



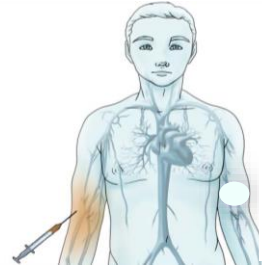
Introduction of ComPACT

Combination Pan-Antigen Cytotoxic Therapy

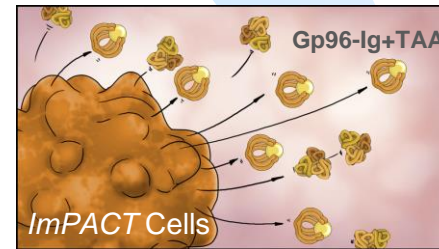
June 15, 2015

ImPACT Immunotherapy Platform

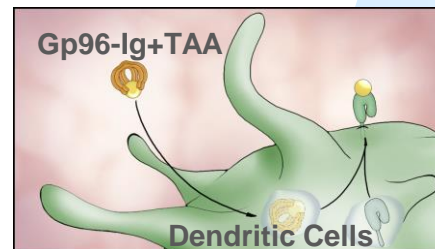
Specifically Activates Pan-Antigen CD8+ T-Cells to Kill Tumor Cells



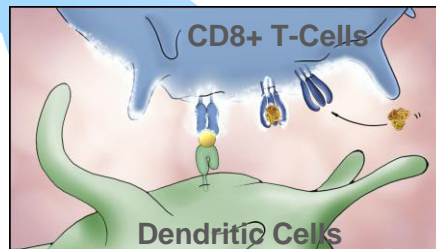
①
Intradermal Injected
ImPACT Cells



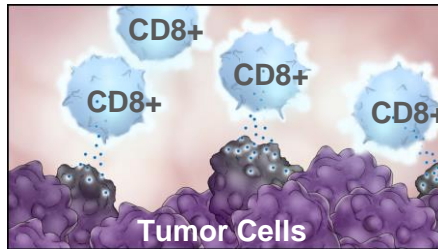
②
ImPACT cells
secrete Gp96-Ig
chaperone + tumor
antigens (TAA)



③
Dual antigen carrier
& adjuvant activates
Dendritic Cells



④
Selectively
activate
CD8+ T-Cells



⑤
CD8+ T-cells
circulate &
eliminate
tumor cells

Combination Immunotherapy Design Objectives

We all know that combination immunotherapy will provide superior clinical benefit than any single checkpoint, co-stimulator or vaccine can as monotherapy.

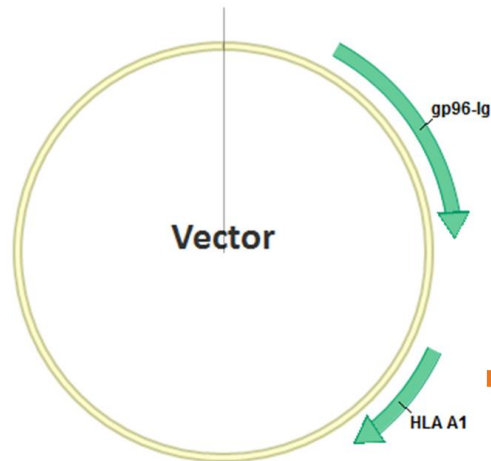
How can we implement combination therapy:

1. In the simplest and most efficacious way
2. With the lowest possible toxicity
3. With a simpler cost structure than $1+1+n$ mAbs/biologics

