

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

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ABSTRACT –non technical

We have previously shown that vaccines can be created against a number of different targets expressed on cancer cells that can be used for therapy against those cancers. PSA is one such target, overexpressed on prostate cancer and rarely expressed on normal tissues. Thus it makes an attractive target for immune therapy. However, we know from our experience that directly injecting PSA protein into a cancer patient produces little if no antitumor activity. Our goal at the Laboratory of Tumor Immunology and Biology (LTIB), NCI is devising vaccine strategies for prostate cancer and other solid tumors, to activate T-cell responses to PSA to a new threshold, which in turn may translate into anticancer activity. These strategies consist of the following: a) Using pox viral vectors containing the gene for PSA which can deliver our target to the immune system in a very efficient manner and increase the immune responses to the target (vaccinia and fowlpox). b) Diversified Prime and Boost- in which we use two different delivery vectors containing PSA which we have previously shown to produce increases in immune responses against that target (1 vaccination priming with vaccinia followed by multiple fowlpox vaccine boosts), c) T-cell costimulation-necessary to activate specific T cells which are necessary to destroy tumor cells (TRICOM), d) cytokines as biologic adjuvants-helps the immune system amplify responses against the tumor target, and e) Agonist epitopes of the PSA (PSA-3A)-which may help the immune system destroy the tumor. Moreover, we have developed an assay to measure immune responses, Elispot assay which allows us to determine if patients receiving the vaccines are mounting increases in immune responses specifically against our target, PSA

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 harming normal cells in our body. 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: 1. Demonstrate that this strategy can be delivered in the clinic as a Phase I trial to obtain safety data with dose escalation, 2. to measure immunologic responses- using the standard Elispot Assay

Study Design- The clinical objectives of this proposal will be:

1. To determine the maximum dose of vaccine of this novel PSA vaccine that can be given safely to patients with prostate cancer which has spread to other parts of the body.
2. To determine the immune responses in patients treated with these vaccines using both the standard Elispot assay analysis versus the modified assay,
3. To document any objective antitumor responses including decreasing or stabilizing PSA levels or decreasing or stabilizing lesions noted on radiographs.

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 four 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 and fowlpox-GMCSF)

We have also developed a modified Elispot assay which is more sensitive in detecting such responses. We hope to demonstrate that increased immunologic responses may translate into improved clinical responses in patients with prostate cancer, and would eventually combine this approach with other therapeutic modalities.