

A PHASE I/II PILOT STUDY OF SEQUENTIAL VACCINATIONS WITH rFOWLPOX-PSA (L155)-TRICOM (PROSTVAC-F/TRICOM) ALONE, OR IN COMBINATION WITH rVACCINIA-PSA (L155)-TRICOM (PROSTVAC-V/TRICOM), AND THE ROLE OF GM-CSF, IN PATIENTS WITH PROSTATE CANCER NCI Protocol Number: 5911

Arlen, Philip, M.

ABSTRACT -Technical

Background:

PSA is a Tumor Associated antigen (TAA) expressed exclusively in prostatic epithelial cells; therefore, it represents an attractive target for immunotherapy. However, TAA have been characterized as weak immunogens because they reflect self proteins. Our goal at the Laboratory of Tumor Immunology and Biology (LTIB), NCI is devising vaccine strategies to activate T-cell responses to TAA to a new threshold of enhanced antitumor activity. These strategies consist of the following: a) pox viral vectors containing the gene encoding the TAA, b) Diversified Prime and Boost Regimens, c) T-cell costimulation, d) cytokines as biologic adjuvants, and e) Agonist epitopes of the TAA. Moreover the potency of these new strategies will be monitored by a unique Elispot assay to measure these immune responses

Hypothesis/Rationale/Purpose:

Based on our evolving understanding of immune responses, we are creating three new constructs using pox vectors, vaccinia TRICOM (rV-PSA-3A, B7-1, ICAM-1, and LFA-3), fowlpox TRICOM (rF-PSA, B7-1, ICAM-1, and LFA-3), and fowlpox-GMCSF that we plan to test in the clinic. We feel that we can elicit with this strategy the strongest T-cell specific response without the development of autoimmunity. It will be through the development of these innovative and more potent vaccine strategies in which these immunologic responses can be translated into improved clinical responses.

Specific Aims: Specific aims

1. To examine the safety of a novel recombinant pox virus based vaccine strategy in patients with metastatic prostate cancer.
2. To evaluate the role of Prime and Boost, Costimulation, and agonist peptides in a Phase I clinical trial concept
3. to measure immunologic responses in a pilot Phase II study- use standard Elispot to detect immunologic responses

Study Design- There are two objectives of this trial. The first objective (Stage 1) is to evaluate the clinical safety of a prime/boost vaccine strategy: priming with a recombinant vaccinia containing the genes for prostate specific antigen (PSA) and a triad of costimulatory molecules (rV-PSA-(L155)-TRICOM) with subsequent monthly boosts using Fowlpox-PSA(L155)-TRICOM (rFOWLPOX-PSA (L155)-TRICOM (PROSTVAC-F/TRICOM). Stage 2 will be conducted as a small, randomized pilot study to compare the immunologic effects of the above vaccine strategy alone, with recombinant GM-CSF, or with either of 2 doses of fowlpox-GM-CSF. The clinical objectives of this proposal will be:

1. To determine the maximum tolerated dose and toxicity profile of this novel PSA-based vaccine, rF-PSA-3A-TRICOM either alone or in combination with a second vaccine, rV-PSA-3A- TRICOM in patients with metastatic adenocarcinoma of the prostate.
2. To determine the impact of colony stimulating factors (GM-CSF and fowlpox-GMCSF) on the immunologic response in patients treated with these vaccines.
3. To determine the change in PSA-3 directed T cells in patients treated with these vaccines using the standard Elispot assay
4. To document any objective antitumor responses that occur.

Relevance

We believe that in order for a therapeutic vaccine to be effective one must rigorously prove a maximal immunologic response. We feel based on our preclinical data that the use of these three new strategies have the ability to enhance T-cell responses to a TAA (i.e. PSA). These strategies are: 1. Diversified Prime and Boost 2. T-cell costimulation- TRICOM 3. PSA agonist 4. Cytokines (GM-CSF or fowlpox-GMCSF)