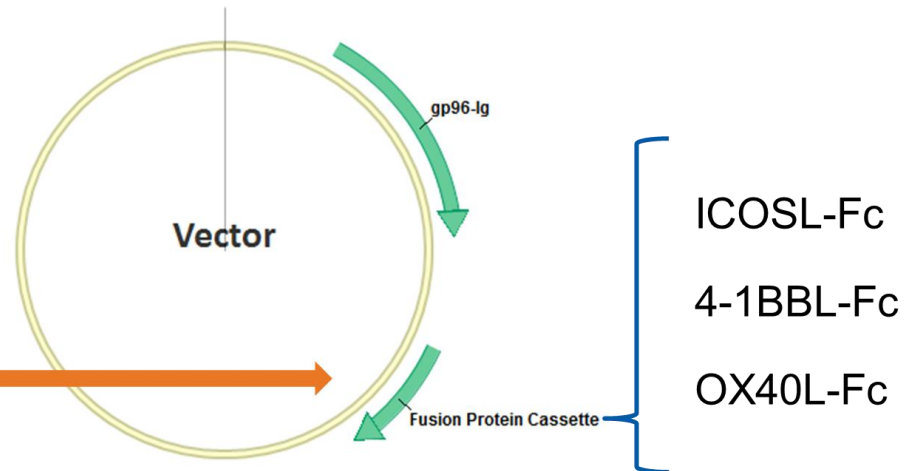
ComPACT Design

Combination Pan-Antigen Cytotoxic Therapy

Original Vector Construct



Combination IO Vector



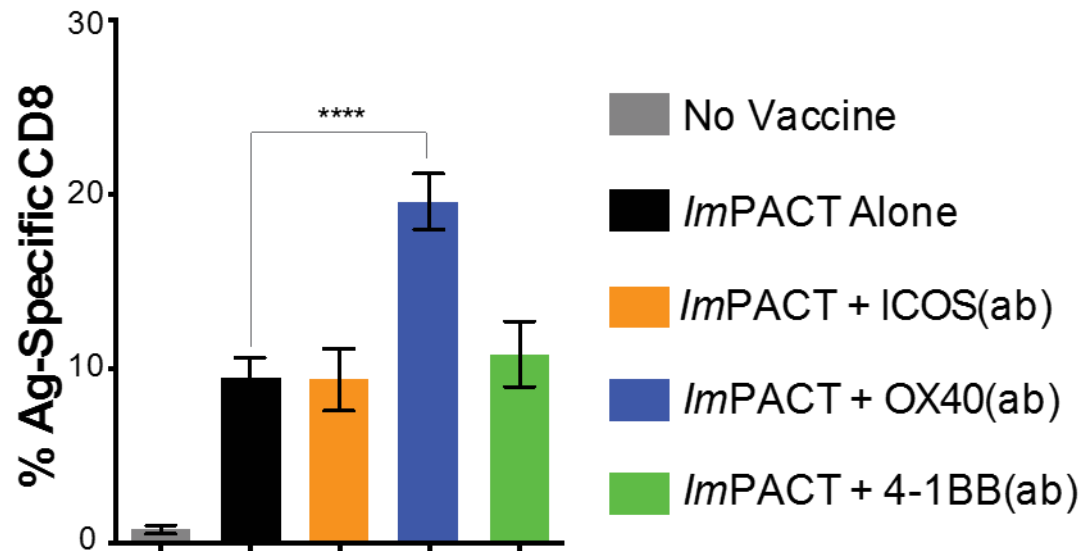


