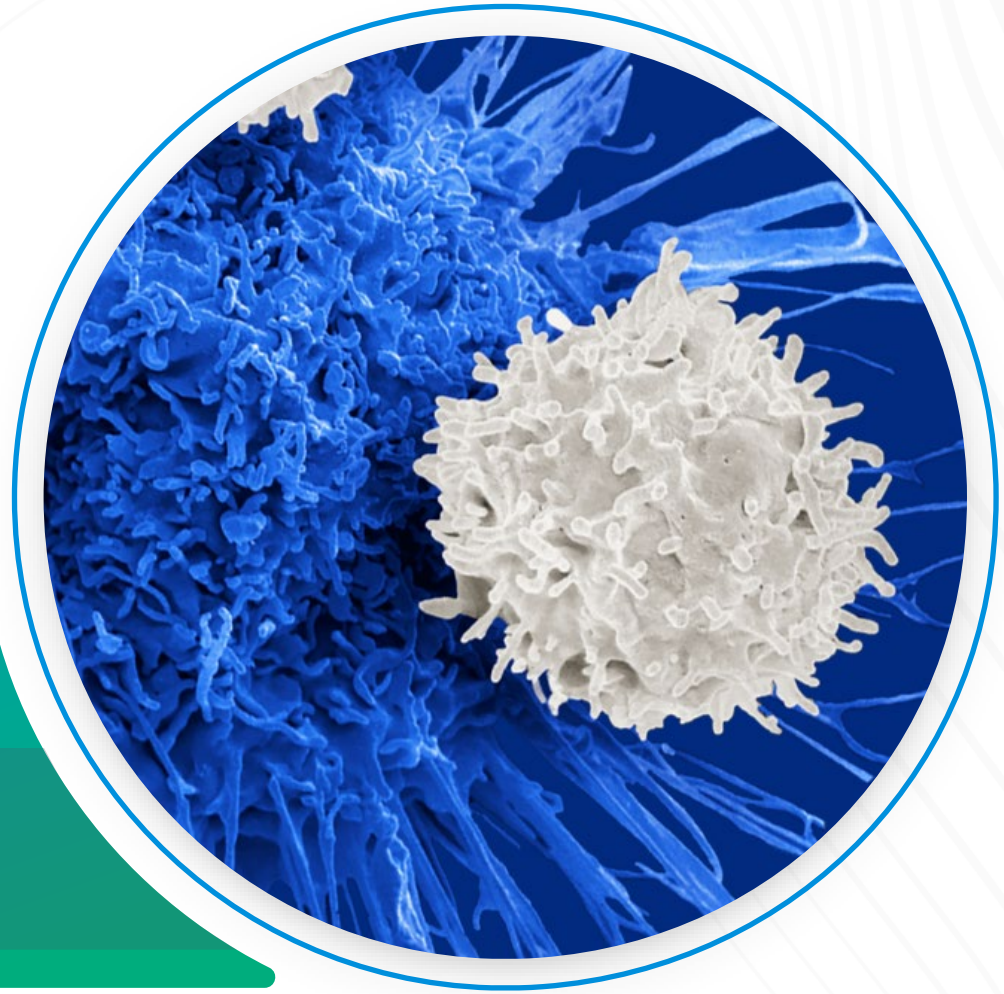
CENTURY THERAPEUTICS

Generation of iPSC-derived CD19 CAR T cells with robust in vivo tumor control and persistence

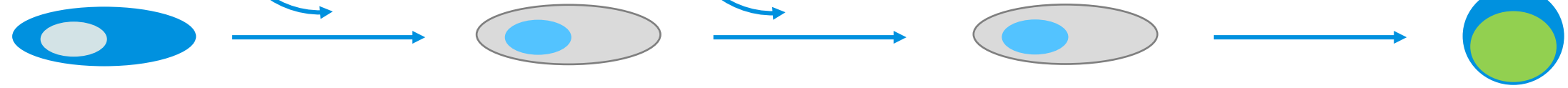


Dar Heinze, ASGCT 2025

iPSC-derived CAR-T cells could be a consistent, off-the-shelf cellular immunotherapy.

Reprogramming
- OCT4
- SOX2
- KLF4
- L-Myc
- LIN28
- P53 shRNA

Allo-Evasion™ 5.0 edits
- IDP
- CD300a TASR
- CAR
- HLA I and II KO



Differentiation

Somatic cells

iPSCs

- Unlimited, consistent supply
- Controlled, validated editing
- Can differentiate into any cell type in the body

iPSCs with validated edits supply cells for lifetime of product.

iPSC- CAR-T cells

A truly off-the-shelf therapeutic

By addressing two key challenges, a new class of successful T cell therapies can be developed.

