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Targeting PI3Ky to reverse immune suppression in lung cancer

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Scientific Abstract:

Non-small cell lung cancer is an aggressive disease with an expected 5-year overall survival of 7.0% in the metastatic setting and 33.5% for regional disease. Outcomes have improved with the addition of immunotherapy in the metastatic, adjuvant, and neoadjuvant settings, but there remains a critical need for novel therapies, as the majority of patients are still unlikely to be cured. Novel therapies offer the greatest hope for patients with metastatic refractory disease, where the response rate to standard therapy is only 10%, and for patients with early-stage disease, where there is potential to provide a lasting cure. Non-small cell lung carcinomas are heavily infiltrated with macrophages and granulocytes, which promote profound immune suppression, angiogenesis, and tumor metastasis. At the Moores Cancer Center, we made the fundamental discovery that the macrophage protein PI3Kgamma controls cancer immune suppression and tumor progression. Based on our findings, the PI3Kgamma inhibitor eganelisib was developed as an immune oncology therapeutic that has shown remarkable success in clinical trials for bladder cancer and triple negative breast cancer. We propose to evaluate the potential of eganelisib to suppress lung cancer progression when combined with chemotherapy and immune checkpoint inhibitors using preclinical mouse and human tumor slice culture models of lung adenocarcinoma and squamous cell carcinoma. We will leverage our extensive experience in single cell RNA sequencing analysis to investigate mechanisms and biomarkers of response and resistance to therapy. These innovative studies will determine the potency of macrophage-targeted therapeutics such as eganelisib for the treatment of lung cancer.

Lay Abstract:

Lung cancer is deadly disease that is largely caused by smoking tobacco. This form of cancer is a leading cause of death worldwide. Within the United States alone, 236,740 new cases of lung cancer and 130,180 deaths are expected in 2022. New treatments that can cure lung cancer patients and promote their long-term survival are still needed. Using laboratory models of lung cancer, we identified an important new immune therapy approach for lung cancer and other cancer patients. We discovered that immune cell types called macrophages and granulocytes accumulate in lung tumors and create an environment that promotes tumor cell evasion from anti- tumor immune responses. A single macrophage enzyme, called PI3Kgamma, controls this evasion and an inhibitor of PI3Kgamma is now showing good clinical benefit in breast and bladder cancer patients. We propose to test the potential of this new therapeutic, eganelisib, to work effectively with standard of care chemotherapy and immune therapy in preclinical models of lung cancer. These models include genetically engineered mouse models of lung adenocarcinoma and squamous cell carcinoma that replicate many of the same aggressive features of lung carcinomas. Additional studies in innovative human tumor cultures in the laboratory will allow us to investigate the effects of the treatment strategy in actual human tumors as well. We predict that eganelisib will show

strong benefit in promoting tumor regression in these models. These studies will ultimately enable the clinical testing of eganelisib as a therapeutic for lung cancer patients.