PELICAN Therapeutics

A Subsidiary of Heat Biologics

TNFRSF25 Agonists for Immuno-Oncology

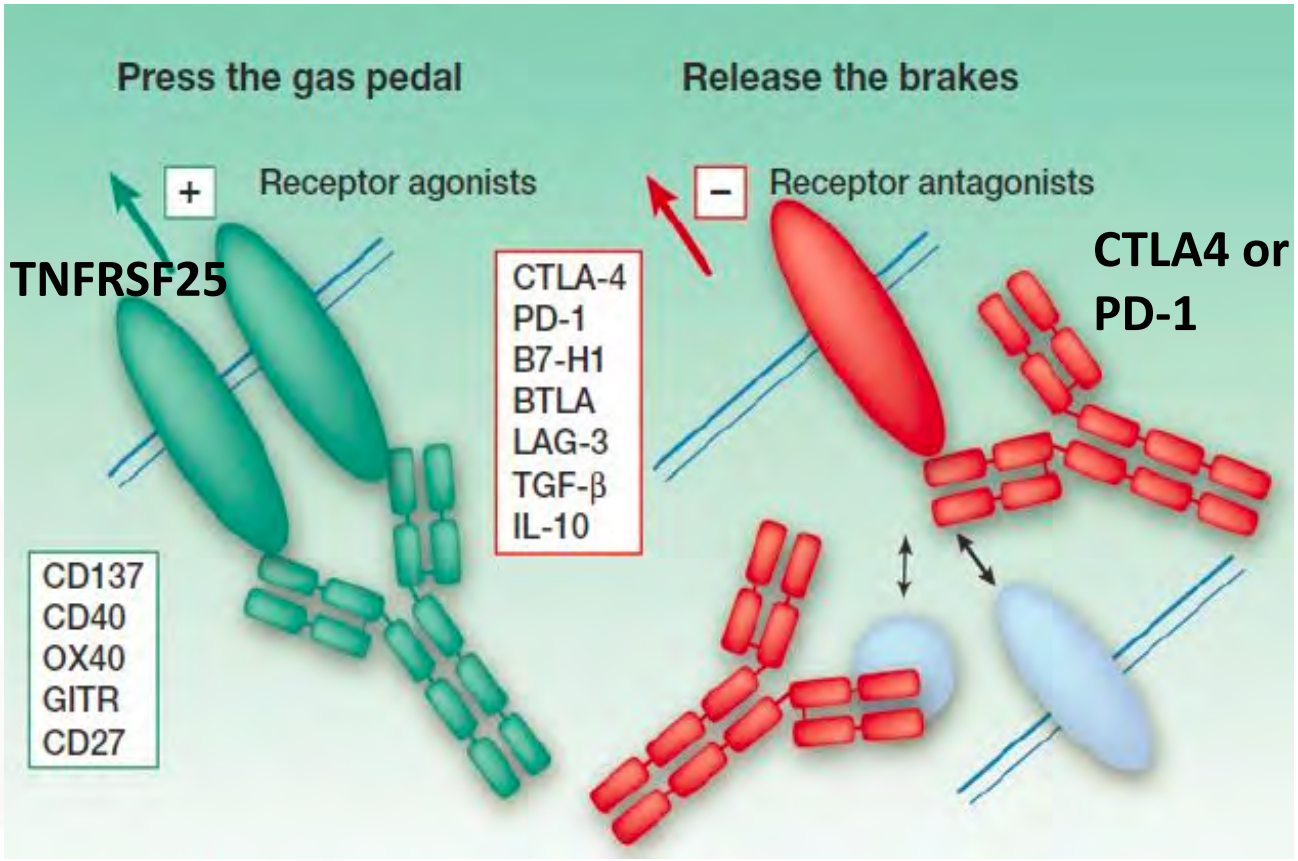
Non-Confidential Presentation

Introduction to Pelican

- **TNFRSF25** is a potential best-in-class T cell co-stimulator due to its preferential specificity to 'memory' CD8+ T cells that are most potent in tumor killing
- **PTX-35**, the lead compound, is a humanized TNFRSF25 agonist antibody with an IND filing expected in approximately 15 months
- Pre-clinical studies with the murine precursor to PTX-35 show **advantages over competing T cell co-stimulator programs** based on CD8+ T cell specificity
- Pelican is the only company with a disclosed program targeting TNFRSF25 for use in immuno-oncology (I/O) with a broad, pioneering intellectual property estate
- Pelican awarded a **$15.2M grant from CPRIT** (Cancer Prevention Research Institute of Texas) to develop PTX-35 through a comprehensive 70-patient first-in-man Phase 1a/b/c clinical trial

