Medicinal Chemistry 3rd Year Seminar

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**Design, Synthesis, and Evaluation of Novel PDHK Inhibitors as a Therapeutic Treatment for Cancer**

Pyruvate dehydrogenase kinase (PDHK) is a non-canonical serine/threonine kinase that has been deemed a glycolytic gatekeeper as it regulates the pyruvate dehydrogenase complex (PDC), a multienzyme complex that controls the metabolism of glucose. Specifically, PDHK negatively regulates pyruvate dehydrogenase (PDH), a component of the PDC, which when unphosphorylated converts pyruvate into acetyl-CoA for entry into the tricarboxylic acid cycle. To sustain proliferation, cancer cells undergo a shift in metabolism that favors aerobic glycolysis instead of mitochondrial oxidative phosphorylation, a phenomenon known as the Warburg effect. To achieve this shift in metabolism, cancer cells have elevated expression of enzymes needed to promote glycolysis and lactate production. This includes elevated expression of PDHK in tumors under hypoxic conditions that display increased reliance on glycolysis. Upregulation of PDHK has been linked to a variety of metabolic diseases including diabetes, hepatic steatosis, cardiovascular disease, and many forms of cancer. Suppression of PDHK activity using siRNA, shRNA or dichloroacetic acid has been shown to upregulate oxidative phosphorylation and inhibit tumor growth in mouse models.

There are four PDHK isoforms (PDHK1-4) that have various expression levels throughout different tissues. Research has shown that PDHK1 deficient mice are viable and healthy, suggesting that isoform selective PDHK inhibition is well tolerated. Moreover, several other studies have shown isoform specific knockdown of PDHK1 or PDHK2 is tolerable in mouse tumor models using shRNA or siRNA. We hypothesize that isoform selective PDHK inhibitors will result in increased therapeutic efficacy while mitigating mechanism-based toxicity.*We are working towards synthesizing isoform selective inhibitors of PDHK by identifying amino acid residue differences among isoforms and incorporating functional groups to target these differences.*

While there are several known PDHK inhibitors, none are currently FDA approved. This is in part due to lack of cellular potency, which has limited clinical success. It has been repeatedly shown that there is an overall discrepancy between PDHK inhibitor potency in enzymatic activity assays versus cellular assays. For example, the known inhibitor VER-246608 inhibits PDHK(2) in biochemical assays with an IC50 of 35 nM but its IC50 for inhibition of PC3 cell proliferation is only 26 μM. One reason for the decrease in cellular potency is that PDHK functions in the mitochondrial matrix, therefore inhibitors must enter the cell and localize to the mitochondria to reach the intended site of action. Prior studies have explored conjugation of low (mM) potency PDHK inhibitors such as dichloroacetic acid and phenylbutyrate to a triphenylphosphonium (TPP) cation to aid in mitochondrial targeting. TPP conjugated PDHK inhibitors have shown improved *in vitro* activity against cancer cells relative to the PDHK inhibitors alone and strongly suggest that subcellular targeting to the mitochondrion improves PDHK inhibitor efficacy by modulating glucose metabolism in cells. *Starting with a highly potent (nM) PDHK inhibitor scaffold, we will use conjugation to a mitochondrial “address label” to increase subcellular targeting of the mitochondrion for overall improved efficacy in cells.* By implementing these strategies, we hope to identify and optimize PDHK inhibitors that are selective and potent for the treatment of cancer.