Scientific Abstract

SU2C Meg Vosburg T-cell Lymphoma Dream Team

"Tailoring CAR-based Immunotherapy Strategies to T-cell Lymphoma"

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

Genetically engineered immune cells that can recognize and destroy cancer cells are powerful new medicines that promise to revise the way we view cancer treatment. T lymphocytes modified to express a chimeric antigen receptor, or CAR, specific for one or more target molecules on tumor cells, have produced exciting results in different cancers involving the blood cells, including diffuse large B-cell lymphoma. However, extending this outcome to non-B-cell malignancies has been challenging and will require answers to a number of pivotal questions.

To address this issue, we have merged the skills and experience of experts in immunology and immunotherapy, as well as bioinformatics, in a T-cell lymphoma Dream Team that will focus on a difficult-to-treat lymphoma arising in both children and adults (resistant or refractory T-cell lymphoma or TCL).

When treated with conventional therapy, patients with this T-cell disease have a poor outcome. Using a mechanism of multi-institutional clinical trials, coupled with new cell biology techniques and innovative bioinformatics approaches, the Dream Team will test the safety and potency of different types of CAR-engineered immune effector cells directed to different target molecules on the TCL lymphoma cells, with the goal of identifying the optimal CAR platform for infusion into patients.

Team members will also submit emerging information from their clinical trials, such as gene expression profiles, cell phenotypes, tumor antigen expression patterns, and clinical responses for central bioinformatics analysis to identify factors (biomarkers) that shape responses to CAR-based immunotherapy.

Finally, the team will test additional modifications of the CAR platform that could further enhance the safety and activity of these treatments. One example is a strategy to genetically disrupt a tumor growth factor receptor as a means to protect the infused immune cells from attacks by the hostile tumor microenvironment.

One of the major strengths of this proposal is that robust programs in cancer immunotherapy and collaborative research already exist at the four member institutions, which should ensure a seamless integration of resources and personnel across sites.

The clinical impact of our findings will be considerable. They will demonstrate, first of all, the feasibility and likely outcome of using CAR-engineered immune cells to treat resistant cases and will reveal whether such therapy can be made available as a banked ("off-the-shelf ') product that is more rapidly available, at a lower cost, than a typical patient-derived product. They may also identify

reasons for therapeutic failures in certain groups of patients and suggest ways that could be tested to reverse this outcome. Finally, it is worth noting that CAR-based genetic engineering, although beginning to revise the management of cancers such as B-cell lymphomas, still faces many hurdles before gaining wide acceptance and application within the medical oncology community. Studies of the type described here should do much to close that gap.