UC San Diego
MOORES CANCER CENTER

2021 Gleiberman Head and Neck Cancer Center Pilot Grant

Interaction-Dependent Identification and Characterization of Tumor Antigen-Specific T Cells for Adoptive Therapy in HNSCC

J Silvio Gutkind, PhD

Scientific Abstract:

Head and neck squamous cell carcinomas (HNSCCs) represent the sixth most common cancer worldwide with an estimated 65,630 cases and 14,500 deaths in the United States last year. Fortuitously, by virtue of their high mutational burden and robust neoantigenome, HNSCCs harbor an abundance of tumor-specific antigen (TSA)-T cells; and, thus, represent an ideal target for autologous adoptive therapy. However, the lack of a reliable biomarker to accurately identify bona fide TSA-T cells among a heterogenous population of tumor-infiltrating lymphocytes (TILs) has precluded the complete translation of this otherwise promising therapeutic strategy. Instead, nearly all ongoing clinical trials employ heterogeneous TILs harvested in bulk, most of which harbor non-TSA, bystander T cells, often terminally differentiated and anergic. Discovering a high-fidelity biomarker to identify and isolate TSA-T cells from a heterogenous TIL pool is paramount to deliver translatable T cell adoptive therapy for HNSCC.

Our central hypothesis is that a rapid and high-throughput method for isolating TSA-T cells that feature stem-like, less differentiated phenotypes will maximize the clinical response of adoptive T cell therapy for HNSCC. To this end, we have developed an interaction-based chemoenzymatic labelling method to rapidly and efficiently identify TSA-T cells. **We aim to profile TSA-T cells identified by proximity-based chemoenzymatic labelling at the single-cell level in a murine model of HNSCC.** Our overall goal is to develop a highly innovative and immediately translatable technique to rapidly identify tumor-specific antigen reactive T cells that can be optimally expanded ex vivo for subsequent adoptive therapy in HNSCC patients.

Lay Abstract:

Cancer immunotherapies have led to major treatment breakthroughs for several different cancers, but the majority of head and neck cancer (HNC) patients do not respond to immunotherapies. Among emerging immunotherapies, autologous delivery of anti-tumor cytotoxic T cells is particularly promising given the highly efficient tumor cell killing potential of cytotoxic T cells and the specificity with which these T cells selectively target tumor cells. While these anti-tumor T cells are abundant in HNC, identifying and isolating them from other non-specific T cells within the tumor represents a major bottleneck in the field. We hypothesize that developing a robust and high-fidelity method to isolate anti-tumor T cells, featuring highly specific tumor cell cytotoxicity, will rapidly advance the translation of this therapeutic option for HNC patients. To this end, we have engineered an interaction-based method in which immune cells that necessarily interact with anti-tumor T cells during T cell priming – a critical event during which T cells gain specificity to tumor proteins – pass a molecular label that irreversibly

and exclusively tags tumor-specific cytotoxic T cells. These molecular labels are readily detectable, and profiling labelled T cells has confirmed their anti-tumor specificity and cytotoxicity. Here, we aim to employ this cellular interaction-based labelling technology to isolate anti-tumor T cells in a mouse model of tobacco- signature HNC and then to study these labelled antitumor T cells at the single cell level. Ultimately, our goal is e way for lowering the cost and accessibility of personalized, autologous T cell-based immunotherapy for HNC patients.