

Novel Compounds that Regulate Autophagy to Treat Cancer

INVENTION:

Autophagy is a normal cellular process that recycles damaged cellular components and is required for cell survival under starvation conditions. Autophagy has been shown to be upregulated in a number of cancers as a supplementary source of nutrients for cell growth and a pro-survival mechanism when tumors cells face metabolic limitations. Investigators at Salk in collaboration with researchers at Sanford Burnham Prebys Institute have focused on the serine/threonine kinase ULK1 as it is the only autophagy-specific druggable enzyme in the upstream half of the well-defined core autophagy pathway. These investigators have developed novel small molecule regulators of ULK1 that robustly and selectively inhibit ULK1 activity in vitro and in cell culture. Multiple biomarkers of ULK1 were developed allowing for in cellulo screening. Potent anti-cancer effects are observed with ULK1 inhibitors as single agents in selected cancers, such as pancreatic cancer and when combined with existing therapies in other cancer indications. Our scientists also showed synergy of a ULK1 inhibitor with a mTOR inhibitor in the induction of apoptosis in non-small-cell lung carcinoma (NSCLC) cell lines. In addition, the ULK1 inhibitor is more potent at inducing cell apoptosis both as a single and combination agent than generic lysosome inhibitors.

APPLICATIONS: Treatment of various cancers

ADVANTAGES:

- ULK1 is the only kinase in the core autophagy pathway, and has proven to be an attractive and potent target for therapeutic intervention
- The compounds robustly and selectively inhibit ULK1
- The compounds synergize well with mTOR inhibitors for effective anti-cancer effects

STAGE OF DEVELOPMENT: Efficacy has been shown in cells and animal models. Our researchers wish to further develop ULK1 inhibitor chemical scaffolds to then be used in a clinical Phase I program to test for safety and efficacy.

BACKGROUND: Autophagy is required to remove damaged cellular components, and utilizes membrane-bound vesicles that fuse with lysosomes for the degradation of those damaged or unwanted organelles. This essential process is also enhanced during tissue repair as well as in certain cancers. ULK1 is a conserved enzyme that triggers the autophagy pathway downstream of mTOR, and is the only kinase in the core autophagy pathway.

INVENTORS: Dr Reuben Shaw & Dr. Nick Cosford

PATENT STATUS: PCT patent application WO 2016/033100 is pending

PUBLICATIONS: Egan, et al. 2015. Mol. Cell, 59:285-297.

CONTACT: Melissa Rodgers; mroddgers@salk.edu; (858) 453-4100 x1481

TECHNOLOGY ID: RD1340

