CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140522

Project Title:
Reversing Vaccination-Induced Impairment of Anti-CTLA-4- Based Cancer Therapy

Award Mechanism:
Individual Investigator

Principal Investigator:
Overwijk, Willem

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

Lay Summary:

Anti-CTLA-4 antibody (ipilimumab, Yervoy®) is an effective new therapy for patients with metastatic melanoma that strengthens the immune system's attack on cancer cells. Experimental vaccines against melanoma, including gp100 vaccine, are designed to do the same. Thus it was a surprise when combination of anti-CTLA-4 with gp100 vaccine did not work better, and in fact slightly worse, than anti-CTLA-4 alone. It is important to understand why vaccination did not improve anti-CTLA-4 therapy, because it was expected to be a very effective ways to improve anti-CTLA-4 therapy for the benefit of more patients with melanoma and possible other cancers. Because of these perplexing results, it is now unclear how to combine vaccine therapy with anti-CTLA-4 for more effective cancer therapy. We have confirmed that anti-CTLA-4 activates killer T cells that travel to tumors and destroy them. However, when gp100/IFA vaccination is added, these killer cells became trapped at the vaccine injection site, and can no longer reached the tumor to destroy it. Yet when we designed new vaccines that do not draw in killer cells and instead release them to go the tumor, they acted in concert with anti-CTLA-4 therapy to cause strong tumor shrinkage. In this research proposal, we address 3 questions: 1) Why do killer cells go to vaccination sites instead of tumor sites? 2) How can we best reverse this process by using new and different vaccines that redirect killer cells to the tumor? 3) Can we identify other inhibitory molecules, similar to CTLA-4, to target with new and even more powerful therapies for patients with cancer? Together, the results from this project will increase our understanding of killer cell trafficking to tumors, and identify vaccination strategies that increase the anti-tumor effect of anti-CTLA-4 therapy. In addition, we will identify new lead candidates for the development of completely new immunotherapies for the treatment of patients with cancer.