Neoantigen-specific T cell responses in exceptional responders to immunotherapy in NSCLC

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Scientific Abstract:

The holy grail in the field of immunotherapy is to identify how immune checkpoint inhibitors (ICIs) induce dramatic and durable responses in some patients, but most patients do not respond. Most groups have focused on tumor mutational burden (TMB) and predicted neoantigens as biomarkers of response, but these approaches have been largely based on bioinformatics and do not identify or evaluate the function of antigen- specific T cells, nor track them over time to correlate with clinical response. No one truly knows how the quality and quantity of tumor-reactive T cells correlate with clinical outcomes. In order to address this problem, we have collected tissue and blood at multiple timepoints from >50 patients with NSCLC who received a-PD-1 immunotherapy as part of a clinical trial at Yale Cancer Center. This cohort will be used to analyze the kinetics, magnitude, and breadth of neoantigen-specific T cells associated with clinical outcomes, including patients who are "exceptional responders" that see long-term durable clinical benefit (LT-DCB), or complete response > 24 months. Our neoantigen-based platform will screen for antigen-specific T cells to compare the quantity and quality of these T cell responses between exceptional responders and non-responders. This project can be accomplished due to interdisciplinary collaborations between the investigators with collective expertise in clinical oncology, T cell memory, antigen discovery, and bioinformatics. Our intent is to uncover key immunological features of anti- tumor T cell responses, such as differences in the magnitude, breadth, and clonality that distinguish patients who respond to a-PD-1 therapy.

Lay Abstract:

A breakthrough in cancer treatment are drugs aimed to revitalize our immune system to attack cancer, also known as immunotherapies. However, the majority of patients are non-responders or their cancer develops resistance months after initially responding to therapy (progressors). A few patients on the other hand, are 'exceptional responders' who experience complete cures with tumors melting away within months. In order to find a "true" cure for cancer, it is critical to understand why some patients' tumors completely regress and others do not. This pilot project will address this question in a way that has not been investigated before by comparing the immune responses induced between 'exceptional responders', 'progressors' and 'non-responders'. By definition, tumors are created by mutations that allow it to outgrow normal tissue. These mutations create 'neoantigens' that could potentially induce immune reactions. Many have tried to identify biomarkers that correlate with positive outcomes, but no study has systematically compared the number or quality of tumor-reactive T cells across these groups to correlate with clinical outcome. We have a time-series of blood samples collected from more than 20 patients with metastatic lung cancer treated with a form of immunotherapy called KEYTRUDA (pembrolizumab) who vary in their responses to treatment. Importantly, we have cryopreserved many T cells from each patient that we can use to enumerate tumor-reactive T cells between patients with

different outcomes. This type of analysis may provide the best understanding of patient responses to immunotherapy to date.