P118

Gp96-Ig/costimulator Combination Vaccine Improves T cell Priming and Enhances Immunity, Memory, and Tumor Elimination

Louis González, Louise Giffin, Jason Rose, George Fromm, Suresh De Silva, Taylor Schreiber, Rahul Jasuja & Jeff Hutchins
Heat Biologics, Durham, NC, USA; Pelican Therapeutics, San Antonio, TX, USA

Abstract

The recent excitement in the field of immuno-oncology has been driven largely by the clinical success of checkpoint inhibitors. This success is tempered by the fact that monotherapy succeeds in only 10-40% of patients. It is widely believed that to improve patient outcomes, new approaches that combine treatments with more than one functionality will be required.

We have developed a next generation cellular vaccine platform – referred to as ComPACT (COMbination Pan-Antigen Cytotoxic Therapy), that incorporates a tumor antigen chaperone (gp96-Ig) with T cell costimulation (OX40L.Ig and TL1a.Ig), into a single anti-tumor cell line that secretes one or both(Cancer Immunol Res. 2016 Sep 2;4(9):766-78).

ComPACT primes both antigen-specific CD4+ and CD8+ T cells, and stimulates activation of CD127+KLRG-1- memory precursor cells. Systemic administration of OX40 agonist antibodies led to toxic proliferation of non-specific CD4+ T cells, Tregs and systemic inflammatory cytokine production. Importantly, ComPACT led to high frequencies of IFNγ+, TNFα+, granzyme-b+ and IL-2+ antigen-specific CD8+ T cells at both priming and boosting, which enhanced rejection of established murine melanoma (B16.F10) and colon cancer (CT26) tumors and increased overall survival.

Here, we have assessed ComPACT in combination with a checkpoint inhibitor and an additional cell-secreted administered T cell costimulator (TL1A.Ig) and show that they synergize effectively with antagonist antibody therapies, amplifying antigen-specific T cells, programming a memory response, and eliminating tumors. ComPACT/αPD1 or αPD-L1 combinations may therefore translate into an efficacious approach to treat human cancers.

gp96Ig and T cell Co-Stimulators

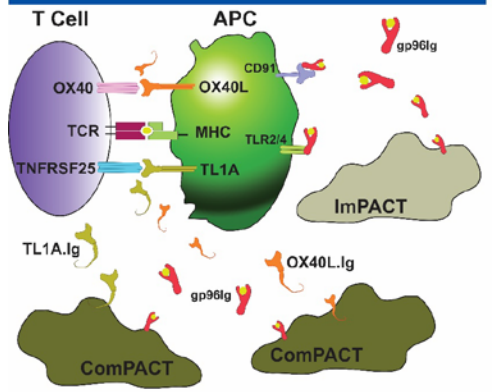

Figure 1. Synergy between ImPACT, ComPACT and T cell co-stimulators. Vaccination with ImPACT or ComPACT generates peptide-loaded gp96Ig complexes that are sensed by scavenger receptor CD91 and TLRs 2/4 as immune activating "danger" signals. Activated APC cross-present antigens to cognate T cells, co-stimulatory molecules (OX40L and TL1A) can enhance proliferation, function, and memory formation. Co-stimulatory molecules, usually provided by pro-inflamatory APC, can be provided by our next-generation vaccine platform, ComPACT, enhancing the quality of the activated effector cell.

ImPACT Synergy with OX40 and TNFRSF25 Agonists

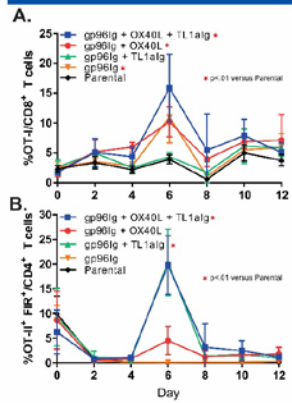

Figure 2. ImPACT synergy with Co-Stimulators. C57BL/6 mice (n=5, group) were adoptively transferred with syngeneic 10^5 OT-I GFP cells and 10^5 OT-II FIR cells on day -2. On Day 0, the mice were vaccinated with B16.F10 cells transfected to express gp96Ig and TL1a.Ig; OX40 stimulation was delivered using an agonist antibody. Mice were monitered for expansion of OT-I and OT-II cells by flow cytometry on the days indicated. A) The addition of OX40 stimulation and TL1a.Ig to ImPACT vaccinations leads to greatest expansion of OT-I cells. TL1a.Ig alone is a poor costimulator; however OX40L stimulation alone leads to robust costimulation. B) The addition of TL1a.Ig augments Treg expansion whereas OX40 stimulation does not.