gp96-Ig

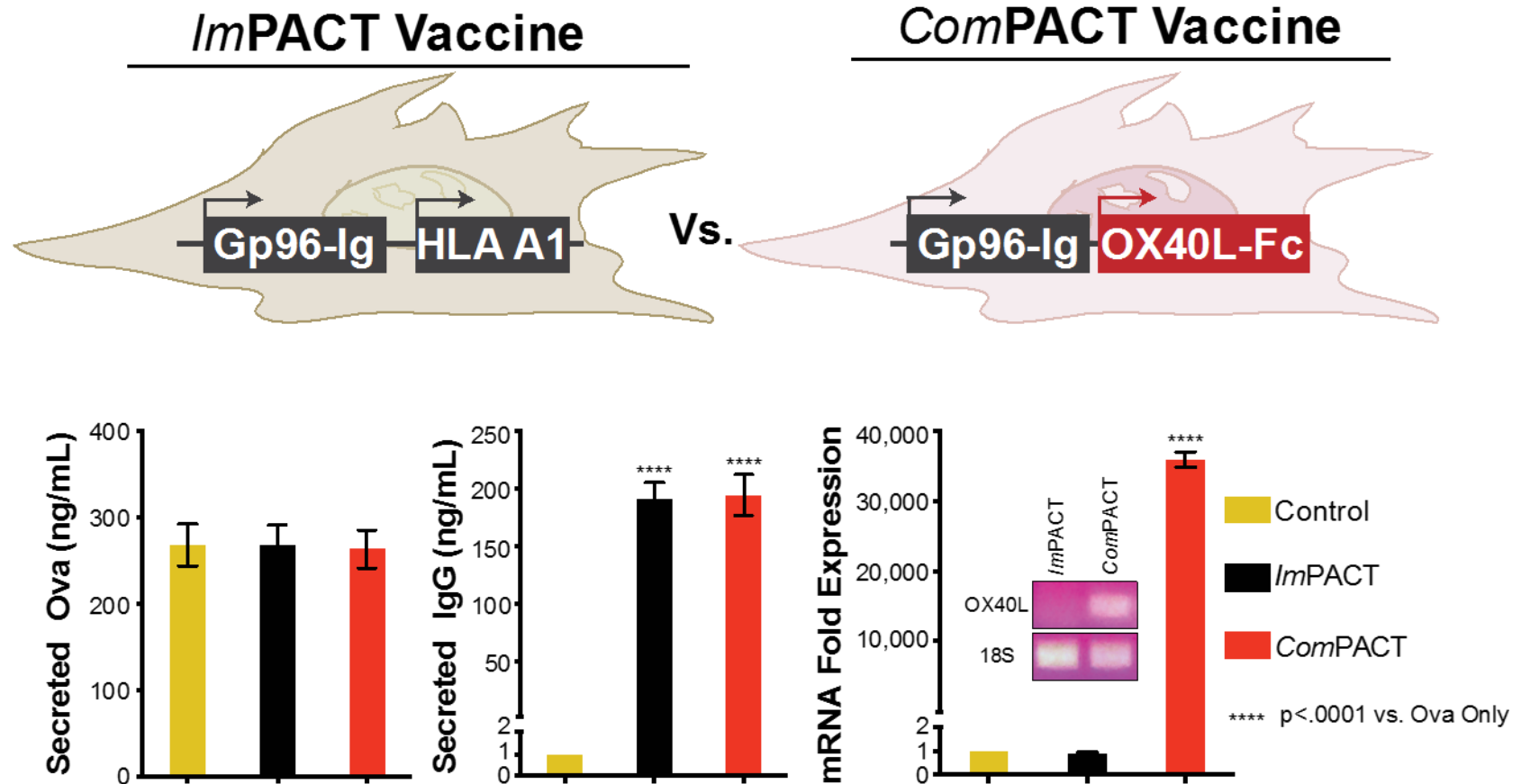
Fc-OX40L

Construct Prioritization Scheme

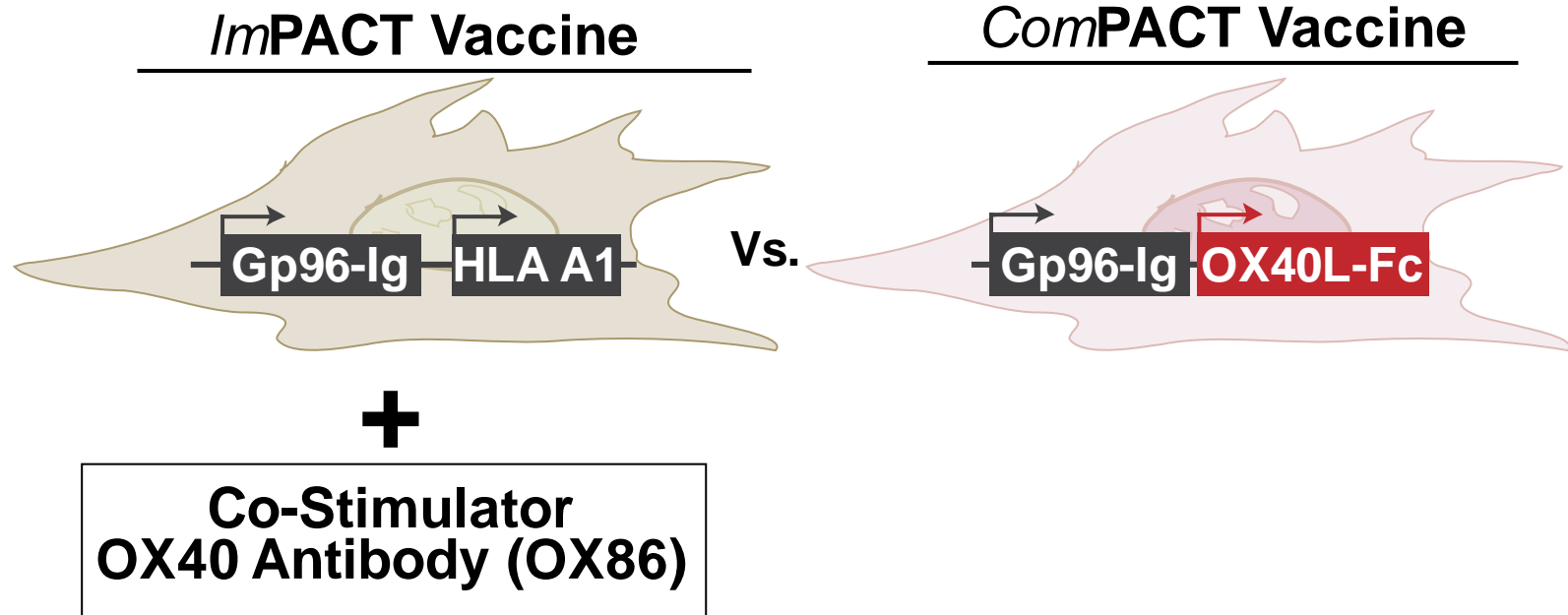
- There are multiple co-stimulatory receptors that may synergize with gp96-Ig based vaccines.
- Feasibility was performed by examining the immune response in animals treated with vaccine in combination with agonist antibodies



