Scientific Abstract

SU2C Single-Cell Multi-omics Convergence Research Team:

"Single-Cell Functional Multi-omics to Characterize and Monitor CAR T Therapy"

[This abstract was provided by the scientists when their application was accepted.]

As the use of immunotherapy becomes more common, especially as first- and second-line treatments, immunotoxicity and autoimmune-like response are emerging as the Achilles' heel of cancer immunotherapy. The exact mechanism of autoimmune response in cancer immunotherapy remains unclear and may differ substantially between patients.

There are two steps of action in T-cell- mediated immunotherapy. The first step is antigen recognition, in which the therapy may have direct off-target toxicity due to expression or cross-presentation of target antigen in normal cells or indirect toxicity due to antigen epitope spreading. The second step is the release of functional signals, e.g., effector cytokines, cytolytic enzymes, etc., from T cells to eradicate tumor cells, which however may elicit unexpected autoimmune effect due to T cell's functional heterogeneity, flexibility and plasticity. For example, Treg cells can be converted into TH17 cells in the presence of IL-6 and TGF-β, which might underlie certain forms of autoimmunity in cancer immunotherapy. The exact functional profile of individual T cells dictating efficacy vs toxicity is inadequately characterized and the mechanism controlling the function of engineered T cells at the transcriptional or epigenetic level is poorly understood. This proposal aims to address this unmet need in response to the SU2C Convergence Q #1 – how can we predict responders and non-responders to CAR therapies and can we predict patients that will develop side effects to these therapies – via combining our single-cell multi-omics technologies and computational models (topology & machine learning) to analyze CAR-T cells from patients.

Despite the demonstrated benefit of emerging chimeric antigen receptor (CAR)-T cancer immunotherapeutics , two major concerns remain:

1) predicting responders and non-responders to CAR therapies pre- infusion, and
2) managing the immuno-toxicity, such as cytokine release syndrome (CRS) and related neurotoxicity, that could be potentially life threatening.

To evaluate the function of engineered T cells for immunotherapy, or endogenous T cells reactivated to battle cancer or infection, a T cell's functional status is largely determined by a spectrum of secreted effector proteins (e.g., cytokines). In a protective immune response, the 'quality' of an immune cell is known to correlate with the extent of polyfunctionality (the ability of a T cell to co-secrete multiple effector proteins).

Scientific Abstract

To detect consistent performance of this "quality" effective and safe response of CAR T cell subsets, a need exists for a new technology to conduct highly multiplexed (30+) measurement of immune effector proteins in single T cells. PI Dr. Fan's laboratory at Yale developed an IsoCode microchip technology to measure up to 42 immune effector function proteins in single cells (see B.1.). Applying it to the characterization of pre-infusion CAR-T product in clinical trials (PIs June and Melenhorst at Penn) revealed a strong association between CAR-T product's polyfunctionality and the objective response of patients. The information obtained with the IsoCode device is rich and can be potentially used to identify cell subsets associated with immunotoxicity and further evaluated with humanized mouse model (Col Halene).

In this project, we will further combine single-cell functional proteomics (IsoCode) and transcriptomics (sc-IsoSeq, see B2) to not only identify cell subsets contributing to therapeutic efficacy vs immunotoxicty (with Microsoft Research Center), but also to reveal the underlying mechanisms by linking transcriptome to CAR-T cell functions at the single-cell level.