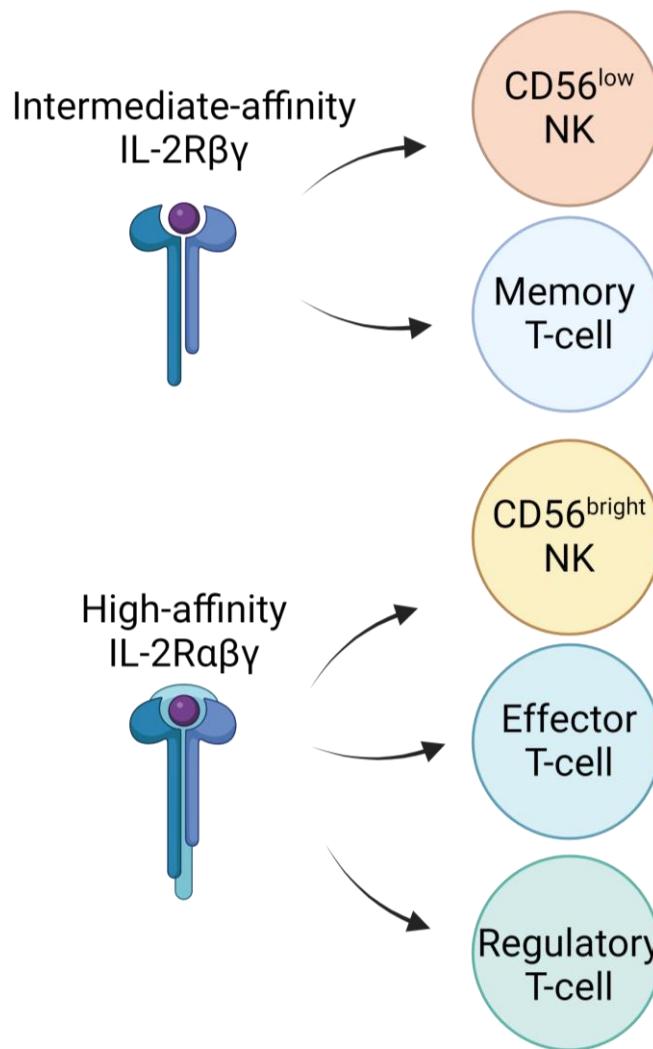


# An Orthogonal IL-2/IL-2R-System Enhances Engineered T Cell Therapies Via a Durable Synthetic Effector State

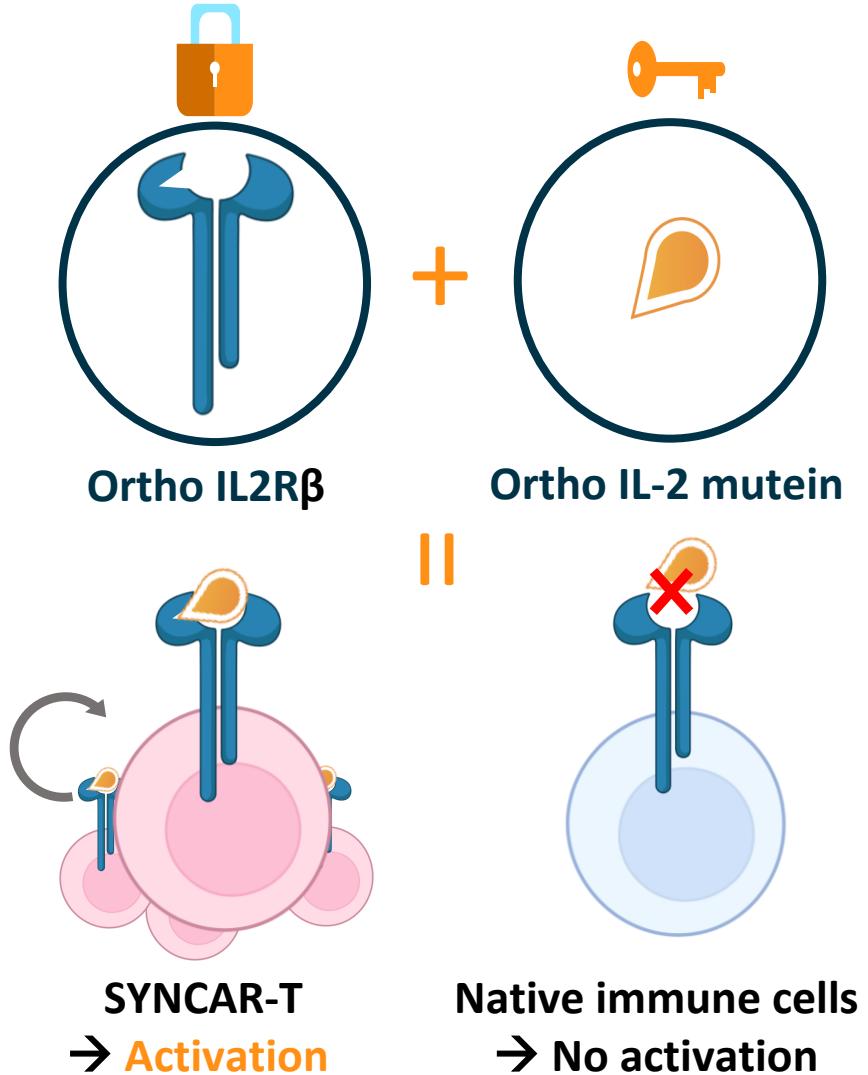
**Inyoung Jung, PhD**  
Principal Scientist  
Synthekine

# IL-2: A Potent Cytokine to Armor Adoptive T Cell Therapy



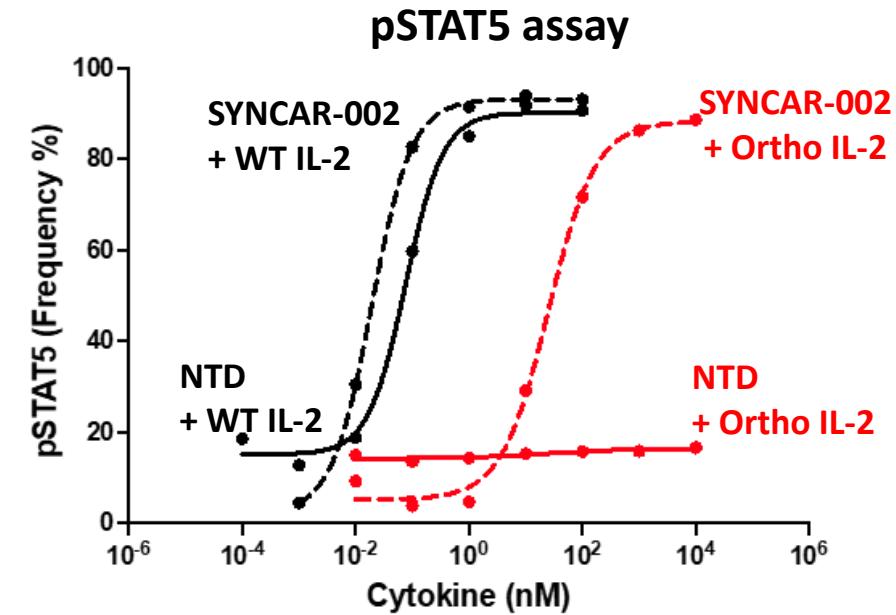
- IL-2 is a pleiotropic cytokine that positively influences the homeostasis and development of different T cell lineages and other immune cells (e.g. NK cells and eosinophils)
- IL-2 signals through the stepwise assembly of the IL-2R complex to primarily activate the JAK/STAT5 pathway
  - IL-2R $\alpha$  increases IL-2 affinity towards IL-2R $\beta$ , then binds to the common gamma chain IL-2R $\gamma$
- Recombinant IL-2 (Proleukin) used as a monotherapy and in combination with TCR and TIL therapies
  - Limited by significant, life-threatening toxicity (small therapeutic window)
  - **Capillary leak syndrome (CLS)**, **hypotension** mediated by non-selective activation of immune cells
  - Antitumor activity compromised by **Treg activation**

