Gp96-Ig/costimulator (OX40L, ICOSL, or 4-1BBL) Combination Vaccine Improves T cell Priming and Enhances Immunity, Memory, and Tumor Elimination

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Abstract

The excitement in the field of immuno-oncology over the last several years, driven largely by the clinical success of checkpoint inhibitors, is tempered by the fact that only 10-40% of patients respond to these drugs given as monotherapy. It is widely believed that to improve efficacy and patient outcome, new approaches that combine treatments with more than one functionality are needed. We have developed a next generation cellular vaccine platform—referred to as ComPACT— that incorporates a tumor antigen chaperone (gp96-Ig) with T cell co-stimulatory molecules (e.g., OX40L or ICOSL) into a single tumor cell line that secretes them both (recently published in Cancer Immunology Research, 2016).

ComPACT primes both antigen-specific CD4+ and CD8+ T cells, and stimulates activation of CD122+ILR5+1 memory precursor cells. Systemic administration of OX40L antibodies led to proliferation of non-specific CD4+ T cells, Tregs and systemic inflammatory cytokine production. Importantly, ComPACT led to high frequencies of IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-2 production by antigen-specific CD8+ T cells at both priming and boosting, which enhances rejection of established murine melanoma (B16.F10) and colon cancer (CT26) tumors and increased overall survival.

Here, we have assessed ComPACT in a 3rd tumor model (MC38—colorectal carcinoma) and show that it synergizes effectively with PD1 and PD-L1 antagonist antibody therapies, amplifying antigen-specific T cell responses, and eliminating tumors. ComPACT/PD1 or PD-L1 combinations may therefore translate into an efficacious approach to treat human cancers.

Gp96-Ig / T Cell Co-stimulator Synergy

Figure 1. Testing synergy between ImPACT and T cell co-stimulators. (A) Diagram of co-stimulator receptors and ligands on T cells and antigen presenting cells (APC). (B) Schematic of gp96-Ig ImPACT vaccine. (C) Co-stimulator antibodies analyzed.

ImPACT Synergy with OX40 Agonist

Figure 2. OX40 antibody synergizes with gp96-Ig vaccine resulting in T cell expansion. Mice adoptively transferred with OT-I (SCID) cells via tail vein injection (day -1), were vaccinated with ImPACT + OX40(ab) antibodies on day 1, and analyzed by flow cytometry on day 35.

ComPACT Exhibits Strong Anti-tumor Efficacy

Figure 3. ComPACT amplifies antigen exclusive T cells. (A) OT-I (CD8+) T cell expansion time-course with boost on day 35. (B) Memory phenotype analysis by flow cytometry in splenocytes (top) and peripheral (bottom) cells on day 8. (C) Immune cell activation after either ComPACT/OX40L or OX40 agonist antibody treatment.

Figure 4. ComPACT increases TIL, blocks tumor growth, and increases survival. Top: CT26 – Murine colon cancer model. (A) Tumor growth, (B) overall survival, and (C) AH1-tetramer+ cells found in CD8+ splenocytes on day 12. Bottom: B16.F10 – Murine melanoma tumor model. (A) Tumor growth, (B) overall survival, and (C) SIINFEKL-tetramer+ intra-tumoral T cells (TL) on day 13.

Figure 5. ComPACT synergizes with PD1/PDL1 checkpoint inhibition to enhance tumor rejection, antigen-specific T cell expansion, and memory response.

Key Concepts

-ComPACT amplifies antigen-specific CD4+ and CD8+ T cells at both priming and boosting, and more MPEC than OX40 agonist antibodies.
-ComPACT demonstrates antigen specificity, without the off-target systemic inflammatory signature seen with OX40 agonist mAbs.
-ComPACT synergizes with checkpoint inhibition (µPD1 and µPDL1) to maximize antigen-specific T cell proliferation, memory cell response, and tumor eradication.
-ComPACT delivers a vaccine and co-stimulatory fusion protein in a single compound, and synergizes strongly with checkpoint inhibitors. Future combinations of the two may significantly improve patient outcomes.

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