Importance of CD8+ T cells and T cell costimulation

- Both, reversal of immune suppression (checkpoint inhibitors) in the tumor microenvironment and boosting of the effector arm (costimulation of CD8+ T-cells) are important
- T cell costimulators could complement checkpoint inhibitors as combination therapies are required to improve patient responses



T cell costimulatory therapy, when combined with checkpoint inhibitors could significantly improve clinical responses for a broader range of patients that are currently non-responsive to checkpoint inhibitors

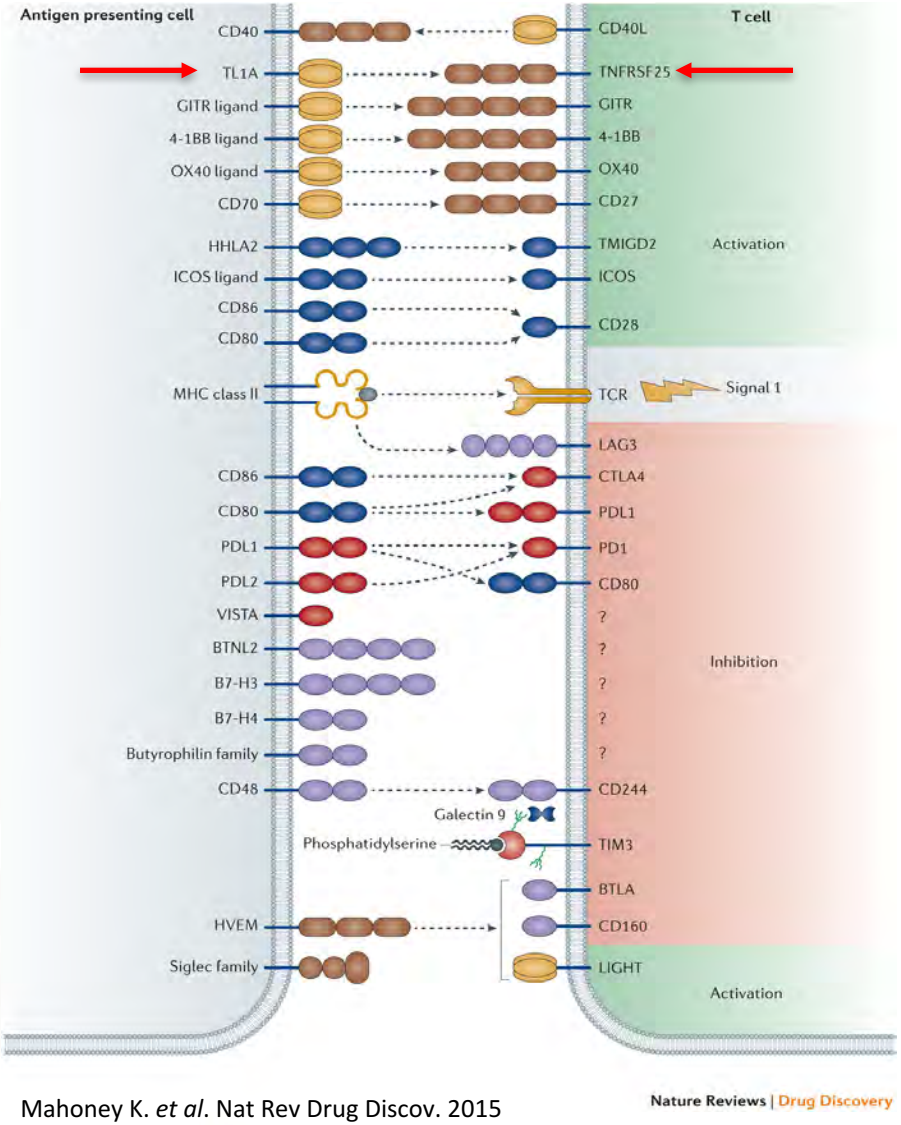
TNFRSF25 as a Novel I/O Combination Target

- TNFRSF25 is the most recently discovered T cell costimulator, and is a rapidly emerging target