ComPACT Characterization

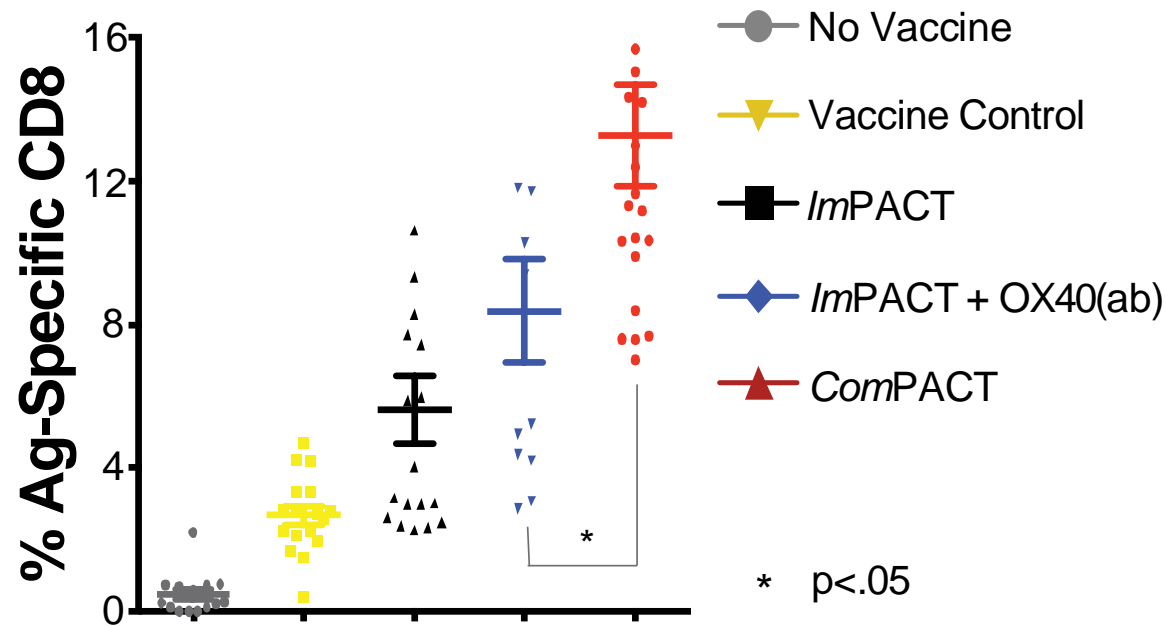


Feasibility Question



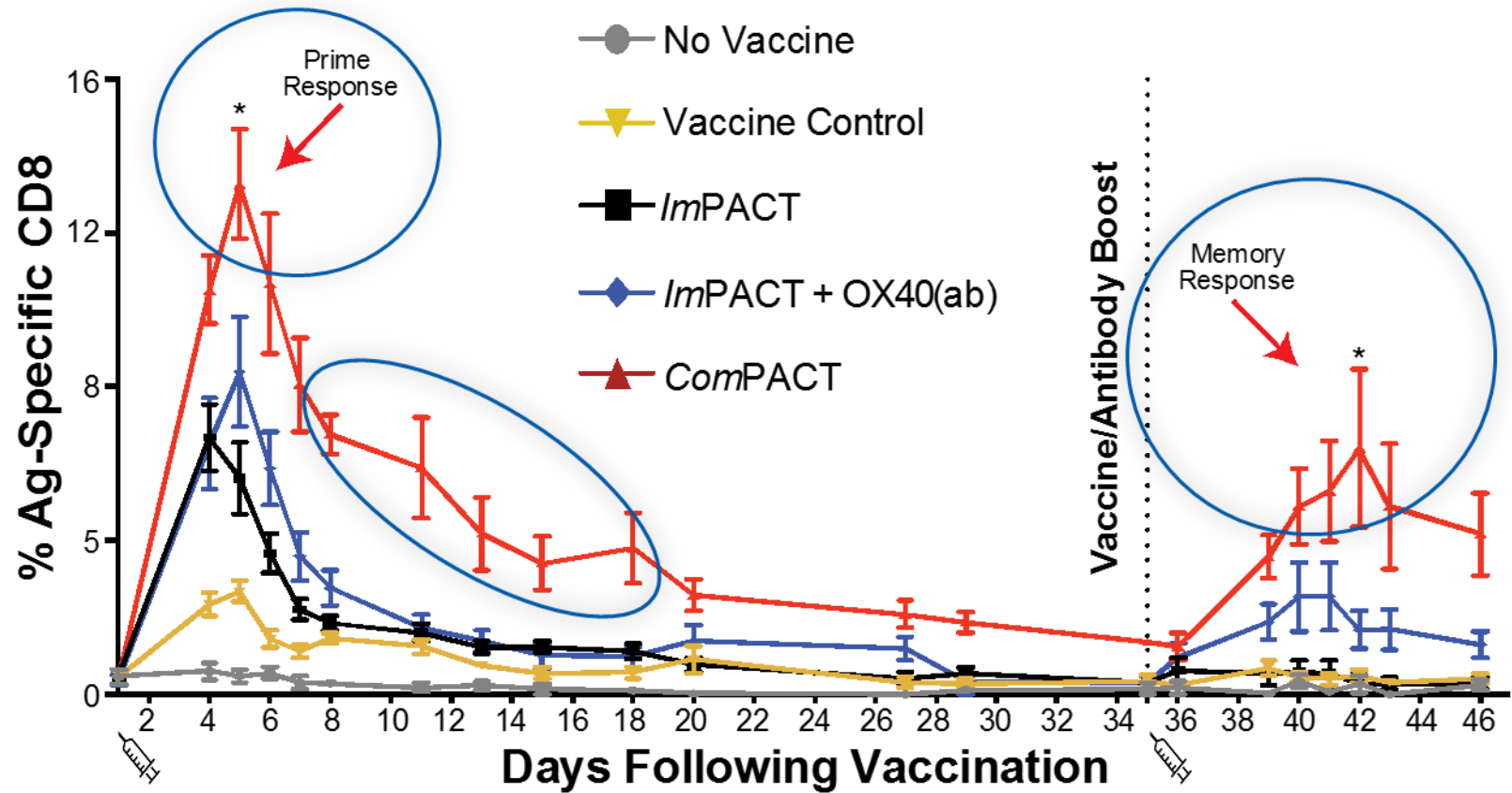
- Antibodies rapidly distribute systemically, and produce systemic effects
- With *ComPACT*, Fc-OX40L is local just in the injection site
- Can high enough concentrations be achieved to have an effect?