# Orthogonal IL-2: A Lock and Key System to Stimulate CAR-T Selectively

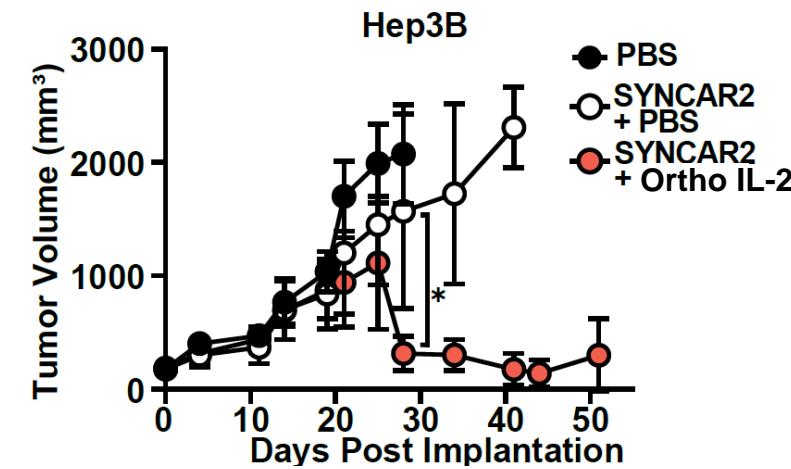
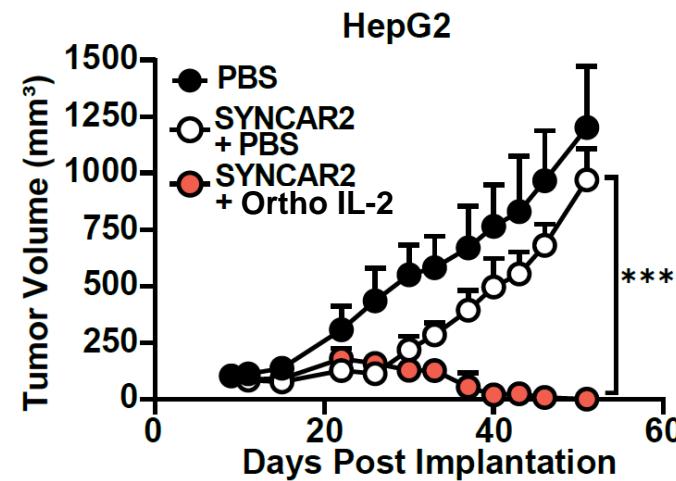
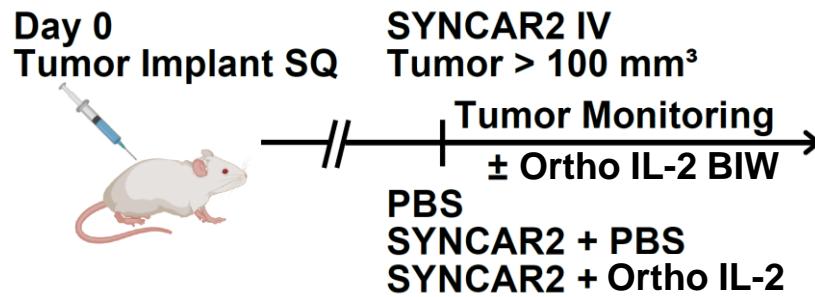


Orthogonal IL-2 selectively activates SYNCAR-T, not endogenous T-cells

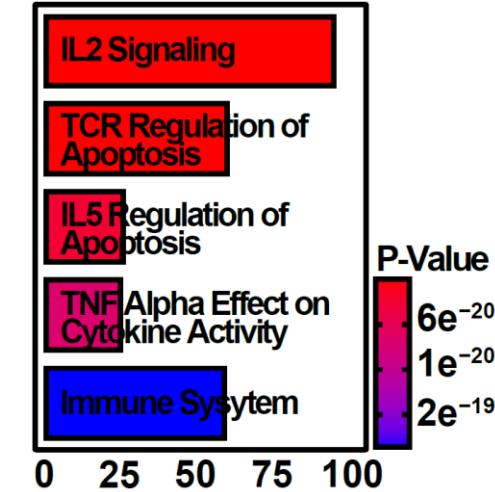
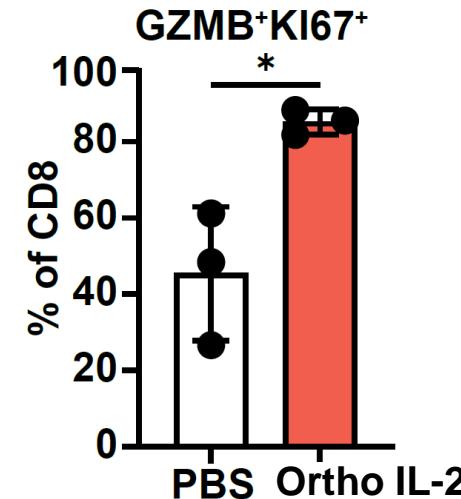
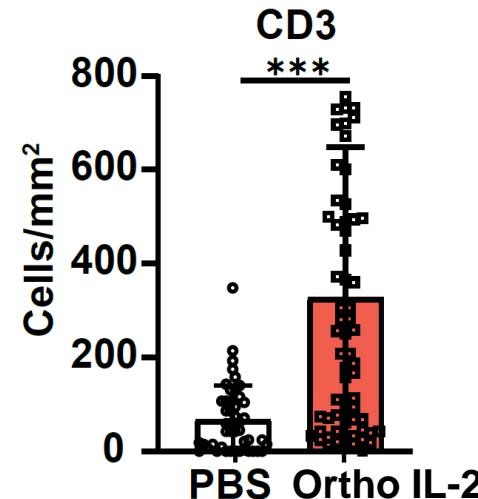
SYNCAR-002   αGPC3 scFv   CD28   CD3z   T2A   oR $\beta$



