Project Title: Novel Inhibitors of phosphoinositide 3-kinase (PI3K) that target scaffold protein-mediated interactions
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Cancer is caused by mutations in specific genes. Some of these genes are found to be mutated in only a few particular types of cancer, while other mutations are found more broadly mutated in many types of cancer. PIK3CA is an example of this second class; it is found mutated 15-30% of breast, endometrial, and colon cancers, and is also frequently mutated in other cancers including melanoma and pancreatic cancer. Indeed, PIK3CA is one of the most frequently mutated genes in human cancer. Moreover, PIK3CA is a central component of a signaling pathway that is deregulated in many other cancers. This makes PIK3CA an attractive drug target. Unfortunately, drugs targeting PIK3CA have had disappointing outcomes in combatting cancer, due their significant side effects and toxicities.

Like many oncogenic drivers, PIK3CA has multiple cellular functions, only some of which are crucial to its ability drive tumorigenesis and promote cancer progression. If it were possible to selectively inhibit these cancer-promoting functions of PIK3CA while leaving other functions relatively untouched, a more selective, less toxic agent could be developed. PIK3CA binds to other proteins, and these protein-protein interactions help bring it to different regions of the cell to perform specific roles. A drug that blocked one of these protein-protein interactions, while leaving others intact, might reduce the side effects associated with PIK3CA inhibition, while still maintaining the anti-cancer effects.

We have discovered a small peptide that can block the protein-protein interaction between PIK3CA and one of its most important binding partners, a protein called IQGAP. Studies with larger peptides that block this interaction have shown that these peptides are able to selectively kill cells derived from triple-negative breast cancer, melanoma, pancreatic cancer, colorectal carcinoma, and other cancers. The smaller version of this peptide that we discovered is of the right size to allow us to perform various chemical tricks that might make it better at getting into cells and binding to its target, thus making it an even better drug lead.

Our goal is create a new type of 'peptidomimetic drug'. Although it is "convential wisdom" that peptides are non-optimal leads for drug discovery, and that targeting protein-protein interactions is challenging, the success of the peptide-based anti-leukemia drug venetoclax provides a striking counter example on both fronts. This work is significant because (i) it will advance the discovery of a new class of drugs targeting PIK3CA; (ii) it will add to our basic understanding of the utility of targeting protein-protein interactions.