ComPACT Enhances CD8 Proliferation

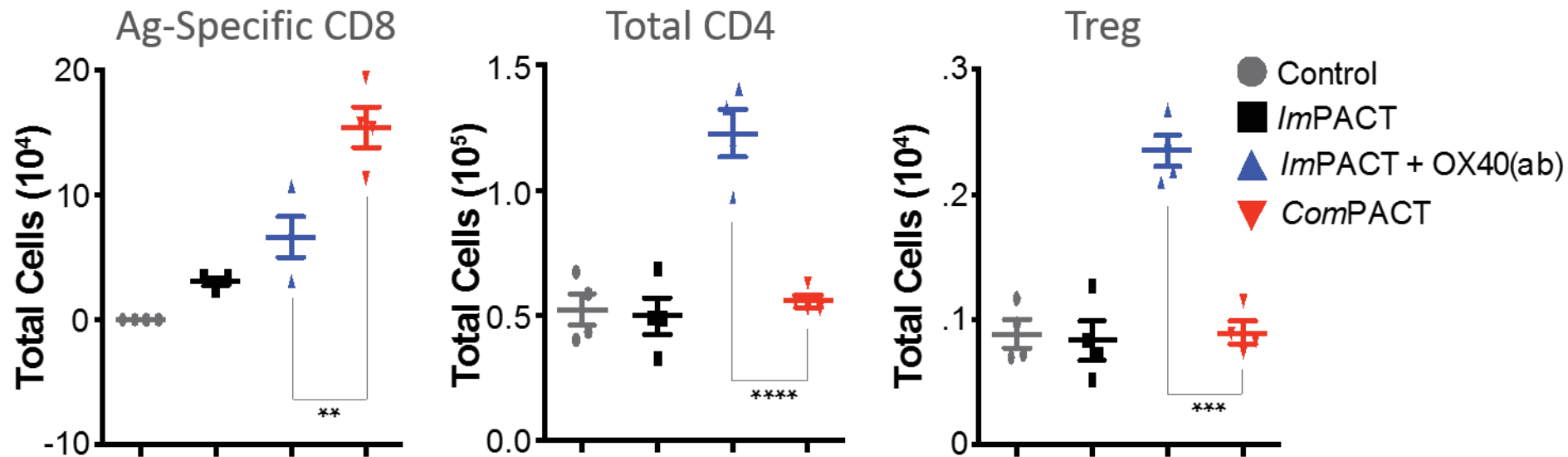


- Following primary immunization, locally secreted Fc-OX40L (in *ComPACT*) produces superior antigen-specific CD8+ T cell expansion than vaccines combined with OX40 antibodies