- Pelican is the only company developing TNFRSF25 agonist antibodies for I/O

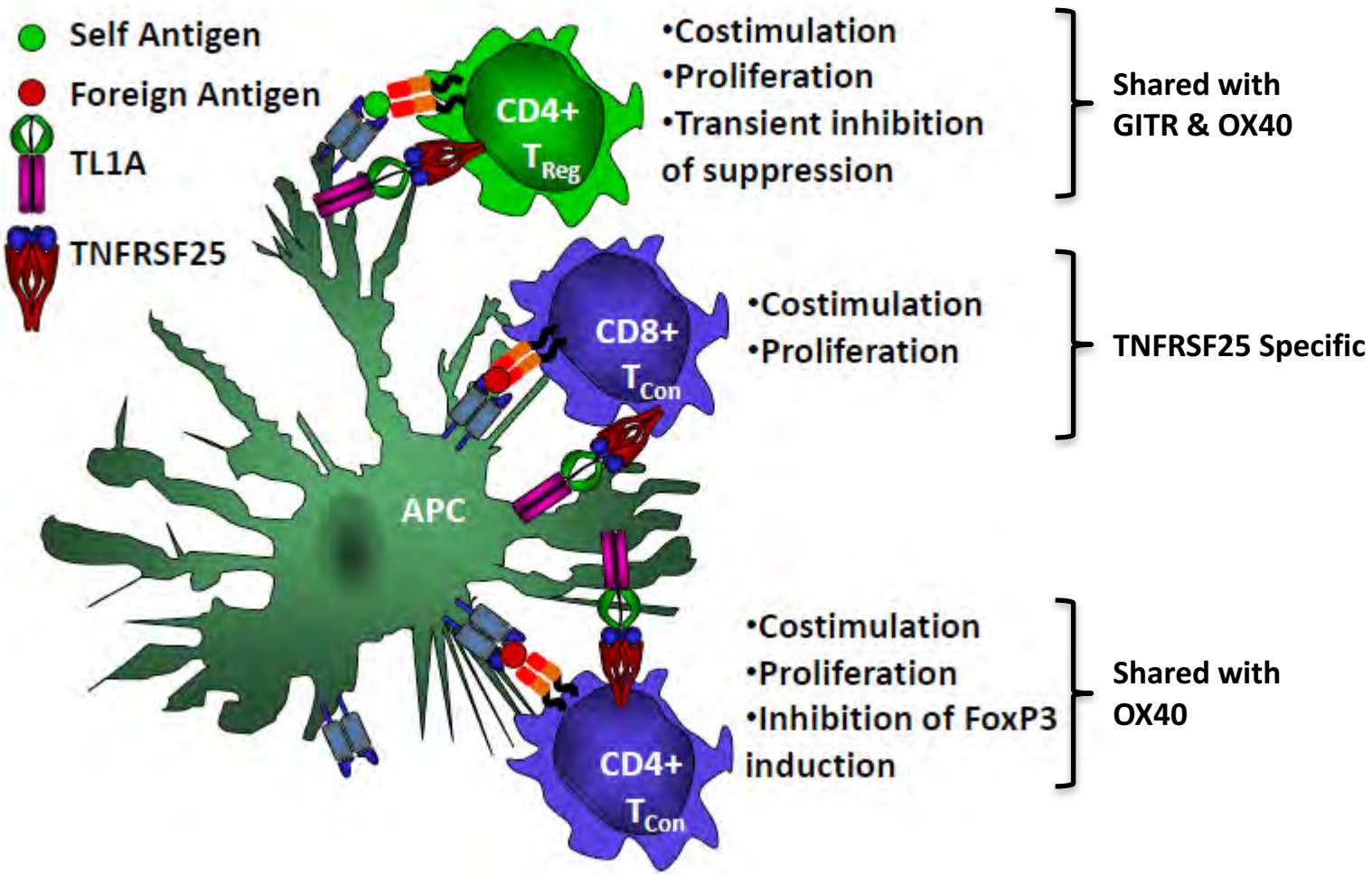
"Although TNFRSF25 is chromosomally localized with 4-1BB, OX40, GITR and CD27, sequence analysis suggests that TNFRSF25 is relatively divergent or perhaps ancestral…Thus we might expect that therapeutics directed against this pathway will have unique activity."

