

Scientific abstract

Hepatocellular cancer (HCC) is a major cause of cancer death globally, and there are no effective systemic therapies for this disease. Previously, we made the novel observation that alpha fetoprotein (AFP) can be recognized by human and murine immune systems. In a murine tumor model, the self-antigen murine AFP can serve as a tumor rejection antigen. We have performed extensive CD8+ T cell epitope mapping and identified several immunodominant and subdominant AFP-derived peptides. In a pilot clinical trial, we immunized AFP+/HLA-A*0201+ HCC patients with the four immunodominant peptides emulsified in adjuvant. These patients were able to respond immunologically by increasing the frequency of AFP-specific T cells in the peripheral blood. We have also tested a DNA prime-adenovirus boost genetic immunization strategy in murine models and found it can approach the levels of immune activation of AFP genetically engineered dendritic cells. In this application, we propose to test this genetic immunization strategy in a phase I/II clinical trial and examine the immunological responses and mechanism in two specific aims.

We will immunize AFP+/HLA-A*0201+ HCC patients in the adjuvant setting with plasmids encoding AFP and GM-CSF then boost with an adenovirus (AdV) encoding AFP. In this aim, we will utilize state-of-the-art immunological assays to detect responses in peripheral blood. By immunizing with the entire 1.8 kb gene, we will stimulate a broad response encompassing CD8+ T cells specific for immunodominant and subdominant epitopes, as well as AFP-specific CD4+ T cells. We will analyze these cells with respect to their frequency, cytokine production, avidity and proliferation. This will indicate not only whether patients have been successfully immunized, but also allow for a thorough immunological assessment of this genetic immunization strategy in human subjects.

To elucidate the mechanism by which injection of plasmid DNA followed by injection of AdV generates T cell responses in human subjects, we will analyze biopsies of AFP vector-injected and control saline injected intradermal sites as well as draining and contra lateral lymph nodes. We hypothesize that the immunizing antigen (AFP) is cross-presented as protein to professional antigen presenting cells (APC) at the vaccine depot which then traffic to draining lymph nodes to interact with T cells. We will test this hypothesis by analyzing draining sentinel lymph nodes and evaluating dendritic cells for vector sequences and their ability to stimulate AFP-specific T cell responses.

These proposed studies will permit us to determine the immunological impact of a plasmid prime-adenoviral boost directed towards a self tumor antigen and to define mechanisms of antigen presentation.