-protein interactions within the Bcl-2 family are thus attractive as therapeutic agents for a variety of diseases. Peptides composed of both α- and β-amino acids (α/β-peptides) can effectively mimic the helical portion of pro-apoptotic proteins and initiate apoptosis, but are unable to cross the hydrophobic cell membrane to carry out this intended function.

The proposed research is aimed at developing strategies to design functional α/β-peptides that are able to cross cell membranes and inhibit intracellular protein-protein interactions. Our approach relies on the replacement of carboxylic acid side chains with labile ester groups bearing lipophilic moieties. We hypothesize that large hydrophobic moieties will associate with the plasma membrane and facilitate the transport of the α/β-peptides into the cell. Once inside the cell, the membrane-penetrating unit will be removed through enzymatic hydrolysis by intracellular esterases to give a fully functional α/β-peptide. In this way, undesired biological functions arising from the presence of the cell-penetrating group can be avoided. If successful, this research will afford the first α/β-peptides derived from a “sequence-based design” strategy that are able to enter cells and elicit an intentional biological response.

We hope to develop robust methods for the design of cell-permeable α/β-peptides that mimic natural protein binding domains. Long term goals of this research include the use of membrane-permeable foldamers as research tools to explore protein binding interactions in vivo, the extension of successful strategies to inhibit a variety of protein-protein interactions, and the potential use of these compounds in living systems for the treatment of disease.