EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

WINSHIP LUNG CANCER SPORE
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Project 1: Evaluating stem-like T cells and improving efficacy of checkpoint inhibitors in NSCLC

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I. EXECUTIVE SUMMARY

Our group has identified stem-like T cells that undergo proliferation after immune checkpoint inhibition. We will characterize these cells in lung tumors, draining lymph nodes and peripheral blood, and study their correlation with treatment outcome. In addition, we will study a novel combination regimen of mTOR inhibition and PD1 inhibition in lung cancer patients.

II. PROJECT AIMS

Aim 1: To identify and characterize the phenotype, location, and function of stem-like CD8 T-cells in lung cancer patients. Aim 1a. Characterize the transcriptional, epigenetic, and functional characteristics of tumor infiltrating stem-like CD8 T cells in NSCLC; Aim 1b. Determine the clonal relationship between T-cell populations in tumor, draining lymph node, and blood using TCR sequencing.

Aim 2: To study the efficacy and immune responses of combined inhibition of PD-1 and mTOR in a neo-adjuvant therapy trial in NSCLC patients. Aim 2a. To examine the clinical efficacy of the combined inhibition of PD-1 and mTOR in a neo-adjuvant therapy trial for patients with early stage NSCLC. Aim 2b. To examine the correlation between immune responses and clinical efficacy of the combination therapy.

Aim 3: To evaluate T cell dynamics in lung cancer patients using in vivo deuterium labeling. Aim 3a. To measure proliferation in T cell populations in NSCLC patients using in vivo deuterium labeling. Aim 3b. To determine the CD8 T cell populations that proliferate in response to mTOR and PD1 blockade using in vivo deuterium labeling.

III. PROJECT DESCRIPTION

Programmed cell death-1 (PD-1) targeted therapies have changed the landscape of lung cancer treatment. While some impressive results have been generated, the mechanisms that dictate which patients will, or will not, respond to this treatment are not well defined. It is important to understand the immunological factors associated with clinical responses not only to improve current therapies but also to identify predictive biomarkers. We have recently identified a novel population of PD-1+ TCF-1+ CD28+ CD8 T cells with stem cell- like features in a mouse model of T cell exhaustion6-8. The proliferative burst of CD8 T cells after PD-1 blockade comes from this stem-like CD8 T cell population and is dependent on signals from costimulatory molecule CD28. Importantly, our preliminary data suggest that stem-like CD8 T cells are present in non-small cell lung cancer (NSCLC) patients. Based on our observations, *we hypothesize that the stem- like CD8 T cells play a critical role in successful PD-1 targeted therapies in NSCLC patients.* One of the major goals of this proposal is to identify and characterize these stem-like CD8 T cells in NSCLC patients. Another important point to be addressed in this proposal is if the presence of these stem-like CD8 T cells correlates with proliferative responses of CD8 T cells as well as clinical efficacy of the immunotherapies.