CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150405

Project Title:
Tumor Cell Epithelial-Mesenchymal Transition in Regulating Immunosuppression and Metastasis in Lung Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
Gibbons, Don

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Lung cancer is an aggressive metastatic cancer that claims 160000 lives in the US annually. Our long-term goal is to develop prevention and treatment strategies for metastasis, to ultimately improve cure rates. To this end, we have been investigating immune therapy. Lung cancer cells recruit and activate diverse inflammatory cells, creating an immunosuppressive environment favoring tumor growth and spread. We have developed genetic mouse models with the mutations found in human lung cancer for detailed study of the determinants of metastasis. We found that metastatic cancer cells specifically turn off killer T cells by expression of a molecule on their surface, called programmed death ligand 1 (PD-L1). Metastatic tumor cells aberrantly express the protein because a switch in their genetic programming silences a group of molecules responsible for blocking PD-L1. Targeting of PD-L1 on tumor cells re-engages the T cells to suppress tumor growth and spread. Experimental findings in the mouse models were confirmed by examination of a large public NIH lung cancer dataset and a separate MD Anderson dataset. We believe that targeting PD-L1 provides an opportunity to specifically attack the cells responsible for metastasis. This treatment has shown remarkable responses in clinical trials for a subset of lung cancer patients, potentially providing long-term, durable effects. To maximize the clinical effectiveness we need to identify the patients most likely to benefit and frame a detailed view of how tumors respond to anti-PD-L1 treatment. To build on our findings and direct the results toward immediate translational impact, this proposal uses unique mouse models and human lung tumor samples to 1) better understand the role of PD-L1 in producing immune system suppression and tumor spread, 2) define the interactions of other immune cells in this process, and 3) investigate how the immune system kills tumors, to identify the potential methods of tumor escape from treatment.