-Gordon Freeman et al



Mahoney K. *et al*. Nat Rev Drug Discov. 2015

Summary of TNFRSF25 Functions



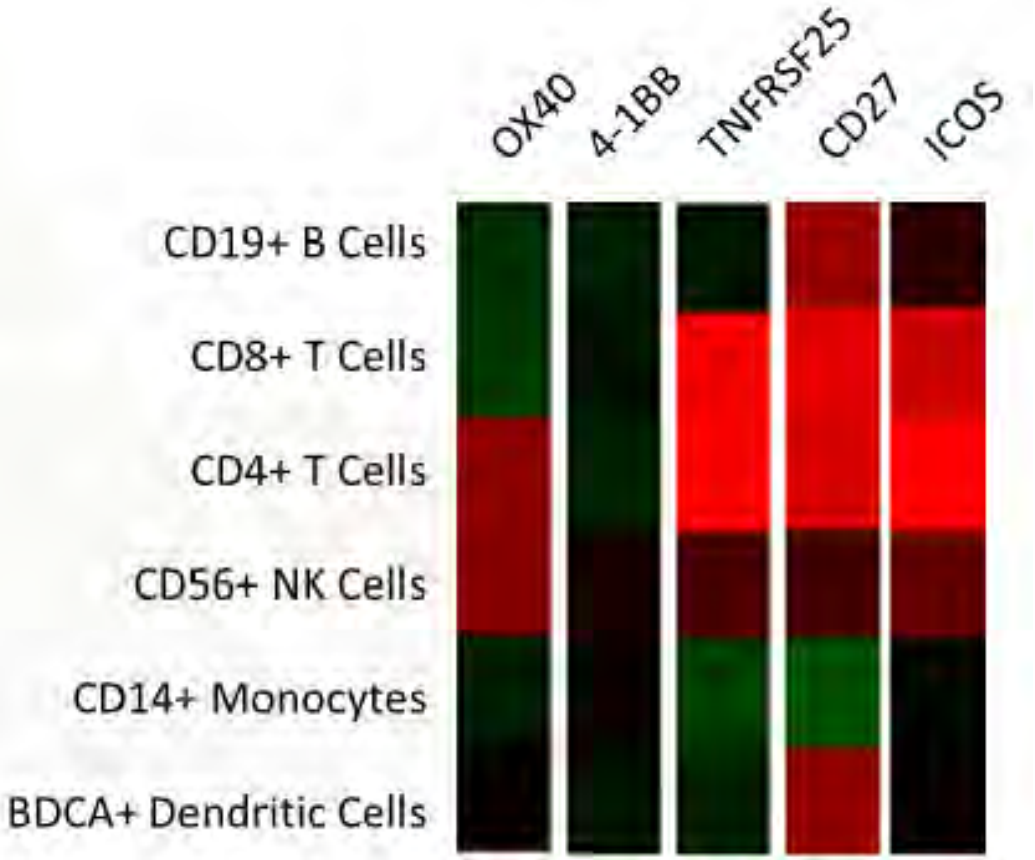
Properties of TNFRSF25 as a Novel T Cell Costimulator

TNFRSF25 is a potent T cell co-stimulator with potential advantages over the competition

- TNFRSF25 agonism leads to antigen-experienced 'memory' T cells (both CD4+ and CD8+) that are instrumental in tumor eradication
- Contrasting with other T cell costimulators, TNFRSF25 agonism leads to a more pronounced 'memory' CD8+ cytotoxic T cell activation - the cells most crucial in tumor eradication
- TNFRSF25 signaling in T cells is dependent upon prior engagement of the T cell receptor (TCR), implying antigen specific T cell proliferation
- Pre-clinical studies with TNFRSF25 agonist mAb have demonstrated potent anti-tumor metrics:
  - antigen driven T cell proliferation
  - increased effector cytokine production
  - Increased effector immune function
  - Increased survival in a B16-F10 melanoma and CT26 colon carcinoma

Expression of T cell Costimulators

- Compared to other T cell costimulators, TNFRSF25 is preferentially expressed on CD8+ T cells



TNFRSF25 is preferentially expressed by human CD8+ T cells (red = high expression)

