Hedgehog Palmitoylation as a Target to Block Pancreatic Cancer

In t ssion is turned off. However, when aber ant Shh expression or signaling occurs in adults, it can drive the biogenesis of multiple human cancers, including pancreatic, breast and lung cancers. Our laboratory is developing drugs that block modification of Shh proteins with palmitate and thereby prevent Shh mediated growth of cancer cells. In order to signal correctly, Shh must be modified by attachment of the 16-carbon fatty acid palmitate to its N-terminus. We aim to exploit Shh palmitoylation as a potential Achilles heel by targeting Hhat (Hedgehog acyltransferase), the enzyme that catalyzes attachment of palmitate to Shh. Since palmitoylation is required for Shh function, Hhat inhibitors that block Shh palmitoylation could be developed into novel chemotherapeutics that will be efficacious in the treatment of pancreatic and other cancers. My laboratory developed an *in vitro* Shh palmitoylation assay that is dependent on Hhat and used this assay for High Throughput Screening (HTS) to identify small molecule inhibitors of Hhat. Our lab first used high throughput screening to identify RU-SKI 43, a novel, first-in-class small molecule Hhat inhibitor that blocks Shh palmitoylation, autocrine and paracrine Shh signaling, as well as human lung, breast and pancreatic cancer cell growth *in vitro*. In partnership with the Tri-I TDI, we optimized RU-SKI 43 into TDI-3410, a potent, selective and bioavailable Hhat inhibitor. TDI-3410 was formulated for PO delivery and we determined an MTD. We are testing the efficacy of TDI-3410 in animal models of lung, breast and pancreatic cancer (xenografts, PDX, genetically engineered mouse models (GEMM)), with a particular focus on cancer stem cells (CSC), a cell population with activated embryonic pathways susceptible to Shh inhibition. We use the MSKCC Antitumor Assessment and Molecular Cytology Core Labs for these preclinical studies.