Scientific Abstract

Pancreatic Cancer Collective Research Team:
"Immunotherapy Targeting Mutant KRAS"

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

This proposal aims to target mutant KRAS (mKRAS) immunologically. We hypothesize that T cell receptors (TCRs) may recognize mKRAS antigens with such fine sensitivity and specificity as to enable the development of precision-engineered TCR adoptive cell therapies (TCR-ACT).

Somatic mutations in KRAS underlie oncogenesis in >95% of pancreatic ductal adenocarcinoma (PDAC), yet there are no KRAS targeted therapies. Drs. Vonderheide and Jaffee have led a prior SU2C-Lustgarten Team that tested novel immune therapies for PDA. More than 600 patients were enrolled across a collaborative network of 6 institutions involving 5 clinical trials. Here, joined by vaccine and neoepitope expert Dr. Beatriz Carreno, we leverage our experience and expertise to test two mKRAS vaccines as a framework to discover and validate a bank of mKRAS-specific TCRs. Identified TCRs (deliverables in Part 1) will enable a clinical study of mKRAS TCR-ACT (Part 2 of this grant).

In prior publications, we have (i) demonstrated reduced PanIN progression in KPC mice vaccinated against mKRAS4, and (ii) identified mKRAS as the most common family of shared neo-epitopes across human cancer. Nevertheless, very few HLA class I/mKRAS peptide complexes have been fully validated, and those that have been reported represent clinically rare opportunities. Hence, further investigation is warranted.

For this proposal, we have developed a screening platform utilizing 3 donor sources to identify mKRAS-specific T cells: (i) healthy individuals, (ii) cancer patients with mKRAS tumors including PDA, and (iii) mKRAS vaccinated PDA patients. In preliminary work, we have successfully generated T cells and cloned TCRs from healthy donors specific for common KRAS mutations and restricted to high frequency HLA-class I alleles. Each proposed vaccine leverages novel technologies developed by team members.

Our goal for Part 1 of this project is to identify validated and broadly generalizable mKRAS-specific TCRs that can be used in Part 2 for novel engineered TCR-ACT. Part 2 would utilize Penn's robust GMP Clinical Cell and Vaccine Production Facility with state-of-the-art experience in CART and DC manufacturing.