T CELL DIFFERENTIATION

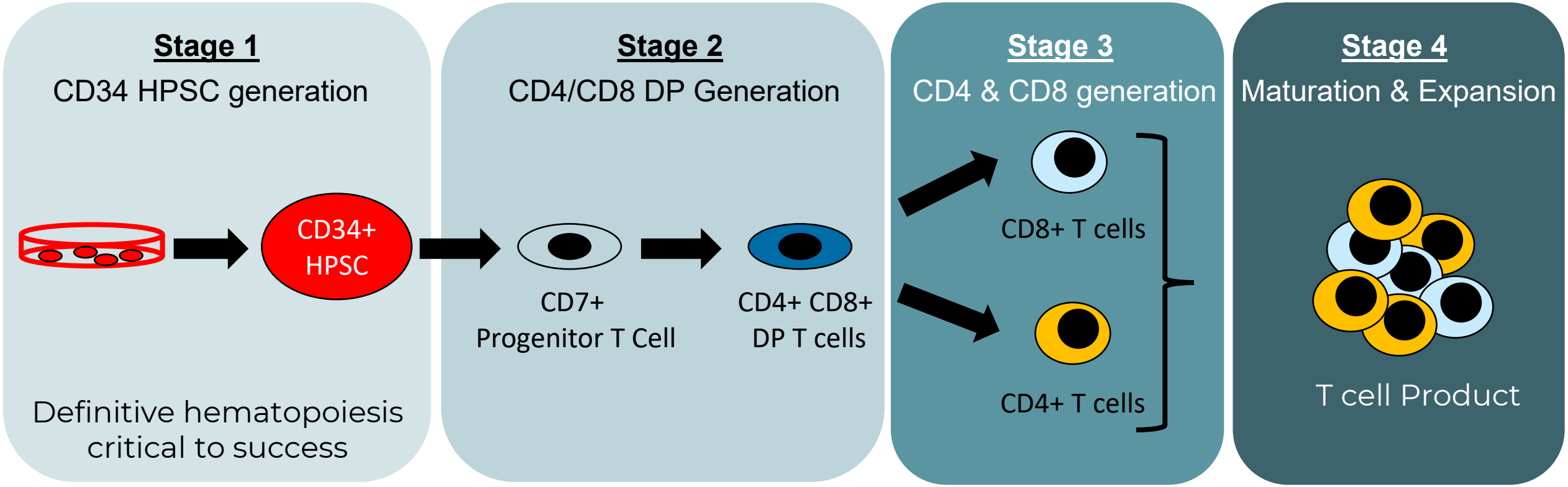
- A feeder free method for generating $CD4^+$ and $CD8^+$ CAR T cells with $\alpha\beta$ T cell performance

IMMUNE REJECTION

- CD300a TASR, a novel pan-NK inhibitor (Zhang et al. 2024; *Blood Advances)*
- Incorporation of a novel Immunoglobulin protease