ComPACT & Anti-Tumor Efficacy

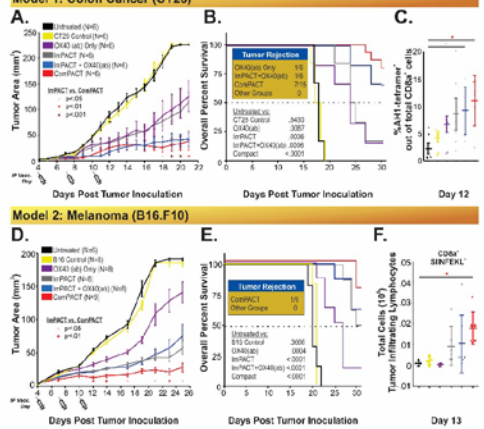

Figure 3. ComPACT increases TIL, blocks tumor growth, and increases survival. *Top: CT26 – Murine colon cancer model.* (A) Tumor growth, (B) overall survival, and (C) AH1-tetramer+ cells found in CD8+ splenocytes on day 12. *Bottom: B16.F10 – Murine melanoma tumor model.* (D) Tumor growth, (E) overall survival, and (F) SIINFEKL-tetramer+ intra-tumoral T-cells (TIL) on day 13.

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ComPACT, Checkpoint Inhibitors & Anti-Tumor Immunity

Model 3: Colorectal Carcinoma (MC38)

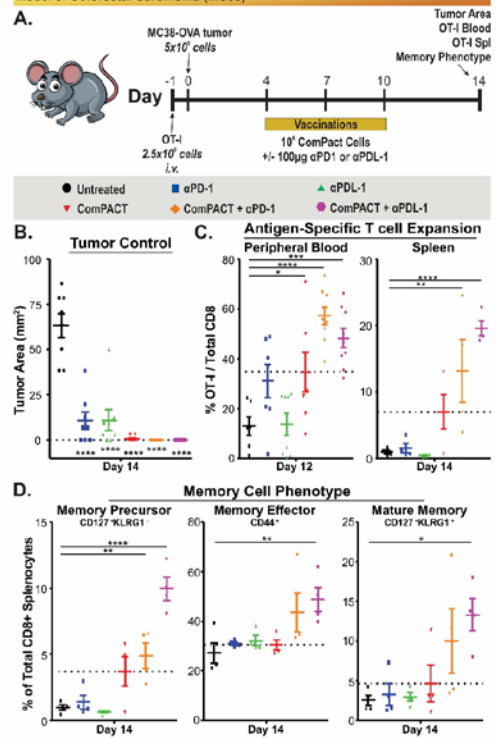

Figure 4. ComPACT synergizes with PD1/PDL1 checkpoint inhibition to enhance tumor rejection, antigen-specific T cell expansion, and memory response.

(A) Schematic of MC38 – Murine colorectal carcinoma model. ComPACT and checkpoint inhibition (both αPD-1 and αPDL-1) synergize to (B) control tumor growth, (C) amplify antigen-specific CD8+ T cells in the spleen and peripheral blood, and (D) generate a robust memory T cell response.

Tumor Models. For all tumor models: $5x10^5$ cells were injected into the rear flank on day 0 and mice were treated on days 4, 7 and 10 once tumors had established.

Statistical Analysis. One-way ANOVA was used for all sample group analyses. Significance is denoted by *: *p<.05, **p<.01, ***p<.001, and ****p<.0001. Sample sizes noted in experiments are from ≥3 distinct biological replicates with bars as SEM.

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 (***αPD1 and αPDL1***) 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.