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Systemic T Lymphocyte Responses to HPV 16 E6 and E7 peptides and Local Cervical Inflammatory Changes in Women with CIN III Treated with Heat Shock Protein-Based Immunotherapy

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Abstract:

Objectives: SGN-00101 (HspE7, Nventa, San Diego, CA) is a novel therapeutic vaccine composed of a fusion protein with an *M. Bovis* BCG heat shock protein (Hsp65) covalently linked to the entire sequence of HPV 16 E7. Here we present some of the translational work of a Phase II trial (NCI 5850) that was designed to evaluate the efficacy and toxicities of HspE7 immunotherapy in HIV(-) women with CIN III. Specific aims were to examine: 1) The association between in-vitro systemic T cell responses to pooled HPV 16 E6 and E7 peptides and clinical response and 2) The relationship between clinical outcome and inflammatory changes in post-vaccination LEEP specimens .

Methods: Women with biopsy-proven CIN III underwent three monthly subcutaneous vaccinations of 500 µg of HspE7 followed by an observation period of up to 7 months followed by a LEEP. Venipuncture was performed at 5 of the clinical visits and PBMCs were cryopreserved. CD4 and CD8 positive T cells were activated with pooled E6 and E7 peptides and tested for interferon gamma production and degranulation (CD107 a/b staining) using flow cytometry. Blinded histologic sections of the final cervical conization specimens were independently graded for inflammation using a standardized protocol (0 no inflammation and 4 the highest level of inflammation). Standard clinical response evaluations were made based on the final cervical cone biopsy pathology.

Results: A total of 57 evaluable patients completed the vaccinations and underwent cervical conization. There was significantly more stromal inflammation in the cervix specimens from patients who did not undergo regression ($p=0.04$ using Mann-Whitney test). Inflammation did not correlate with type-specific HPV infection. Preliminary data reveal no correlation between clinical response to vaccination and in vitro T cell responses.

Conclusions: There was significantly more cervical inflammation in patients who did not undergo regression after HspE7 immunotherapy. Local inflammation did not correlate with type-specific HPV infection or systemic T cell responses to HPV peptides; however, this study may be underpowered to predict these observations in this subset of women with heterogeneous T cell responses. Further studies to examine the T-cell subsets that are locally and systemically correlated with clinical regression to immunotherapy are currently underway.

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