THE EPITOPE-ENHANCED TARP PEPTIDE CAN INDUCE SPECIFIC T CELLS THAT CAN RECOGNIZE WILD-TYPE TARP TETRAMER BY EITHER PEPTIDE OR PEPTIDE-PULSED DC VACCINATION IN PATIENTS WITH PROSTATE CANCER

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Background TARP is expressed in >90% of prostate cancer throughout Gleason score and stages. Two TARP-targeting vaccines were developed at the NCI (figure 1). HLA-A*0201-restricted epitopes Wild Type 27-35 (TARP27-35WT) and Epitope-Enhanced 29-37(9V) (TARP29-37(9V)EE) of TARP were injected with an adjuvant or on autologous dendritic cells (DCs). Previously, the first-in-human clinical trial studying TARP-targeting vaccines in biochemically recurrent prostate cancer was reported.1,2 This is a follow-up report focused on immunogenicity.

Methods TARP-specific T cell responses were assessed on study weeks 0, 12, 18, and 24 with vaccinations at weeks 3, 6, 9, 12, and 15 (Peptide vaccine =21, DC vaccine =20). PBMCs to assess the T cell response were collected and cryopreserved for batch testing. PSA was tested every 3 weeks. PSA-slope log was calculated using the MSKCC nomogram. Decreased PSA-slope log following vaccination at week 24 or week 48 was defined as the study-specific response as previously reported.

Thawed PBMCs were in vitro stimulated (IVS) with either TARP27-35WT, TARP29-37EE, or TARP29-37WT-pulsed monocytes in the presence of IL-7.[1] After 7 days of IVS, the cells were tested for tetramer-specific T cells by flow cytometry and for peptide-specific IFN-gamma response by ELISPOT.

Results Peptide-pulsed DC immunization induced tetramer-positive T cells at weeks 12, 18, and 24 post-immunization. The TARP29-37EE peptide performed as intended to induce specific T cells, the vast majority of which reacted equally well to the WT version of the EE sequence by 2-color flow cytometry. Only a small proportion reacted uniquely to EE, but not to the WT version of the EE sequence by 2-color flow cytometry.

Conclusions This first-in-human TARP vaccine study of peptide versus peptide-loaded DC platforms showed immunogenicity by peptide-HLA-tetramer assay and ELISPOT to detect IFN-gamma-producing cells. Importantly for proof-of-principle, the T cells recognizing the EE peptide immunogen recognized equally well the WT counterpart present in the tumor, as required for epitope-enhancement to be effective. The ability of high IFN-gamma ELISPOT response to the vaccine peptides to predict clinical responsiveness as measured by decreased PSA-slope log supports a protective role of antigen-specific T cells.

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REFERENCES

Ethics Approval The study was approved (09C0139) by the Institutional Review Board of the National Cancer Institute/NIH. All participants were informed of the investigational nature of the study and provided written informed consent prior to enrollment.

Abstract 557 Figure 1 Structure of TARP and peptides used in TARP vaccines
A) Structure of TARP; TARP peptides in the vaccines; B) peptide vaccine in ISA51 adjuvant; C) Manufacturing of TARP-DC vaccine.

Abstract 557 Figure 2 TARP-specific CD8 T cells were detected by tetramer.
A. PBMCs from patients immunized with peptide-pulsed DC were stained with either TARP27-35WT, TARP29-37EE, or TARP29-37WT-specific tetramers after 7 days of in vitro stimulation (IVS) (% Tetramer-positive CD8 T cells minus background; error bar = SEM). Note: TARP29-37WT was not used in the vaccine; R, responder; NR, nonresponder. B. Representative FACS plot of the tetramer staining; top, TARP29-37EE and TARP29-37WT co-stained, bottom, TARP27-35WT stained alone.
Abstract 557 Figure 3  The highest IFN-gamma ELISPOT responses against TARP peptide
Six patients with the highest IFN-gamma ELISPOT responses of PBMCs to one or both vaccine peptides at serial time points were all among the responders based on decrease in PSA-slope log at week 24 or 48. Patient's study number and stimulating peptides are indicated at the bottom. Colored bars represent different time points. Vertical axis is IFN-gamma ELISPOTs per 100,000 cells.