Kinetics of CD8+ T Cell Response

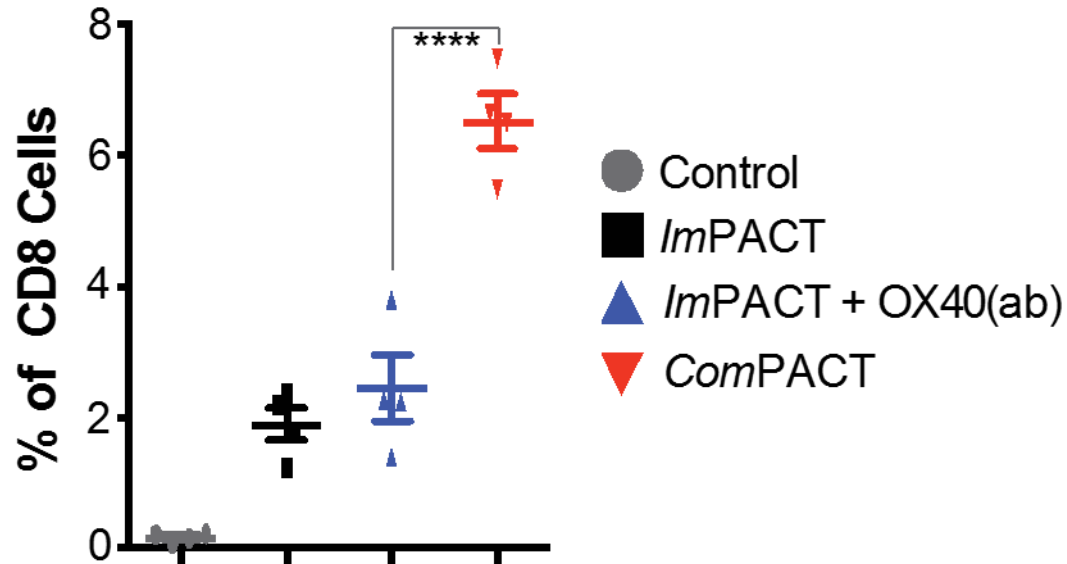


ComPACT Increases Specificity



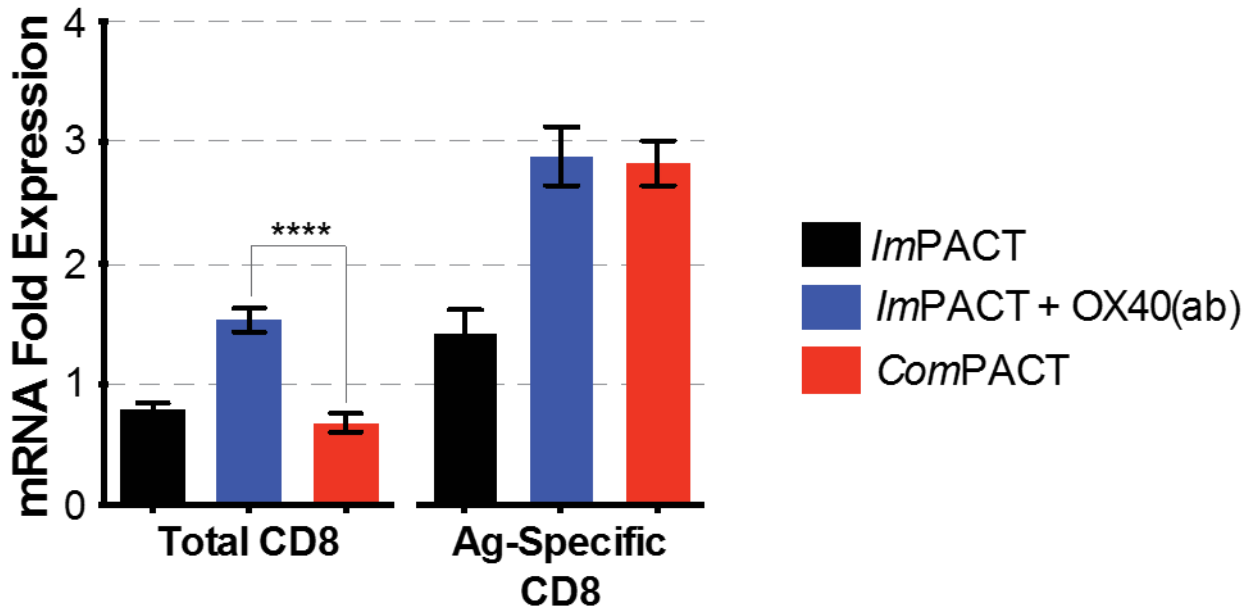
- *ComPACT* leads to increased antigen-specific CD8 cells
- OX40 antibodies also lead to non-specific increases in CD4 cells and T regulatory cells

