Synergy of Immune Checkpoint Blockade with a Novel Synthetic Consensus DNA Vaccine Targeting TERT

Elizabeth K. Duperret,1 Megan C. Wise,2,3 Aspen Trautz,4 Daniel O. Villarreal,3 Bernadette Ferraro,2 Jewell Walters,2 Jian Yan,2 Amir Khan,2 Emma Masteller,2 Laurent Humeau,2 and David B. Weiner1

1Vaccine Center, The Wistar Institute, Philadelphia, PA 19104, USA; 2Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA 19462, USA; 3University of Pennsylvania, Philadelphia, PA 19104, USA

Immune checkpoint blockade antibodies are setting a new standard of care for cancer patients. It is therefore important to assess any new immune-based therapies in the context of immune checkpoint blockade. Here, we evaluate the impact of combining a synthetic consensus TERT DNA vaccine that has improved capacity to break tolerance with immune checkpoint inhibitors. We observed that blockade of CTLA-4 or, to a lesser extent, PD-1 synergized with TERT vaccine, generating more robust anti-tumor activity compared to checkpoint alone or vaccine alone. Despite this anti-tumor synergy, none of these immune checkpoint therapies showed improvement in TERT antigen-specific immune responses in tumor-bearing mice. CTLA-4 therapy enhanced the frequency of T-bet+/CD44+ effector CD8+ T cells within the tumor and decreased the frequency of regulatory T cells within the tumor, but not in peripheral blood. CTLA-4 blockade synergized more than Treg depletion with TERT vaccine, suggesting that the effect of CTLA-4 blockade is more likely due to the expansion of effector T cells in the tumor rather than a reduction in the frequency of Tregs. These results suggest that immune checkpoint inhibitors function to alter the immune regulatory environment to synergize with DNA vaccines, rather than boosting antigen-specific responses at the site of vaccination.

INTRODUCTION
The magnitude of an adaptive immune response to a foreign antigen is determined not only by the strength of interaction between the major histocompatibility complex (MHC) and the T cell receptor (TCR) but also by co-stimulation at the immunological synapse.1 Without co-stimulation, T cells will fail to initiate an effective immune response. Additional co-stimulatory molecules or immune checkpoint molecules exist to control the amplitude of T cell activation to prevent autoimmune responses. These immune checkpoints (CTLA-4, PD-1, LAG3, and TIM3) are often necessary for initiation of an immune response; however, as antigen persists, these checkpoints ultimately serve to dampen the T cell effector function against the foreign antigen.2 CTLA-4, PD-1, LAG3, and TIM3 are all expressed on T cells and limit T cell effector activity. Antibodies blocking these molecules have been shown to augment the effector activity of tumor-specific T cells and additionally inhibit regulatory T cell (Treg) activity and reduce tumor burden in preclinical models and/or in clinical trials as mono-therapies.3–5

In particular, blockade of the immune inhibitory checkpoints PD-1 or CTLA-4 has shown promising results in the clinic for dozens of tumor types, and PD-1 blockade has become a standard of care for melanoma and non-small-cell lung cancer.6–8 However, response rates to these mono-therapies are relatively low (33.7% response for pembrolizumab [z-PD-1] and 11.9% response for ipilimumab [z-CTLA-4] in melanoma patients), leaving room for improvement.9 The lack of response for the majority of such patients may be due to a lack of pre-existing tumor-associated T cell responses. Strategies to combine PD-1 or CTLA-4 blockade with therapies that prime T cells, such as radiation or irradiated cell-based vaccines, have shown improvements in pre-clinical models or in clinical trials.5,10–17 These approaches, however, may rely on T cell responses to neo-antigens within the tumor.18,19 Enhanced T cell priming by vaccines may therefore be required to break tolerance to self-antigens for patients with poor response to immune checkpoint blockade. However, the mechanistic interactions between immune checkpoint blockade antibodies and vaccines are poorly understood.

Therapeutic peptide or DNA vaccination represents a more targeted approach for directing T cells toward specific, less variable tumor-associated antigens (TAs). In mouse models, peptide vaccines have been shown to synergize with immune checkpoint blockade.20,21 However, peptide vaccines are histocompatibility leukocyte antigen (HLA) restricted and therefore cannot be used for all patients. Unlike peptide vaccines, synthetic DNA (synDNA) vaccines are not HLA restricted, are robustly presented on both MHC class I and MHC

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Correspondence: David B. Weiner, The Wistar Institute, 3601 Spruce St., Philadelphia, PA 19104, USA.
E-mail: dweiner@wistar.org
Figure 1. Delivery of αCTLA-4 or αPD-1 Post-first Vaccination Synergizes with TERT DNA Vaccine above Checkpoint Alone in Generating Anti-tumor Immune Response

(A) Experimental setup. Mice were implanted with TC-1 tumor cells on day 0 and then immunized four times at 1-week intervals starting 7 days after tumor implant. Mice were given antibodies (200 μg per mouse) every 3 days starting 1 day after the first immunization. Antibody delivery was continued until 1 week after the final vaccination. (B, D, F, and H) Tumor volume measurements over time for naive mice, mTERT vaccine-treated mice, or mice treated with mTERT vaccine plus αCTLA-4 (B), αPD-1 (D), or a combination of αCTLA-4 and αPD-1 (F). (C, E, and G) Mouse survival over time for naive mice, mTERT vaccine-treated mice, or mice treated with mTERT vaccine plus αCTLA-4 (C), αPD-1 (G), or a combination of αCTLA-4 and αPD-1 (G). For (B)–(G), n = 12–13 mice per group. (H) Tumor volume measurements over time for naive mice

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