Fluorescently labeled lanthanide bound probes which dock to Trp rich domain of X-linked Inhibitor of Apoptosis Protein (XIAP)

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XIAP, a member of the Inhibitor of Apoptosis Proteins, is an anti-apoptotic protein which inhibits controlled cell death by non-covalently binding pro-apoptotic proteases called caspases. XIAP is naturally inhibited during apoptosis by the mitochondrial protein Smac (Secondary Mitochondrial Activator of Caspases), which binds to XIAP's BIR3 domain through its four N-terminal residues. However in some cancers, XIAP is upregulated and can overwhelm Smac's regulatory response. In this case, the development of small molecule XIAP inhibitors based on Smac's N-terminal sequence could be valuable in freeing caspases to facilitate apoptosis. Earlier work by the McLendon lab and others has shown that tetrapeptides based on Smac's sequence bind to the BIR3 domain as well as or better than wild-type Smac.

This project seeks to develop a novel method to determine the relative binding strength of different short peptides to the BIR3 domain of XIAP. Peptide-based probes which target BIR3 and either strongly chelate Tb^{3+} or have other fluorophores have been developed and characterized. We will discuss the use of such fluorescence based probes for binding and therapeutic applications.