2016 ACS-IRG Pilot Grant

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Project Title: T lymphocyte repertoire determinants of cancer immunotherapy response

Abstract:

Background: The emergence of immunotherapy, encompassing both cellular therapies and agents designed to stimulate the immune system, has initiated a revolution in cancer therapy. Cancer immunotherapy is becoming an increasingly important treatment modality. However, objective responses are observed in only a subset of patients. Several studies have examined tumor-intrinsic factors that affect the anti-tumor immune response. However, the immune system is not a monolithic entity, but rather a dynamic system formed by multiple leukocyte lineages. Principal among these are the extremely diverse repertoire of T lymphocytes that act as both direct mediators of cellular immunity and as regulators of immune responses. Antigen-specificity of the T cell repertoire is shaped throughout human life by stochastic elements, antigen encounter, and clonal selection.

Hypothesis: We propose that patient T cell repertoire is a critical determinant of the success of cancer immunotherapy. We hypothesize that effective clinical response to checkpoint blockade immunotherapy, which enhances natural anti-tumor T cell-mediated immunity, depends on broad T cell repertoires capable of recognizing multiple tumor antigens.

Specific Aims: Determine the T cell repertoire characteristics and effector gene signatures of responding T cells that differentiate clinical response to immune checkpoint blockade in cancer.

Study Design: The study will examine peripheral blood samples from patients undergoing treatment with anti-PD-1 or anti-PD-L1 as treatment for melanoma or head and neck cancer at UCSD Moores Cancer Center. Peripheral blood samples will be taken at baseline, at a time point correlating with clinical response (or time-matched samples from patients without clinical response), and at disease relapse.

Cancer Relevance: Immunotherapy is becoming an increasingly important treatment modality for cancer. However, depending on the underlying disease, many patients do not demonstrate clinical benefit. Identifying T cell-specific factors that differentiate between responders and non-responders could enable development of novel diagnostics to personalize treatment protocols and provide prognostic information during treatment, and develop innovative treatment modalities to support or refine current immunotherapies.