**Discovery and Optimization of Pyruvate Dehydrogenase Kinase (PDHK) Inhibitors for Modulation of Tumor Metabolism**

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Pyruvate dehydrogenase kinase (PDHK) is a non-canonical serine/threonine kinase that negatively regulates the pyruvate dehydrogenase complex (PDC). Inactivation of the PDC restricts entry of acetyl-CoA into the tricarboxylic acid (TCA) cycle and shifts metabolism in tumors toward an increased reliance on glycolysis (the Warburg effect). Inhibition of PDHK using RNAi or small molecule inhibitors such as dichloroacetic acid (DCA) reverts this glycolytic phenotype and has been shown to inhibit tumor growth *in vitro* and *in vivo*. Despite this phenotypic validation, there are currently no FDA-approved PDHK inhibitors. Previously described PDHK inhibitors suffer from poor cellular potency, inadequate pharmacokinetic profiles, and a lack of isoform selectivity. We have devised two approaches to discover and develop novel and/or selective PDHK inhibitors to address these challenges and further probe PDHK biology:

1. *Optimization of putative allosteric PDHK ligands previously disclosed in the literature.*

We have selected PDHK ligands from the literature to explore the ligandability of distinct allosteric sites and assess their potential for achieving isoform selectivity within those pockets. Based on our data, putative lipoamide site ligand 6u appears to be selective for PDHK4. Efforts to further validate these observations and potentially exploit this selectivity are ongoing.

1. *Identify novel PDHK ligands using computational methodologies.*

In addition to optimizing known ligands, we aim to discover new chemotypes of PDHK inhibitors. Using various computational approaches to ligand selection and design (e.g., virtual screening, *de novo* design), we have identified novel PDHK inhibitors amenable to medicinal chemistry. From our collaboration with Atomwise Inc., a series of novel, selective PDHK1 inhibitors was discovered via iterative virtual screening against the PDHK1 ATP site. Efforts to improve the potency of this series and elucidate its mode of inhibition are ongoing.

Through these orthogonal approaches, we have identified a novel series of selective PDHK1 inhibitors and may have uncovered a path forward for a selective PDHK4 inhibitor. We will continue to optimize these inhibitors for use as tool compounds and, ultimately, for development into therapeutic agents for the treatment of various cancers.