Scientific Abstract

Pancreatic Cancer Collective Research Team:

"Adoptive Transfer of TGF-β Resistant TIL to Defeat Immunosuppressive PDAC New Therapies Challenge"

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

The production of transforming growth factor beta (TGF-β) by stromal cells in the tumor has recently been associated with the lack of response to anti-PDL1 agents in a phase II clinical trial in metastatic bladder cancer, as well as in pre-clinical models of colorectal cancer and mammary tumor, associated with a phenotype of immune cell exclusion from the tumor. Lack of tumor infiltration by T cells has been directly linked to the presence of TGF-β in Pancreatic Ductal Adenocarcinoma (PDAC) tumor microenvironment (TME). TGF-β is a well-known potent suppressor of T-cell function -- repressing activation, proliferation, cytotoxicity and cytokine secretion in effector CD4+ and CD8+ T cells.

The Team group has extensive expertise with the treatment of metastatic melanoma patients using expanded tumor-infiltrating lymphocytes (TIL). In a cohort of 74 patients, they have reported a 42% response rate with 20% of the patients enjoying long term progression-free survival. They are pursuing second generation TIL trials in melanoma where they shield the TIL from TGF-β mediated suppression, by genetically modifying the TIL to express a dominant negative TGF- β receptor II, TGFβDNRII. Robust clinical activity was seen in the first 9 patients.

Recently the Team has focused their efforts on cold tumor types where they believe the greatest medical unmet need resides. There is a modest immune infiltrate containing anti-tumor CD8+ TIL in a series of primary and metastatic PDAC samples. These PDAC TIL can be expanded to large numbers *ex vivo*. Based on these results, a pilot trial is ongoing at MD Anderson Cancer Center to assess response to TIL therapy in patients with PDAC. While TIL therapy may be a solution to overcome the paucity of TIL in PDAC, nonetheless, the ability of these TIL to remain functional upon infiltrating the markedly immunosuppressive PDAC tumor microenvironment (TME) is unclear.

Given that TGF-β has been shown to be a key immunosuppressive molecule restricting TIL infiltration in PDAC TME, the Team hypothesizes that TIL engineered to be resistant to TGF-β will overcome the highly immunosuppressive TME found in PDAC and will succeed in eliminating the tumor. Their goal is to develop and test TGFβDNRII-transduced TIL therapy for metastatic PDAC patients.

The Team's aims are:

- Aim 1: Optimization of PDAC TIL retroviral transduction method.
- Aim 2: Test the impact of the expression of TGFβDNRII on PDAC TIL function
- Aim 3: In vivo efficacy of tumor-specific TGFβDNRII-transduced T cells in patient-derived preclinical models of pancreatic cancer