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# "Characterization of a GOLPH3 Pathway Inhibitor to Enable a Hit-to-Lead Grant to Develop a Novel Cancer Therapeutic"

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## SCIENTIFIC ABSTRACT

To more effectively combat cancer we need new therapies directed at new targets. GOLPH3, and proteins that interact with it, play a key role in Golgi secretory trafficking and are the first examples of oncogenic cancer drivers that function in Golgi trafficking. Interference with these proteins is preferentially toxic to cancer cells, raising interest in small molecule inhibitors as potential novel therapeutics for lung, breast, prostate, and colorectal cancers. Using a phenotypic screen we identified a potent inhibitor that acts via MYO18A to cause characteristic inhibition of the Golgi, and to preferentially kill oncogenically transformed cells. Further develop- ment of this hit into a pharmaceutical lead depends on identification of its direct target. It structurally resembles a protein kinase inhibitor, and inhibits PDGFR signaling, although PDGFR is not its mechanistic target. We propose to identify the critical kinase target, develop more potent, specific, and drug-like structural analogs, and perform preliminary ADME/PK to lay the groundwork for a compelling hit-to-lead R01 application to NCI.

## LAY ABSTRACT

To more effectively combat cancer we need new therapies directed at new targets. We discovered a signaling pathway involving a protein called GOLPH3 that drives a high fraction of cancers that together cause a high proportion of cancer deaths, including lung, breast, prostate, and colorectal cancers. The GOLPH3 pathway is unlike other pathways that drive cancer, and so inhibitors of the pathway provide a unique approach to cancer treatment. Existing data indicate that inhibition of the GOLPH3 pathway preferentially kills cancer. We have identified a potent inhibitor of the pathway, and propose experiments to better define its mechanism of action to enable further development to produce a compound that would be suitable as a novel therapeutic agent, completely unlike all current therapeutic strategies for cancer.