Metabolic Targeting of Tumor Cells with Hyperactive TORC1

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Lymphangioleiomyomatosis (LAM) is an often-fatal destructive lung disease of young, nonsmoking women. LAM cells carry mutations in the tuberous sclerosis complex (TSC) genes, resulting in activation of mammalian target of Rapamycin (mTOR) complex 1 (TORC1). TORC1 is a “master regulator” of protein translation, cellular metabolism and autophagy. Treatment of tumor cells in TSC or LAM patients with mTORC1 inhibitors (Rapalogs) results in a cytostatic response and the tumor cells regrow when the drug is discontinued. Therefore, prolonged therapy, with accompanying toxicity, is required. There is a significant unmet medical need for treatments that induce a cytocidal response in mTORC1 hyperactive tumor cells in TSC, LAM, and sporadic human tumors with hyperactivation of mTORC1, including kidney cancer and bladder cancer.

We propose a completely novel strategy for tumors with hyperactive TORC1: targeting TORC1-dependent metabolic vulnerabilities, and not directly targeting TORC1 itself. We previously screened 6,600 compounds at the ICCB in TSC2-deficient, patient-derived cells for agents that induce cell death selectively in the setting of TORC1 hyperactivation. Here, we will complement this small molecule screen to identify molecular targets that selectively induce death in TSC2-deficient cells.

Novel strategies targeting the metabolic vulnerabilities of cells with hyperactive mTORC1, leading to durable remissions and thereby preventing progression to end-stage lung disease and death in LAM and making life-long use of Rapalogs unnecessary in children with TSC. Thus, our project will have high clinical impact for LAM, TSC, and cancer patients whose tumors have mutations in the PI3K/Akt/TSC/mTOR signaling network.