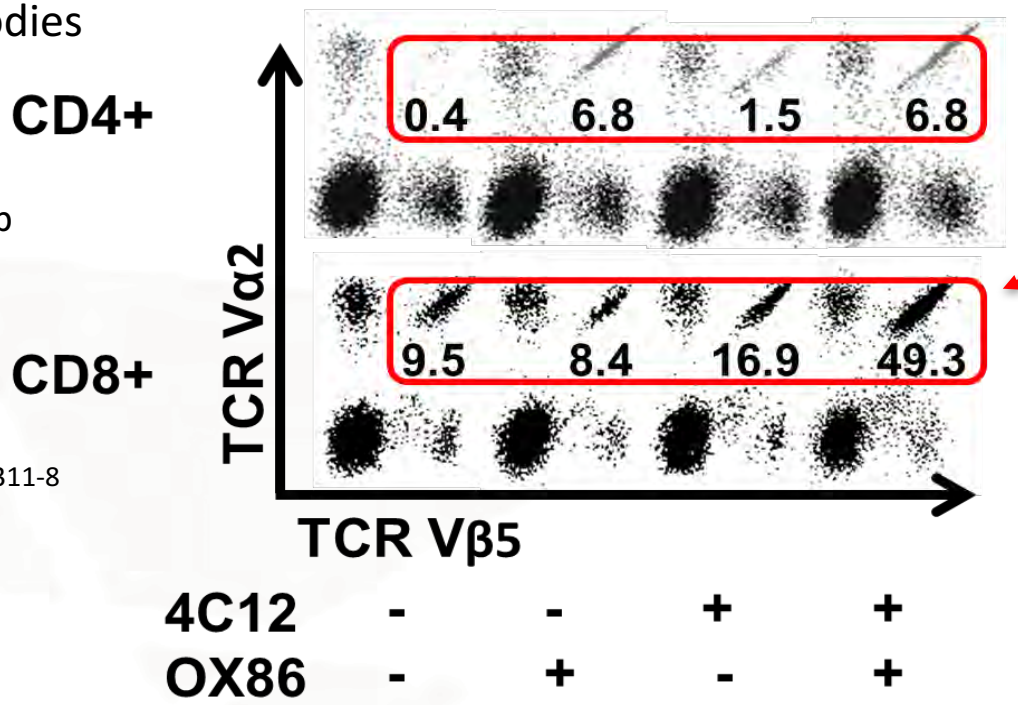
Genomics Institute of the Novartis Research Foundation
Su *et al*. PNAS 2004:**101**(16);6062-7

Preferential CD8+ T cell Induction

Pre-clinical Studies with murine agonist antibody shows preferential CD8+ T cell Induction; differentiation from other T cell costimulators

- The frequency of antigen-specific memory CD4+ or memory CD8+ T cells were examined following treatment of mice with a vaccine alone, or in combination with OX40 (OX86) or TNFRSF25 (4C12) antibodies

4C12 = TNFRSF25 Agonist mAb
OX86 = OX40 Agonist mAb



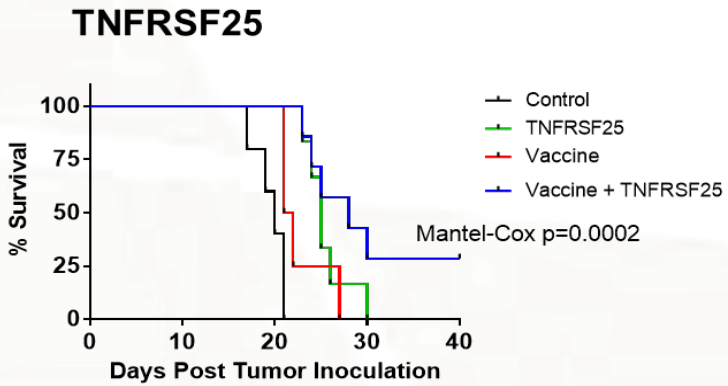
Schreiber et al. J Immunol 2012:189(7);3311-8

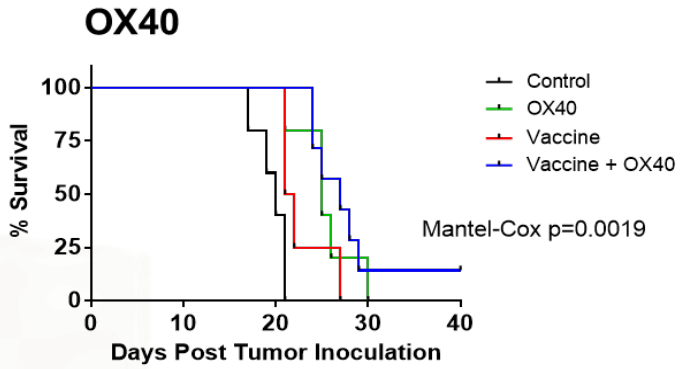
- **TNFRSF25 preferentially 'boosts' CD8+ T cell immunity, whereas OX40 is preferential to CD4+ T cells**

