A Novel Alphavirus Vaccine Encoding Prostate-Specific Membrane Antigen Elicits Potent Cellular and Humoral Immune Responses

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Purpose: Prostate-specific membrane antigen (PSMA) is an attractive target for active immunotherapy by virtue of its abundant expression in advanced prostate cancer and limited extraprostatic expression. Alphavirus-based vaccine vectors have demonstrated preclinical promise in eliciting immune responses to poorly immunogenic tumor antigens. This study investigated the immunogenicity in mice of non-replicating alphavirus vaccine replicon particles that encode PSMA (PSMA-VRP).

Experimental Design: Mice were immunized with single subcutaneous or multiple ascending doses of PSMA-VRP and evaluated for the magnitude, durability and epitope specificity of the anti-PSMA immune response. Antibodies to native, cell-surface PSMA were measured by flow cytometry, and CD8+ and CD4+ T cell responses were measured by interferon-γ ELISPOT. The cellular responses elicited in BALB/c and C57BL/6 mice were mapped using overlapping 15-mer PSMA peptides.

Results: Robust T and B cell responses were elicited by a single injection of 2 × 10^5 infectious units (IU), and responses were boosted following repeat immunizations. Anti-PSMA responses were detected following three immunizations with 102 IU and increased at doses ranging to 106 IU without overt toxicity. PSMA-specific responses were characterized by Th-1 cytokines and IgG2a/IgG2b antibodies. The T cell responses in BALB/c and C57BL/6 mice were directed towards different PSMA peptides.

Conclusions: PSMA-VRP elicited potent, Th-1-biased cellular and humoral immunity in mice, and specific anti-PSMA responses were significantly boosted upon repeat dosing. PSMA-VRP represents a promising approach for immunotherapy of prostate cancer.