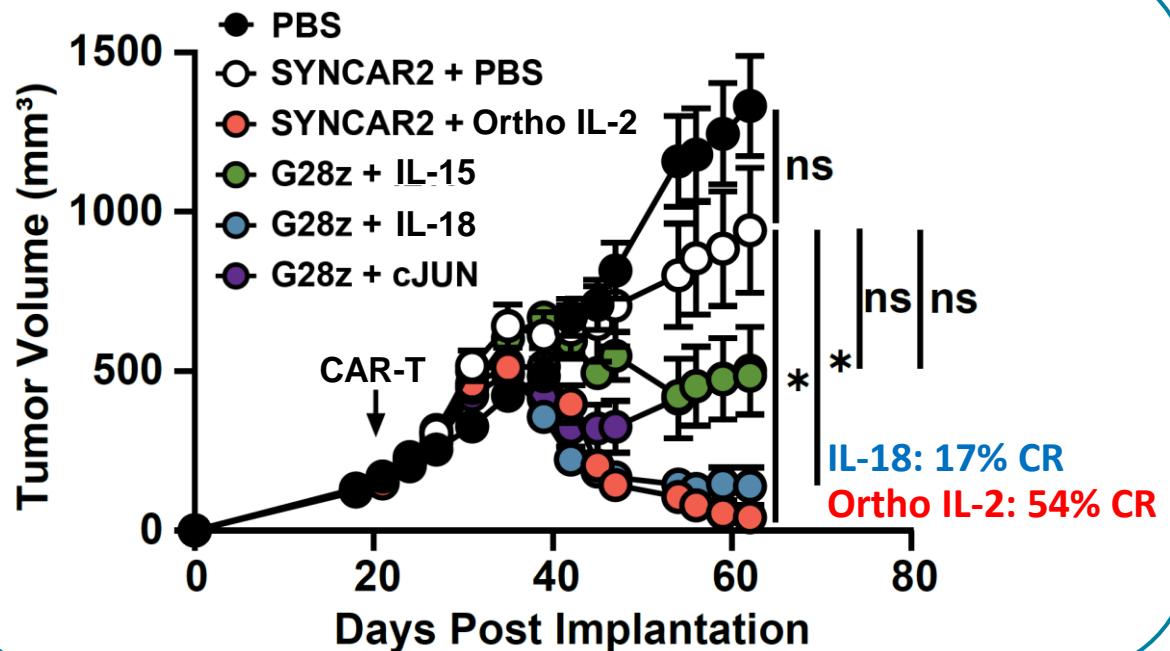
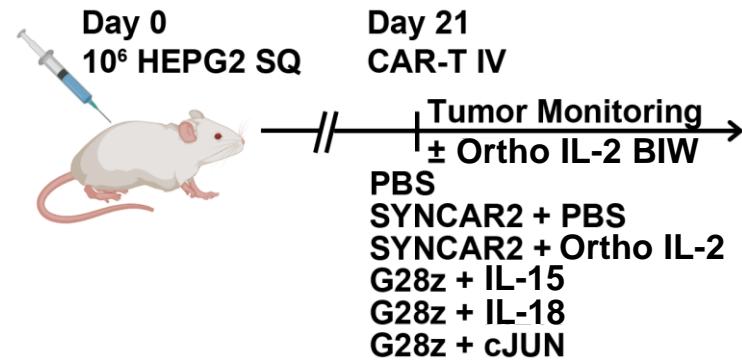
# Orthogonal IL-2 Enhances Antitumor Potency of CAR T-cells in HCC Models



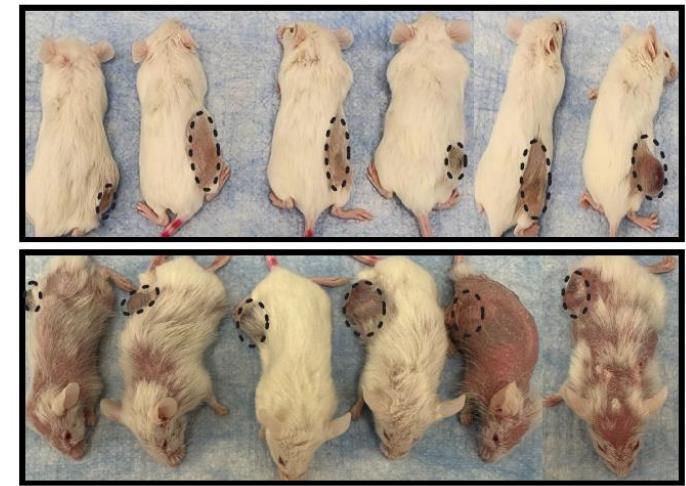
Orthogonal IL-2 increases **proliferative effector** CAR T-cells in tumor characterized by an elevated IL-2 pathway.



# Orthogonal IL-2 Outperforms Other CAR-T Armoring Strategies



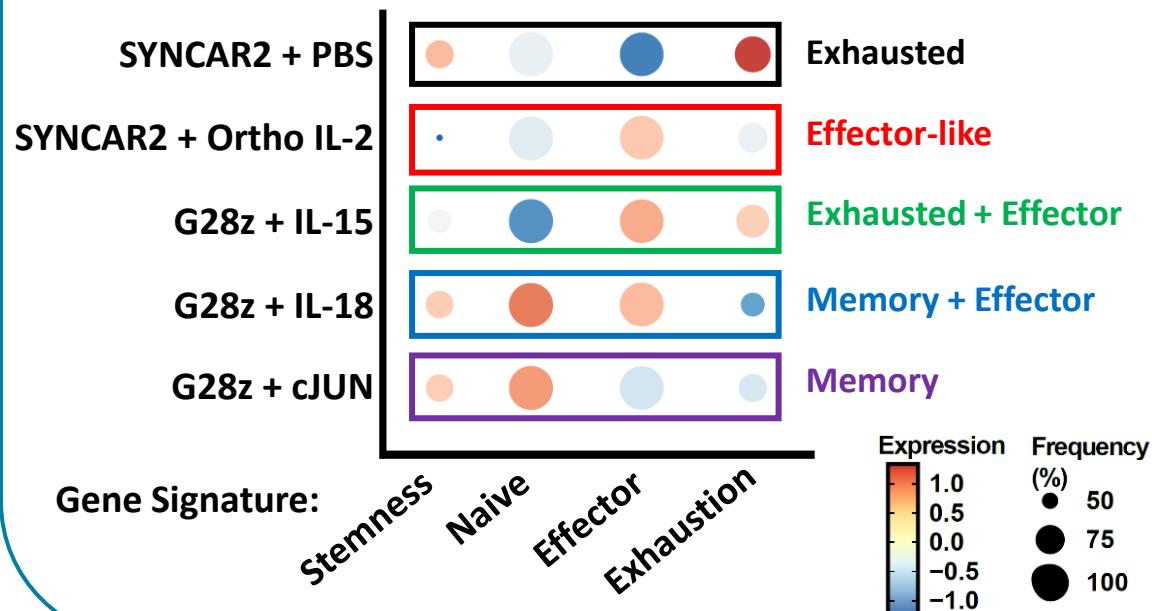
IL-18 armoring induces xGVHD, while orthogonal IL-2 does not.



