

## MCC-C3 Padres Pedal the Cause Spring 2020

### Examination of inhibitors of the ULK1 autophagy kinase as therapeutics in NSCLC



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#### Scientific Abstract:

Lung cancer remains the number one leading cause of death from cancer, and non-small cell lung cancer (NSCLC) represents the common (~85%) form of the disease. The current standard-of-care ("SOC") for metastatic lung cancer includes platinum chemotherapy, immunotherapy, and targeted therapies. Despite extensive understanding of the genetic driver events in NSCLC and advances in targeted therapies, only a subset of NSCLC (~30- 40%) have an 'actionable' genetic mutation (EGFR, ALK4, ROS1, BRAF, NTRK) for which there is an existing first line FDA-approved targeted therapy that is effective in reducing tumor burden. Of these targetable NSCLC oncogenes, EGFR-activating mutations are observed in 15-18% of patients. Tyrosine kinase inhibitors (TKIs) have provided an illustrative example of the successes in targeting oncogene addiction in cancer and the role of subsequent tumor-specific adaptations conferring therapeutic resistance. Third-generation TKIs (e.g. osimertinib) have improved progression-free survival by suppressing the activating mutation and preventing the rise of the resistant clones. However, therapeutic resistance to third-generation inhibitors is complex and not fully understood. Developing new combinatorial therapies is a direction forward for targeting minimal residual disease and bypass pathways early, based on projected resistance. One of the proposed mechanistic underpinnings of therapeutic resistance to both chemotherapies and TKIs is the upregulation of autophagy. We have developed the first orally-available selective inhibitors of the core autophagy kinase ULK1, which we have tested in NSCLC xenografts and observed synergy with SOC. Here we propose to test ULK1 inhibition in PDX models to examine its broad therapeutic potential against chemo- and TKI-resistant NSCLC.

#### Lay Abstract:

Lung cancer is the number 1 cause of cancer deaths per year, causing more deaths annually as colon, breast, and prostate cancer combined. One of the reasons underpinning the high mortality rate of lung cancer is the rapid development of therapeutic resistance to chemotherapies, as well as resistance to targeted therapies in those select patients for which genetically targeted therapies are applicable. ULK1 is a key enzyme in a cellular process known as autophagy. Autophagy is normally used in cells to survive starvation conditions by recycling internal stores of nutrients, but autophagy gets upregulated in tumor cells, especially in response to therapy. We and other hypothesize that autophagy allows lung cancer cells to evade cell death in response to chemo- and targeted therapies, causing resistance. We have very recently developed new orally available small molecule inhibitors of ULK1, which we have shown suppress autophagy and work without toxicity in animal models. Here we propose here to test our new ULK1 inhibitors in the first-of-its-kind study for the treatment of lung cancer, and further to specifically to see if they will re-sensitize human tumor samples to standard therapies. We believe autophagy inhibitors have unique promise against a broad set of lung cancers, when used in combination with existing therapeutics.

*There are 2 reasons why this team is likely to succeed where others have failed: First, when it comes to **drug discovery in GC**, this team employs **precise and unbiased** AI-based approaches to expose previously unknown and undefined intermediate stages before GCs and reveal how to stop progression. *Second*, when it comes to **drug testing**, this team has developed human models that are reverse engineered with the GC-causing bug, the stomach lining and the immune cells to mimic the **human “stomach- in-a-dish”**. These human-relevant models are expected to enable rapidly translation of discoveries.*