CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120777

Project Title:
P4: Will Suppressing Mast Cell Function Improve Immunotherapy for Pancreatic Cancer?

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Therapy for pancreatic ductal adenocarcinoma (PDAC) have lagged behind advances for most other cancers. PDAC is resistant to most conventional cancer therapies, including immunotherapy. The resistance to immunotherapy is paradoxical. Tumor antigens are found on PDAC cells, and cancer reactive cytolytic T cells are found in the blood of pancreatic cancer patients. Obviously, the immune system can recognize antigen(s) on pancreatic cancer cells and can mount a response against them. But the dismal survival rates suggest that the immune system is not clearing the cancer in the patient. Current thinking suggests that tumor-induced immunosuppression is the reason, and countering immune suppression may provide a new avenue for treatment. Our preliminary findings have indicated that immune regulatory mast cells play an important role in the growth and development of PDAC. Although once considered to function primarily as allergic effector cells, immunologists now realize that mast cells regulate adaptive immunity. In preliminary studies we observed that mast cells are found in both human and mouse PDAC. Increased mast cell numbers in human PDAC is a poor prognostic indicator. Orthotopic implantation of pancreatic tumor cells into mast cell-deficient mice results in decreased tumor growth compared to wild type controls.

This proposal will test the hypothesis that mast cells mediate the local immune suppression that promotes the growth and development of PDAC. Using mouse strains that spontaneously develop pancreatic cancer and faithfully recapitulate the clinical stages, histopathology, and molecular lesions found in human PDAC, we will test the following specific aims: 1: Confirm the essential role of mast cells in the development of PDAC. 2: Determine if agents that inhibit mast cell function will inhibit the induction of PDAC. 3: Determine whether blocking mast cell function in vivo enhances immunotherapy.

Most immunotherapies for cancer simply try to boost immunity. Our approach is innovative because we intent to block mast cell-induced immune suppression while simultaneously activating the immune response (i.e. release the brake and apply the accelerator). In collaboration with Projects 1-3, which focus on enhancing the immune response to pancreatic cancer, we will determine if blocking immune suppression coupled with new approaches to activate the immune response to PDAC, will provide a better approach for pancreatic cancer immunotherapy.