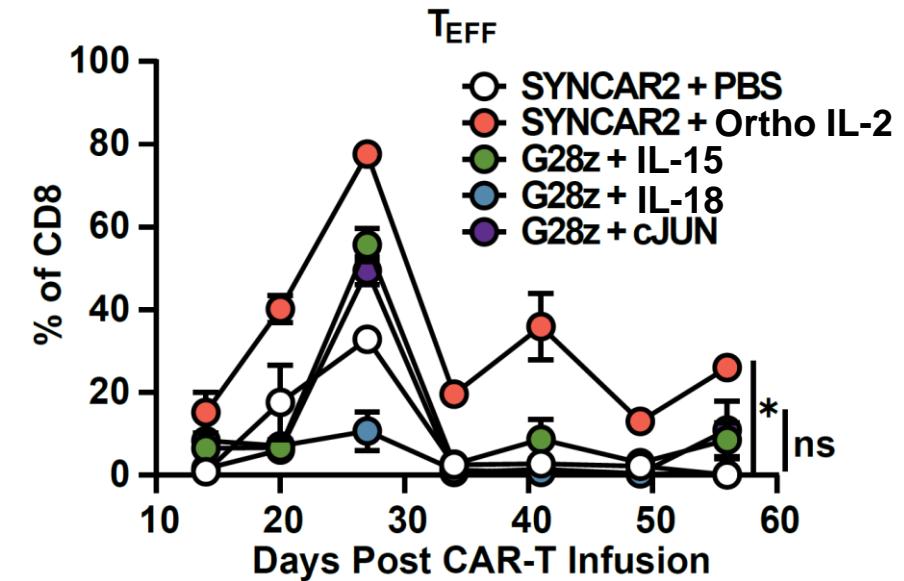
# Orthogonal IL-2 Repograms T-cells Toward Durable Effector Cell

Chronically activated CAR-T cell (*in vitro* restimulation assay)

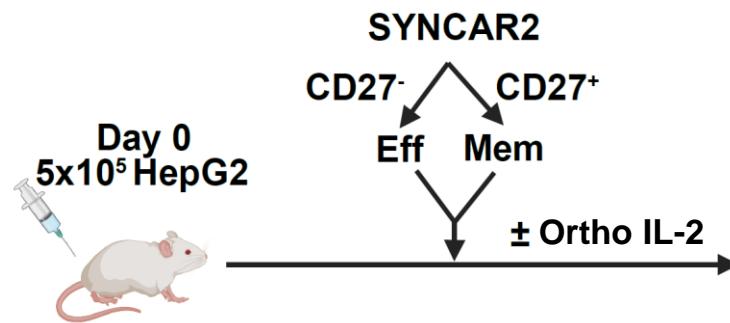
## Cell state induced by armoring



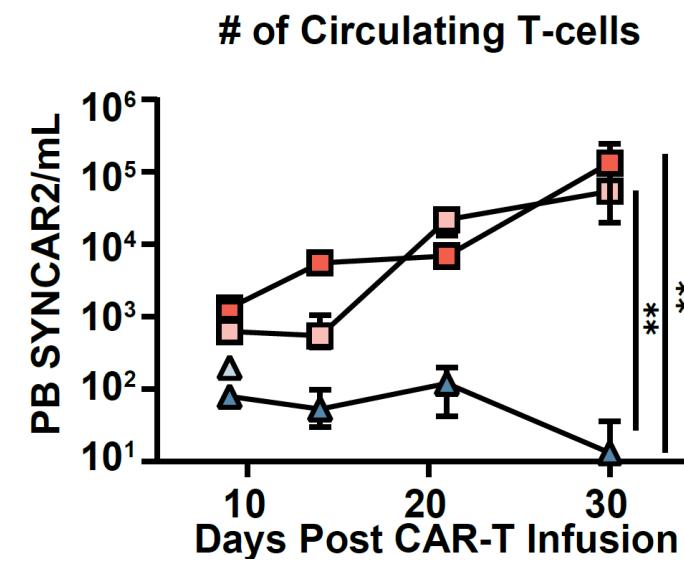
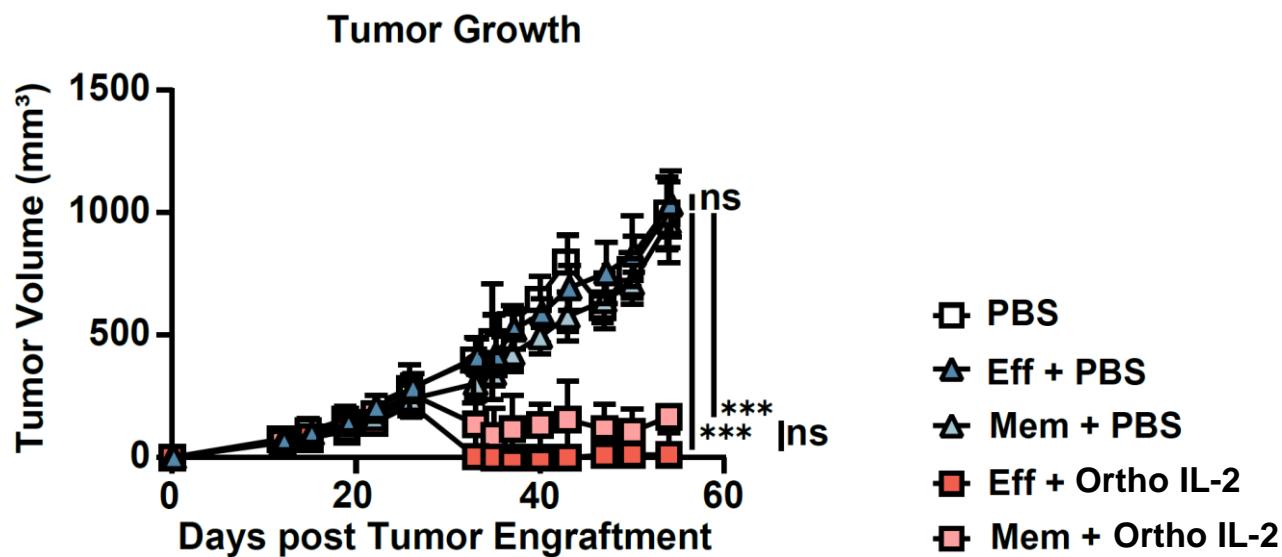
## Long-persisting effector signature



