

**813** **CANCER VACCINE TRIPLE SYNERGISTIC COMBINATION  
IMMUNOTHERAPY ENHANCES ANTI-CANCER EFFICACY**

<sup>1,2</sup>Jay Berzofsky\*, <sup>2</sup>William Becker, <sup>2</sup>Purevdorj Olkhanud. <sup>1</sup>NIH, Bethesda, MD, USA;  
<sup>2</sup>National Cancer Institute, Bethesda, MD, USA

**Background** The discovery of checkpoint inhibitors (CPIs) has revolutionized cancer treatment, but many cancers remain resistant. In many cases, resistant tumors are considered “cold” because they lack infiltrating T cells that can be reinvigorated by the CPIs. Cancer vaccines may overcome this resistance by inducing the needed T cell immune response against the tumor. Conversely, cancer vaccines may not be effective alone if immunoregulatory mechanisms inhibit the immune response. Overcoming such regulatory mechanisms by CPIs or other immunomodulatory agents can improve vaccine efficacy. Thus, these complementary therapies can synergize

**Methods** Here we used a B6 mouse tumor model, TC1, expressing HPV16 E6 and E7 oncogenes, and utilized a vaccine consisting of an E7 synthetic long peptide 43-77 combined with alpha-galactosylceramide (a potent NKT cell agonist) and GM-CSF as adjuvants. We examined combinations of CPIs with the vaccine for increased efficacy in control of TC1 tumor growth.

**Results** We found triple synergy among the E7 vaccine, anti-TIGIT, and anti-PD-L1, more effective than any pairwise combination. Further, whereas the protection was dependent on CD8 T cells, depletion of CD4 T cells surprisingly improved the vaccine response, suggesting it was removing a suppressive CD4 T cell. Experiments are in progress to determine whether this putative suppressive cell is a Foxp3+ Treg cell. The triple therapy enhanced the number of E7-specific T cells infiltrating the tumors by tetramer staining. Further, the triple therapy was effective, although slightly less so, in aged mice as in young mice, suggesting it may be effective in older humans in whom cancer is more frequent.

**Conclusions** These studies show proof-of-concept for use of a synergistic combination of cancer vaccine immunotherapy to generate tumor-specific T cells and multi-checkpoint inhibitor therapy to overcome resistance in order to inhibit tumor growth and improve survival in mouse cancer models that is translatable to human cancer patients.

**Ethics Approval** This study was approved by the NCI Animal Care and Use Committee under ACUC Protocol METB-033.

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