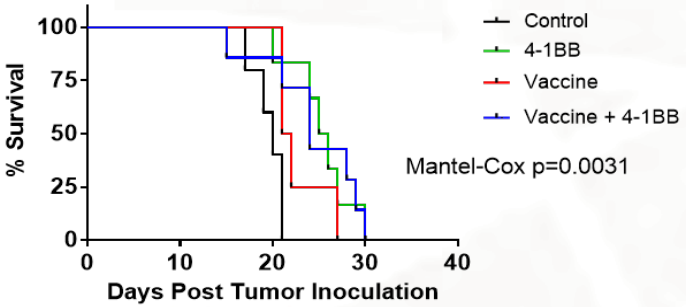
Comparative Anti-Tumor Activity

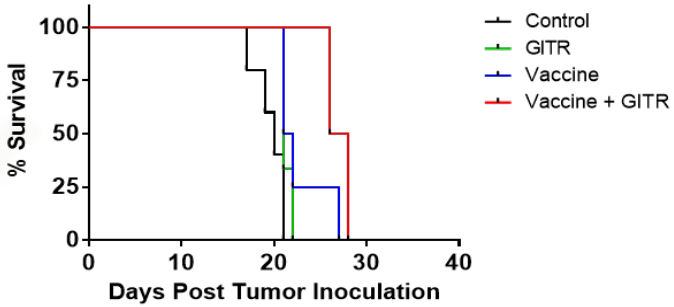
TNFRSF25 agonism with murine agonist mAb shows increased survival compared to agonism of other costimulators

- Comparative activity of OX40, GITR, 4-1BB and TNFRSF25 agonist mAbs in a long-established (9-day) B16-F10 melanoma model