# Orthogonal IL-2 Restores the Persistence of Effector CAR T-cells

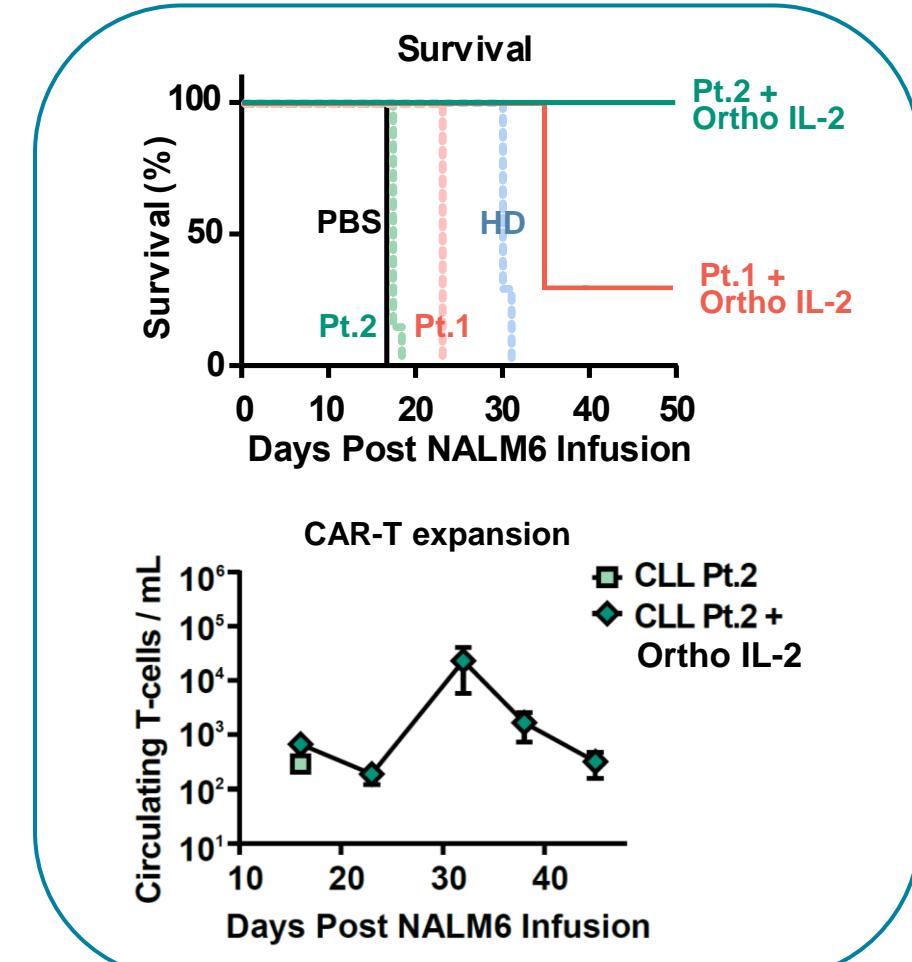
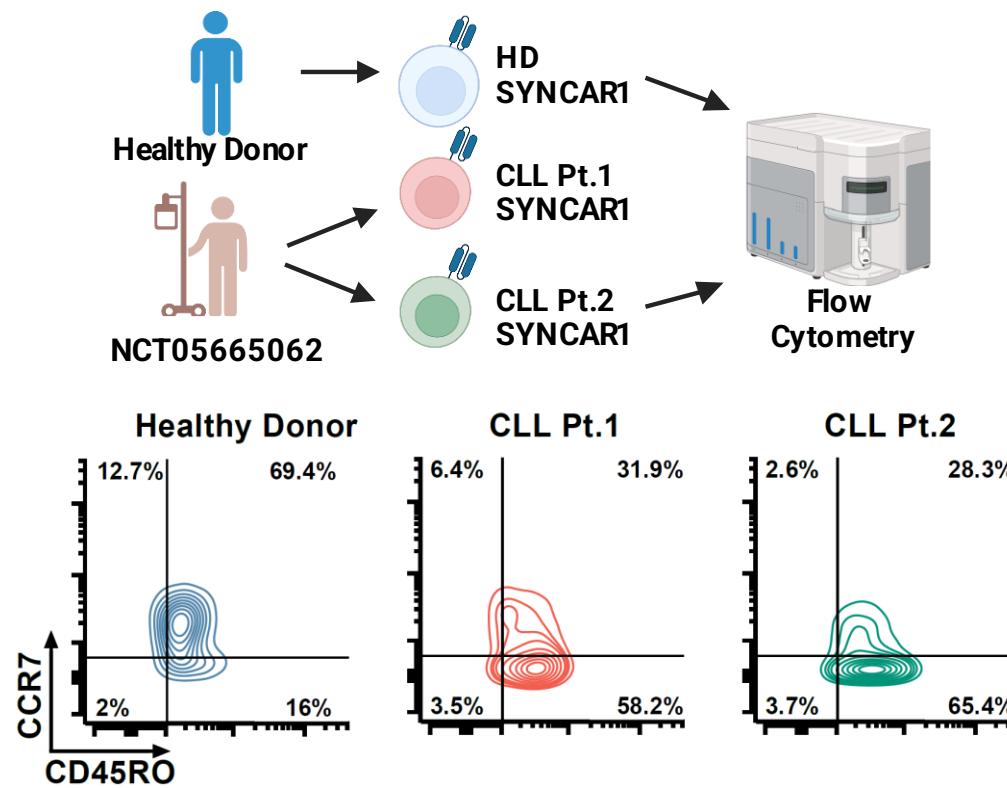


Conventional effector and memory T-cells exhibit poor tumor control and persistence. In contrast, orthogonal IL-2 restores antitumor activity and persistence of effector CAR-T cells.



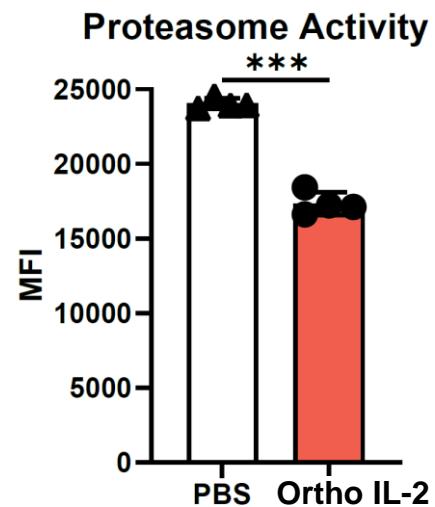
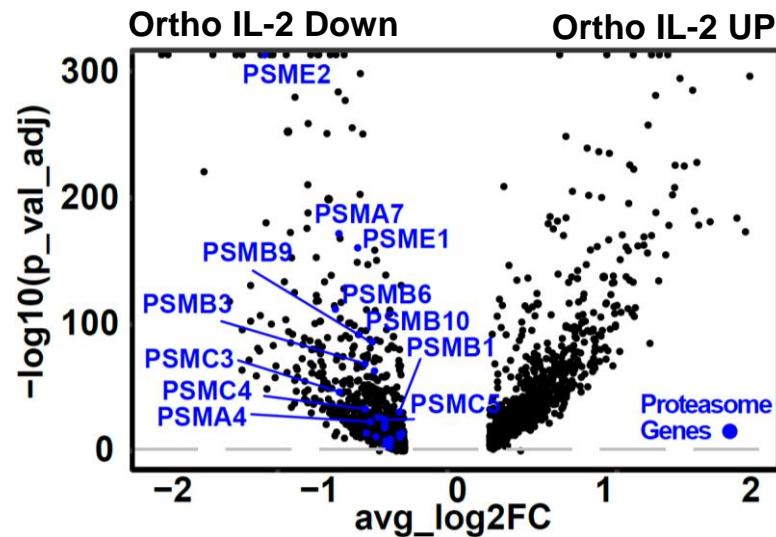
# Orthogonal IL-2 Enhances the Potency of Effector-skewed CD19 CAR T-cell Products Derived from CLL Patients