ComPACT Increases CD8+ Memory



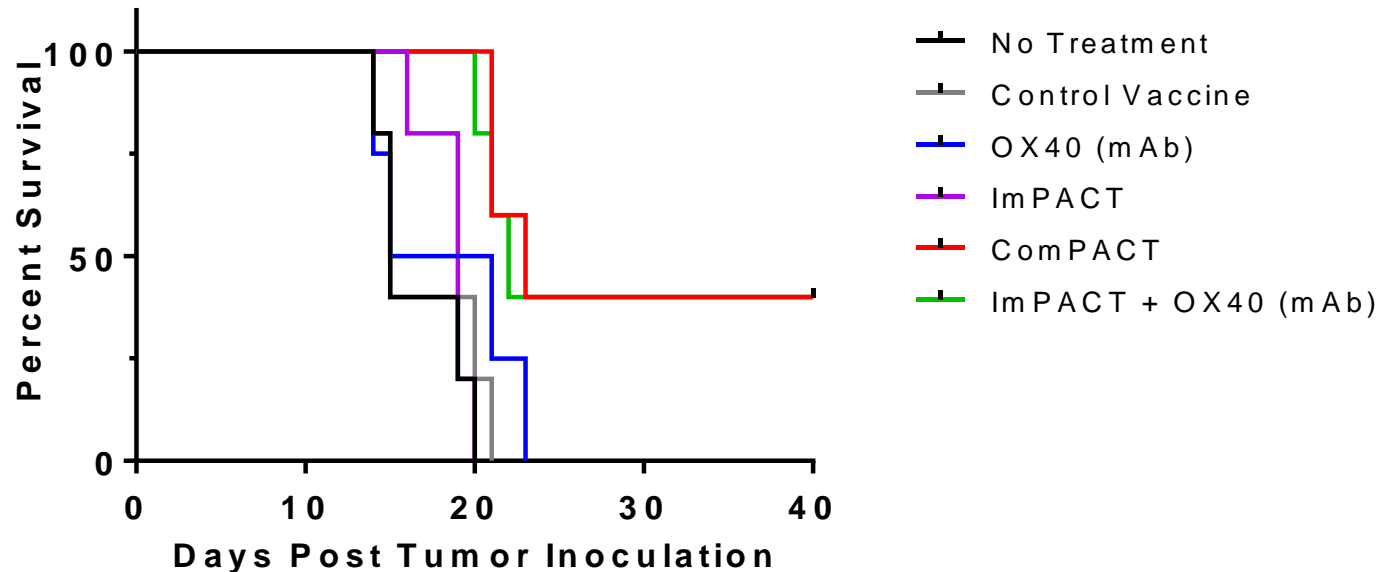
- The increase in antigen-specific CD8 cells seen with *ComPACT* is associated with an increase in memory precursor cells (CD127⁺KLRG1⁻), not seen with OX40 antibodies

ComPACT Increases Ag-Specific CD8+ Activation



- OX40 antibodies lead to increased activation of both Ag-specific and non-specific CD8, while *ComPACT* activates only Ag-specific CD8 cells

Therapeutic Tumor Immunity



- *ComPACT* leads to improved survival in a mouse colon cancer model, similar to OX40 antibody combined with vaccine

Summary

- ✓ Incorporation of OX40L-Fc into a gp96-Ig vaccine vector is feasible
- ✓ This construct leads to enhanced antigen-specific immunity at both priming and boosting
- ✓ The immune-stimulatory effect of *ComPACT* is superior to separate administration of vaccine and OX40 agonist antibody
- ✓ This is due to enhanced specificity, with OX40 antibodies causing systemic cytokine release and off-target proliferation
- ✓ Heat plans to file its first IND for the *ComPACT* platform in 2H 2016



ComPACT Video



Heat Biologics

