Identification of Tumor Cell and Microenvironmental Determinants of Response to Immune Checkpoint Blockade in Lung Cancer

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Abstract: One of the most exciting recent advances in cancer medicine is the demonstration that immunotherapies, notably immune checkpoint inhibitors, are clinically effective in a variety of cancer types including lung cancer, kidney cancer and melanoma. Despite the observed clinical activity, which far surpasses that observed with prior immunotherapies and most chemotherapies, the molecular underpinnings governing response and resistance to these agents are poorly understood. We believe that this is due to a lack of coordinated and comprehensive efforts to utilize cutting-edge techniques in immunologically intact model systems and patient specimens to define the key biomarkers in this field, focusing on both the tumor and its immune microenvironment. The goal of this proposal is to integrate clinical response information with deep characterization of the properties of the tumor cell (genomic landscape, neoantigen expression, co-stimulatory ligands) and the immune microenvironment (resident cell types and their activation status and gene expression profiles, T cell repertoire) to identify the key drivers of response to immune checkpoint blockade. Candidates will be validated in appropriate isogenic mouse models to facilitate moderate- to high-throughput evaluation of hypotheses generated from analysis of clinical specimens. The expected outcome of this program is to rapidly and comprehensive advance our knowledge of biomarkers associated with response to therapy in the field of immuno-oncology and to facilitate translation of these findings into the clinical development of novel immunotherapies. Given that lung cancer is the leading cause of cancer-related mortality world-wide we will focus our studies on this cancer type during the project period.