CD19 CAR T-cell products derived from **CLL** patients are **effector-skewed**, which is known to be associated with **unfavorable clinical response**

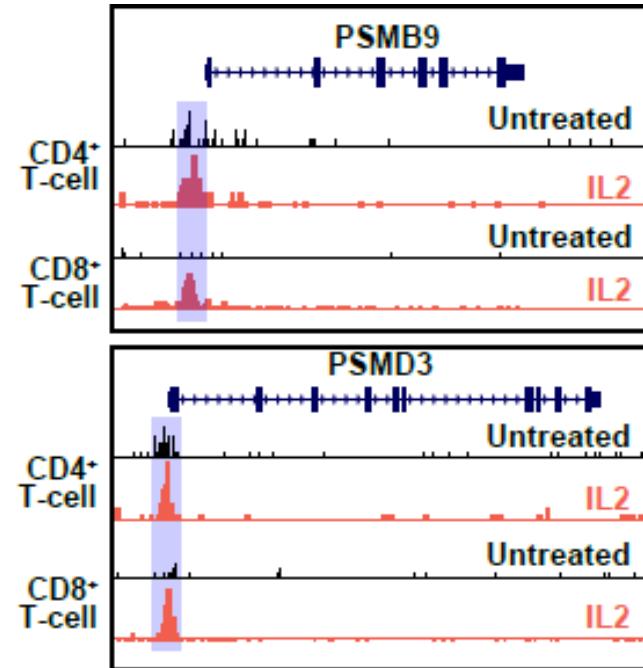


# Orthogonal IL-2 Suppresses Proteasome Activity

Decreased proteasome activity  
in response to ortho IL-2

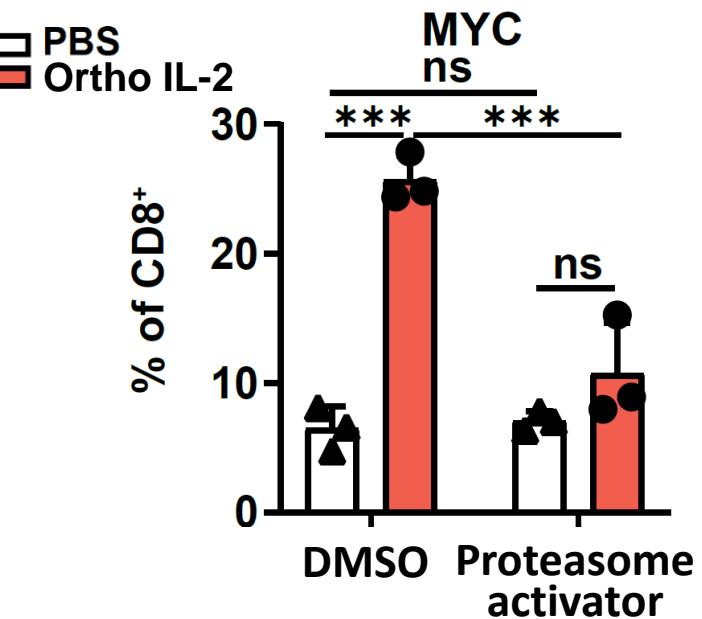
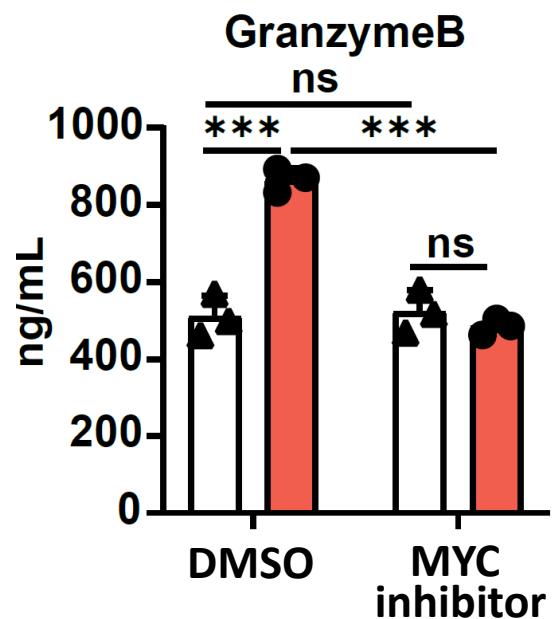
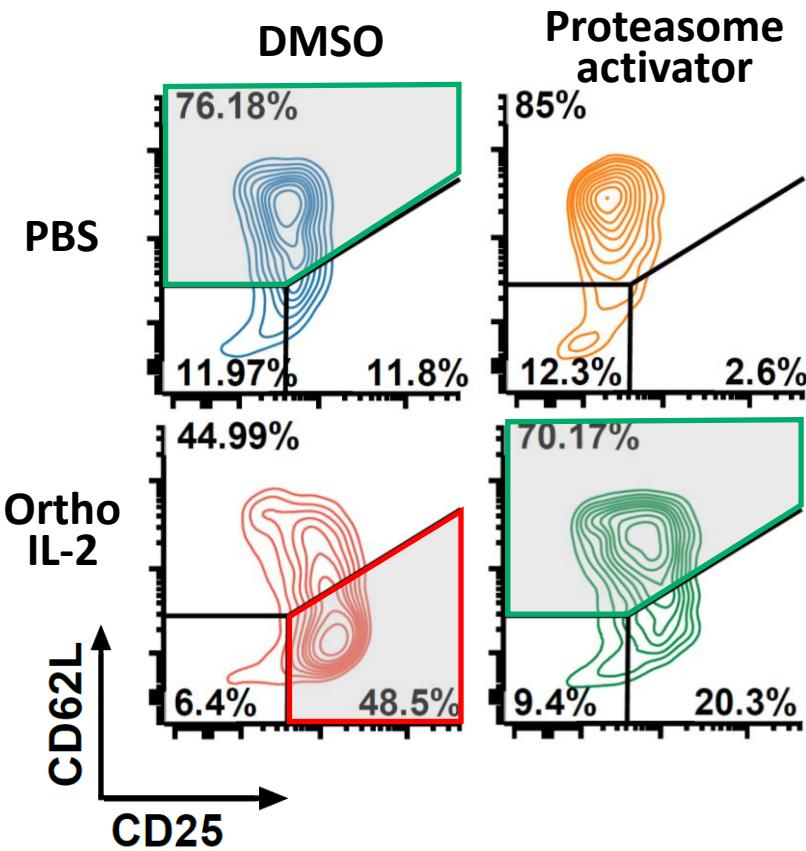


