Scientific Abstract

SU2C-CRI Cancer Immunology Dream Team:

"Immunologic Checkpoint Blockade and Adoptive Cell Transfer in Cancer Therapy"

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

The goal of the Dream Team is to induce anti-tumor T cell responses either by blocking inhibitory mechanisms intrinsic to T cells thus allowing them to expand, infiltrate and kill cancer cells, or by creating large quantities of such T cells in the laboratory and adoptively transferring these cells back to patients to obtain the same final effects of anti-tumor T cell responses.

The underlying basis for integration of adoptive T-cell therapy (ACT) and checkpoint blockade is that the *in vivo* activity of adoptively transferred T cells will likely be attenuated by interaction of checkpoint receptors, many of which are upregulated upon *in vitro* activation, with inhibitory ligands in the tumor. Therefore, the approaches to evaluate expression of checkpoint ligands in the tumor microenvironment (Aim 1) will be employed to evaluate checkpoint expression in tumor biopsies both pre- and post-ACT with the various proposed engineered T cells. These studies will guide the rational determination of which checkpoint inhibitors would be most likely to enhance the clinical benefit of ACT. Analysis of post-ACT biopsies may further define adaptive responses by tumors to attack by transfer of activated anti-tumor T cells.

Additionally, analyses of T cell repertoire and multiplex analyses of T cell function at the single cell level can be used to study specificity and function of tumor infiltrating lymphocytes in the pre-surgical neoadjuvant checkpoint blockade trials. The non-small cell lung cancer clinical trial analyzing adoptive transfer of T cells engineered for WT1 specificity will be designed in a pre-surgical neoadjuvant format in alignment with the anti-PD-1 pre-surgical neoadjuvant trial, allowing for direct comparative analysis of ACT and checkpoint blockade applied as individual agents. These studies are expected to reveal potential complementarity between the approaches that may further inform combination strategies between these modalities.

The research plan is based on the integration of clinical trials and sample analyses. The Dream Team will conduct clinical trials in patients with several malignancies based on immune checkpoint modulating antibodies, ACT, and combinations of both strategies. Data from these clinical trials will be logged into the MD Anderson Cancer Center database and analyzed by Team members to provide a comprehensive understanding of potential pathways/mechanisms that contribute to anti-tumor responses or enable resistance to therapy. This is a committed Dream Team of scientists who are experts in the field of immunotherapy and will address key factors currently limiting the efficacy and wide applicability of tumor immunotherapy.