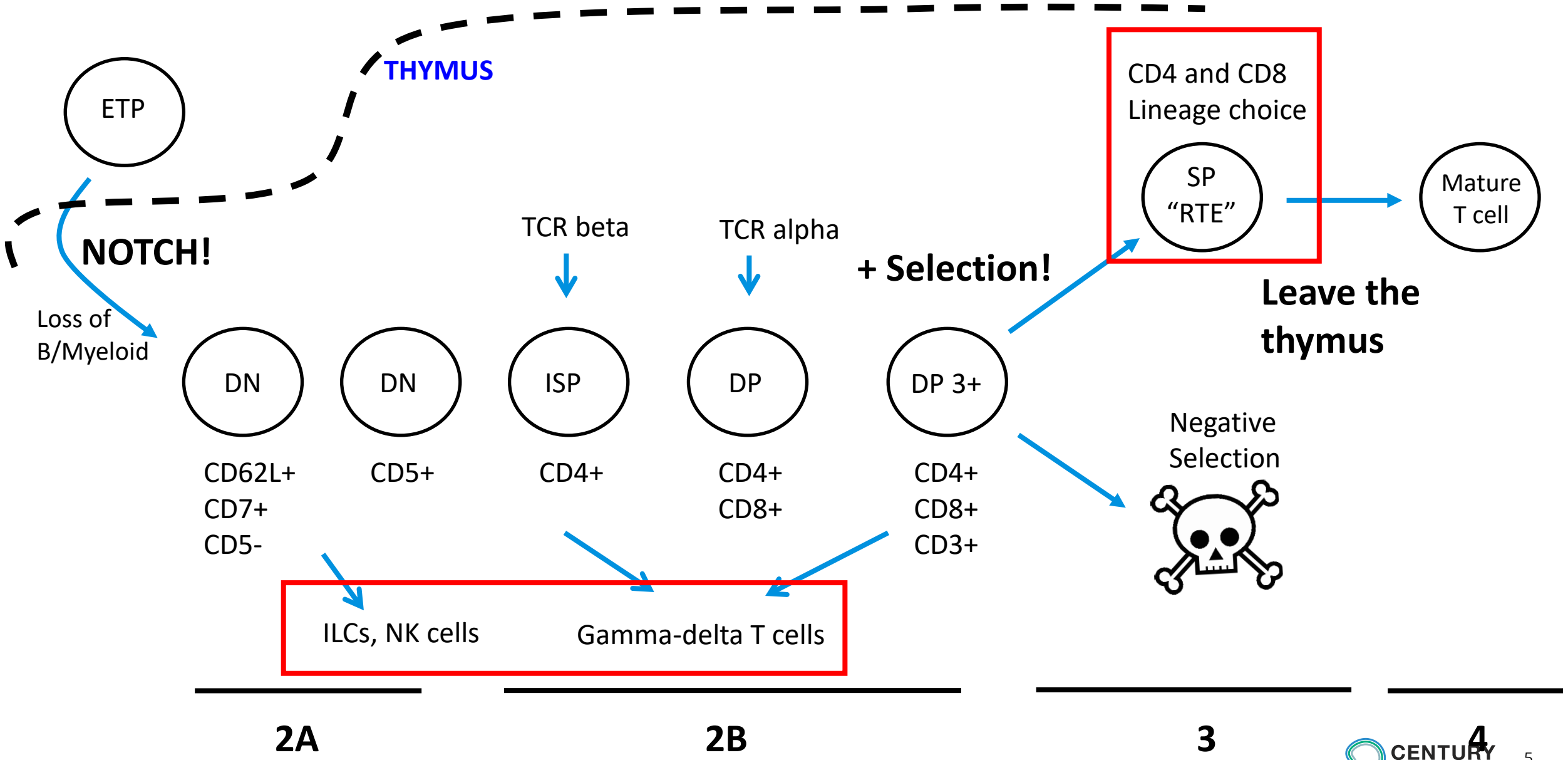
T Cell Development in a Dish: An engineering and biological challenge

Goal: Generate a scalable, feeder-free process that properly mimics the complex series of instructional cues that occur during normal human T cell development



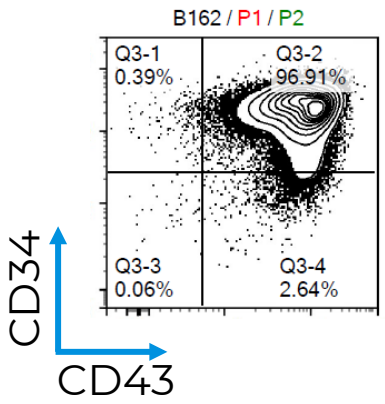
CENTURY THERAPEUTICS

Developing T cells require Notch and MHC selection signals in the Thymus



Century's iT cell process follows expected development with high yield and viability.