IL-2-induced STAT5 binds to  
TSS of proteasome genes



Ortho IL-2 → Proteasome ↓

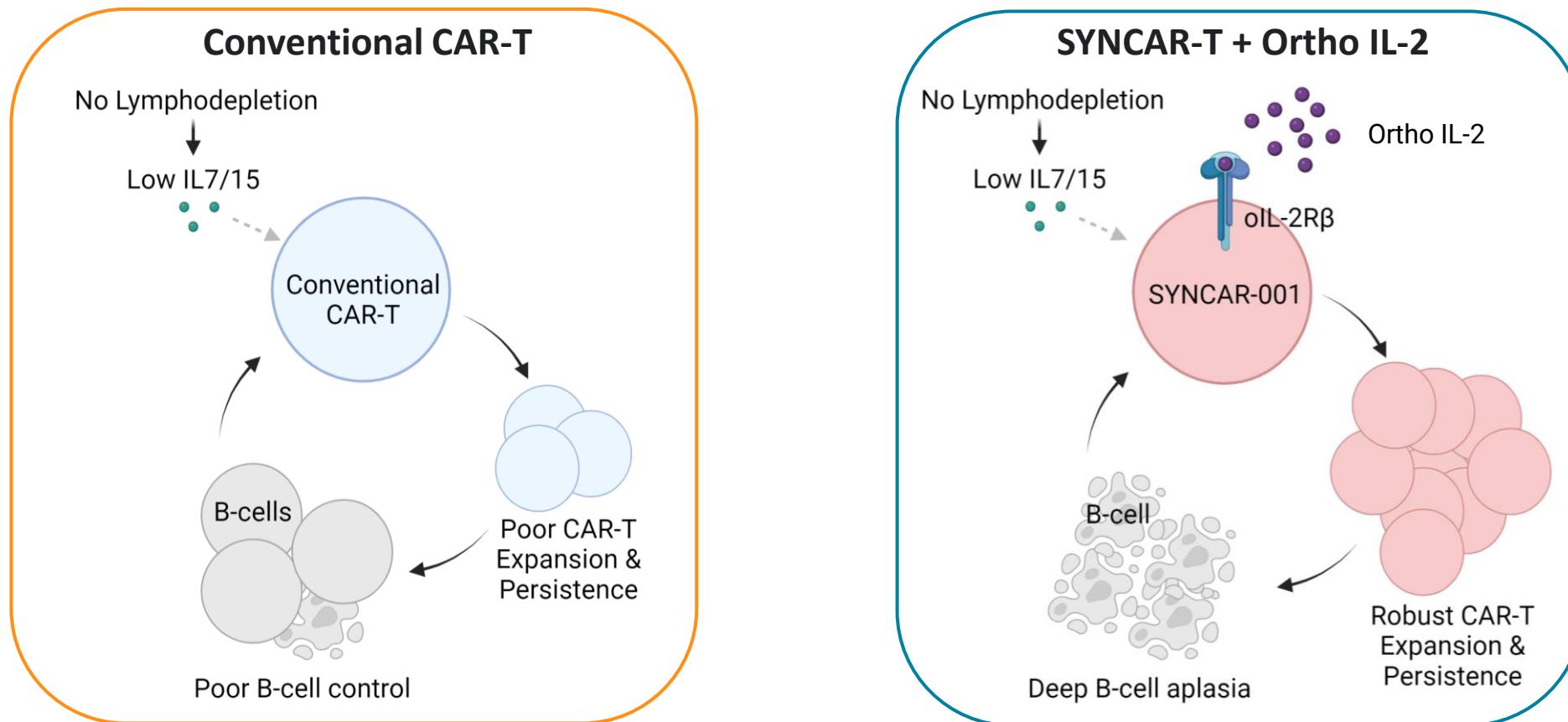
# Orthogonal IL-2 Promotes MYC Expression by Dampening Proteasome Activity, Thereby Fostering Effector Differentiation



Ortho IL-2 → Proteasome ↓ → MYC → Effector

# Potential of Orthogonal IL-2 to Support CAR-T Proliferation Without Lymphodepletion

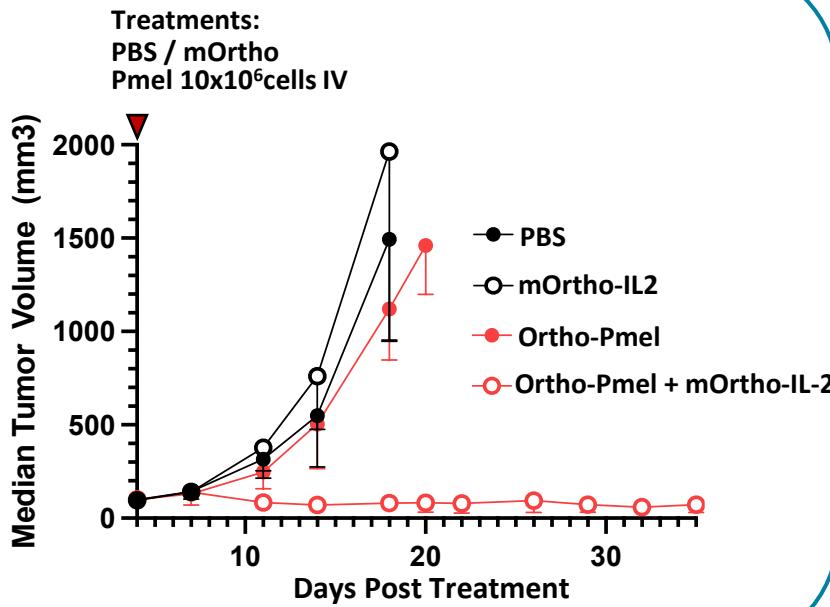
Ortho IL-2 provides signal 3 (STAT5) required for CAR-T expansion and persistence in a lymphoreplete condition.