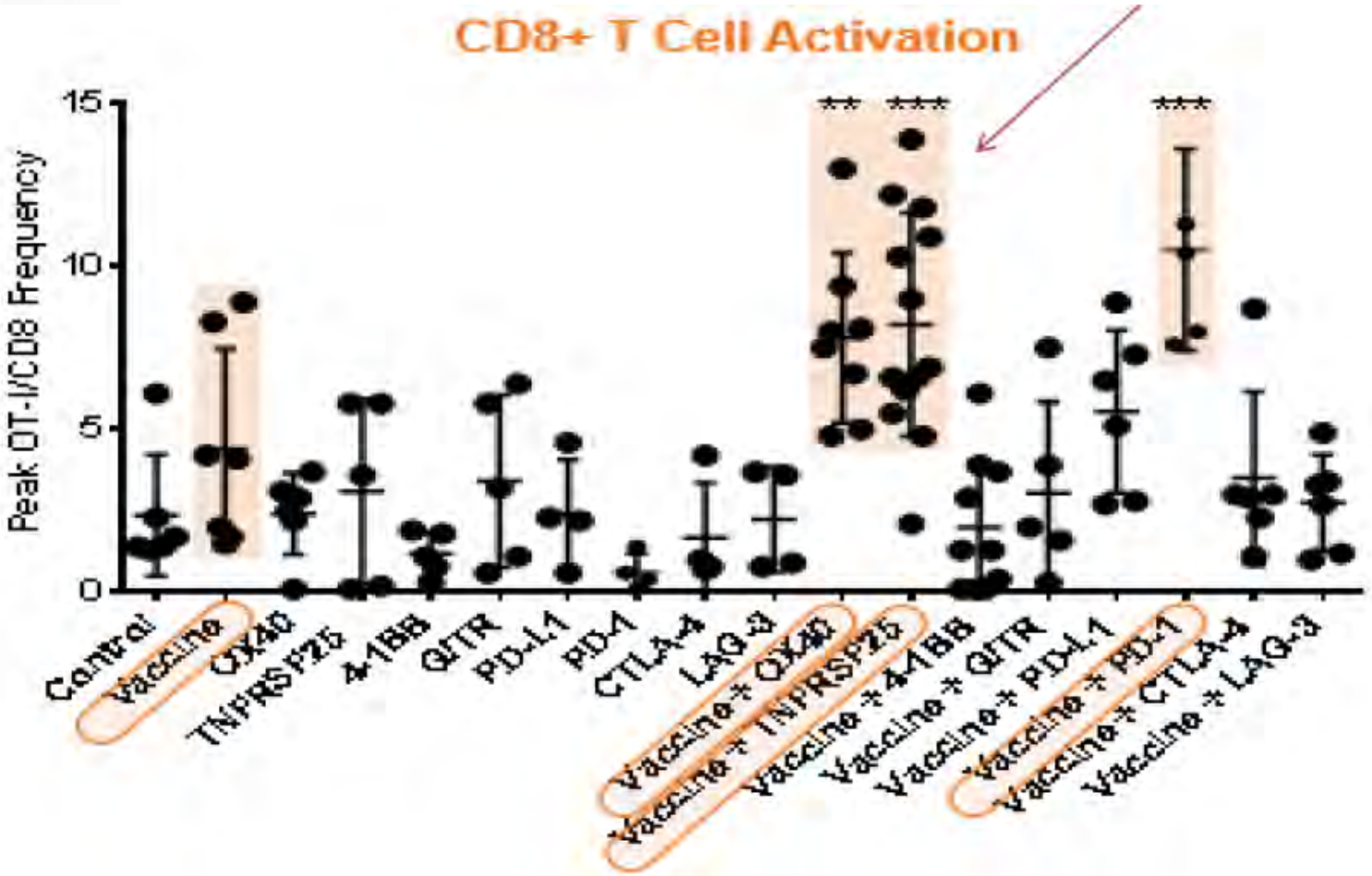






Schreiber T. *et al*. SITC 2014

Comparative CD8+ T cell Potency – TNFRSF25 Stand out



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Major Highlights from Pre-clinical Studies

- mAb to TNFRSF25, drives the development of **antigen-specific CD8+ T cells** (this effect mimics TLIA, the natural monogamous ligand of TNFRSF25)
- mAb to TNFRSF25 results in costimulation and expansion of antigen-experienced memory T cells, both CD4+ and CD8+; notable is a significantly enhanced effect on **memory CD8+ T cells**, the cell type most potent in tumor eradication
- Costimulation occurs only in the context of **TCR recognition of antigen**
- TNFRSF25 appears to have **superior activity** in stimulating memory CD8+ cells relative to OX40, 4-1BB and GITR
- Agonism with TNFRSF25 mAb leads to increases in **effector cytokine** and **effector immune function,** and **increases survival in mouse models**
- In mouse melanoma models, TNFRSF25 mAb results in increased survival **compared to agonism of OX40, GITR, 4-1BB** with respective agonist mAbs

Completed and Ongoing Steps in PTX-35 Development

IND Enabling Studies are Planned Under CPRIT Award

- ✓ Lead Antibody Generation
- ✓ Humanization
- ✓ Sequence Analysis
- ✓ Functional Analysis
- ✓ Affinity Measurement
- ✓ Competition with TL1A for Binding
- ✓ Epitope Mapping
- ✓ Backup mAb Generation
- ✓ Affinity maturation
- ➢ Biophysical Characterization
- ➢ Cell Line Development
- • GMP Manufacturing
- • IND Enabling Tox Package

- ✓ Completed
- ➢ Ongoing
- • Planned

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CPRIT Funded Preliminary Phase 1 Design

Accelerated Titration Cohort | *Expansion Cohort*

Phase Ia	Phase Ib	Phase Ic
Population: Confirmed solid tumor with ≥ 1 measurable lesion refractory to standard therapy Biomarker driven PD endpoint: Proliferation of antigen-specific CD8+ T cells in the peripheral blood 5 days post treatment		Population: Confirmed solid tumor (no more than 3 tumor types) with ≥ 1 measurable lesion refractory to standard therapy OR in combination with I/O SOC (for example Opdivo or Keytruda)
• N = 1 patient per cohort • Starting dose defined in NHP • 100% dose increase per patient • PD defined as above • Proceed to Ib when a single DLT or 2 grade 2 events are observed	• 3 + 3 Design • Starting dose (MABEL) defined in Phase Ia • 40% dose increase per group • PD defined as above • MTD determined by maximum dose at which <1 DLT occurs in the 6 patient cohort	• ~ 30 patients enrolled • Therapeutic dose defined in Phase Ib • PD defined as in Phase Ia and Phase Ib • PK/PD interactions monitored for combination therapy • Preliminary assessment of efficacy in refined tumor indication

Summary

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Thank you for your consideration.