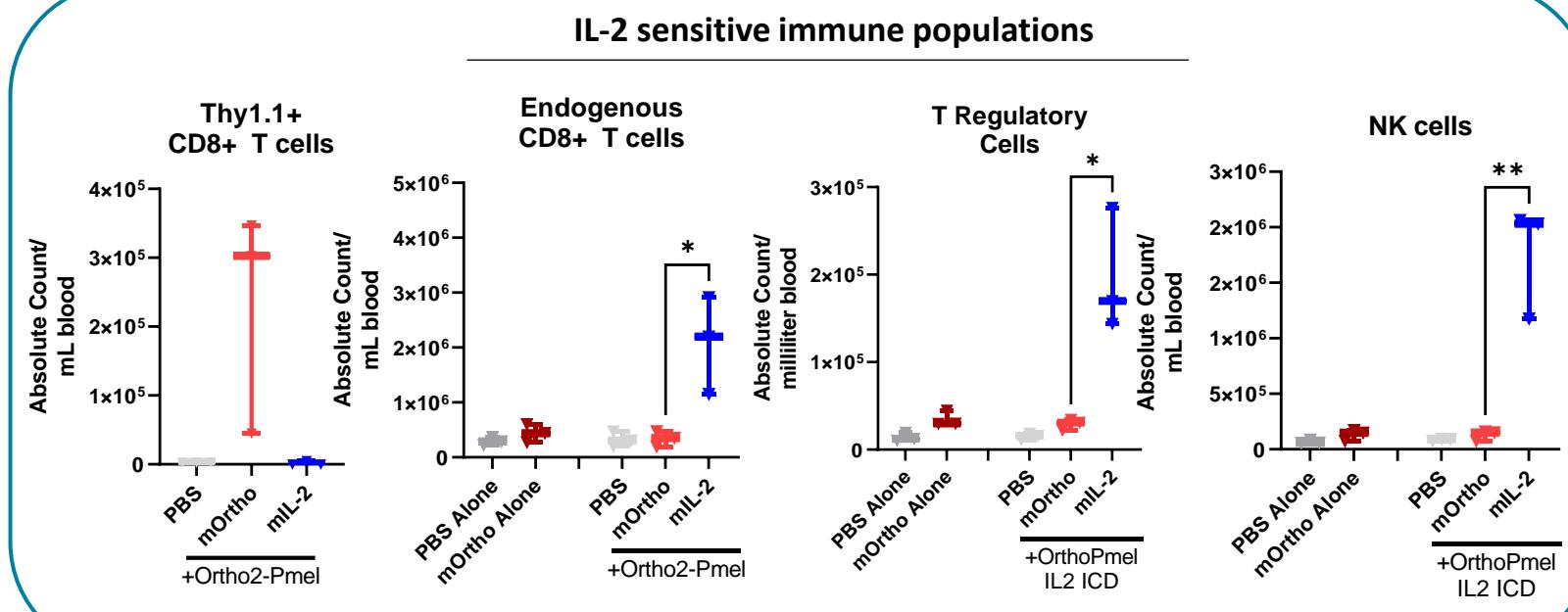
# Orthogonal IL-2 System Provides Adoptive Cell Therapy Efficacy Without Lymphodepletion

B16 mouse melanoma model with Pmel-TCR Transgenic T-cells and a mouse ortho IL-2

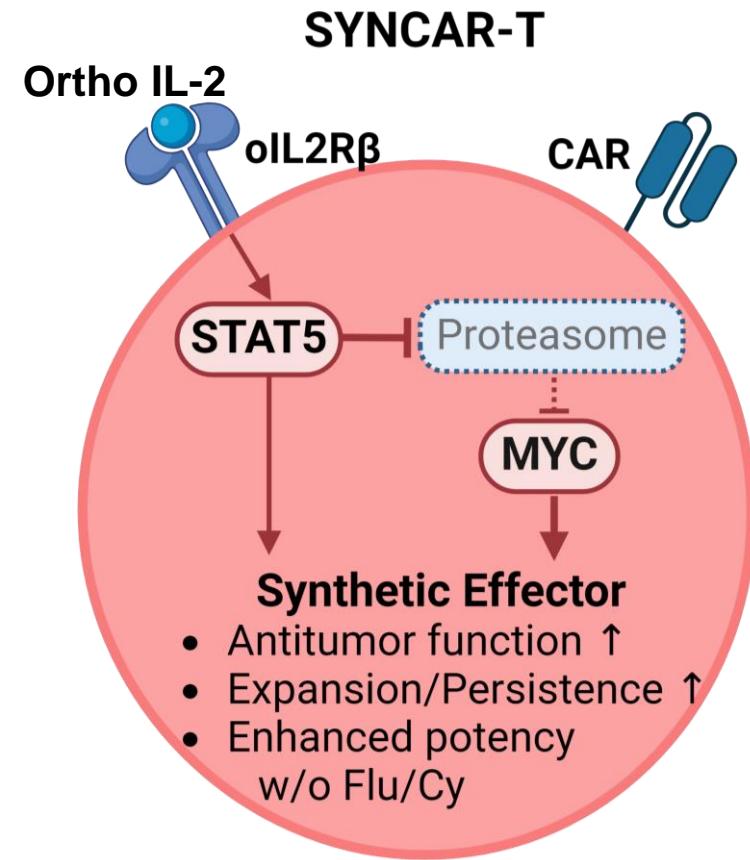
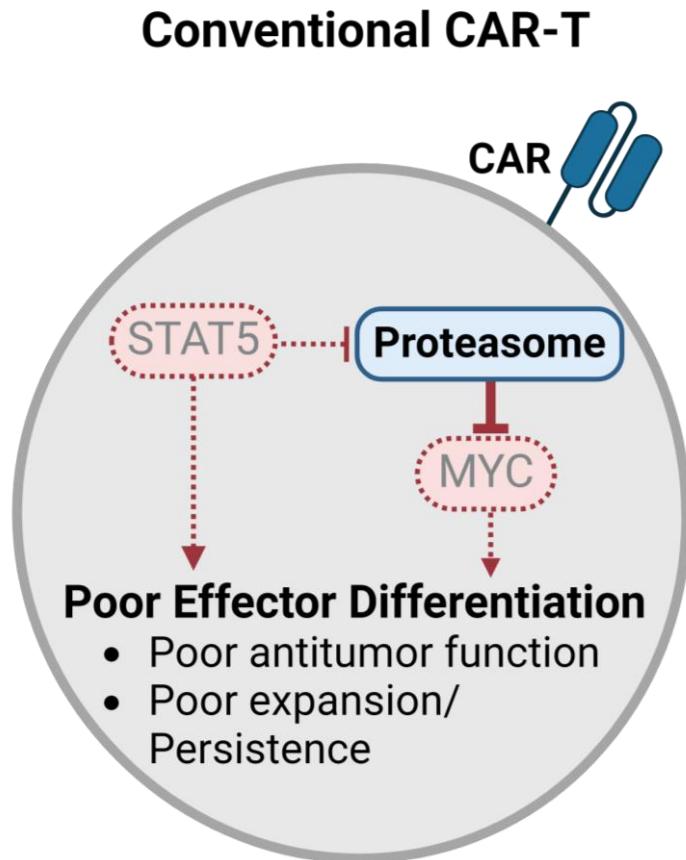
OrthoPmel + Ortho IL-2 shows tumor growth inhibition in a *non-lymphodepleted* model



Ortho IL-2 *specifically* expands orthoPmel T cells *in vivo*



# Orthogonal IL-2 Summary



# Acknowledgements

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