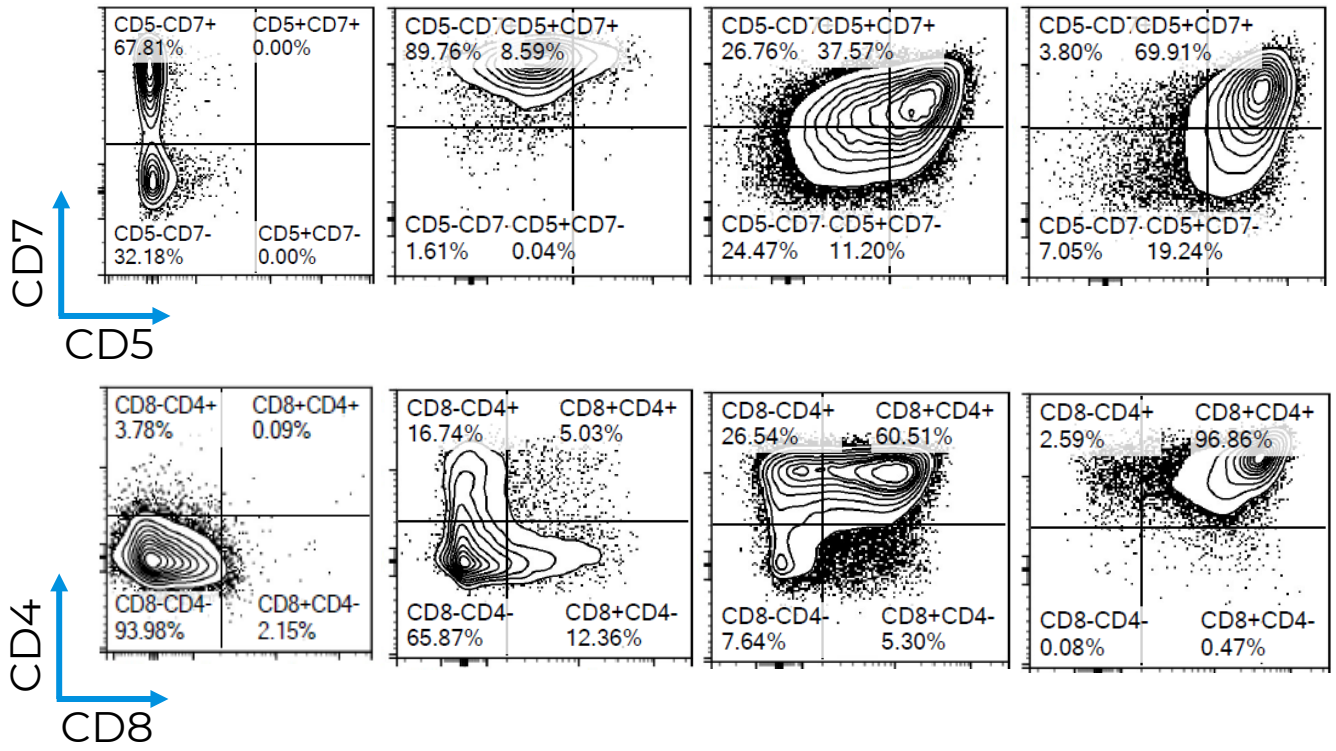
Day 13

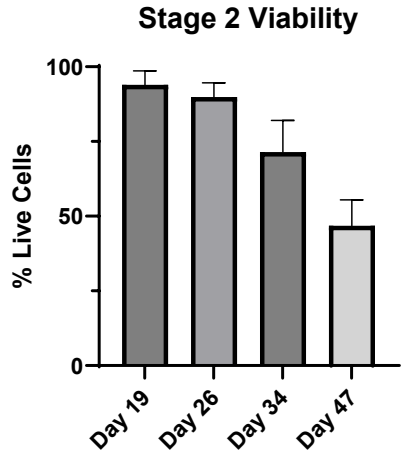


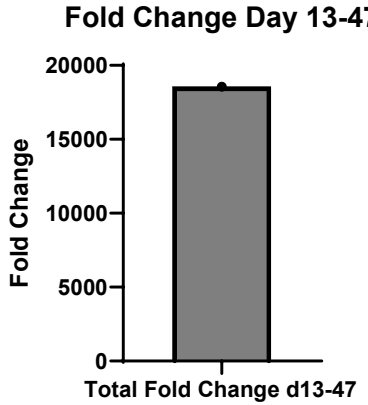
Negative for:

- CD235a
- CD41
- CD36
- CD62L

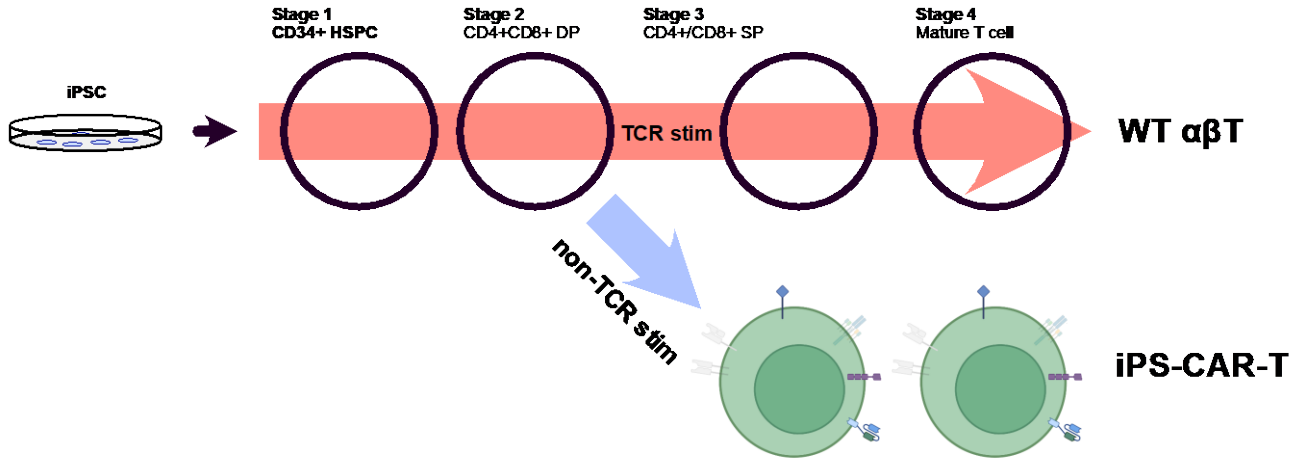
Day 19 | Day 26 | Day 34 | Day 47



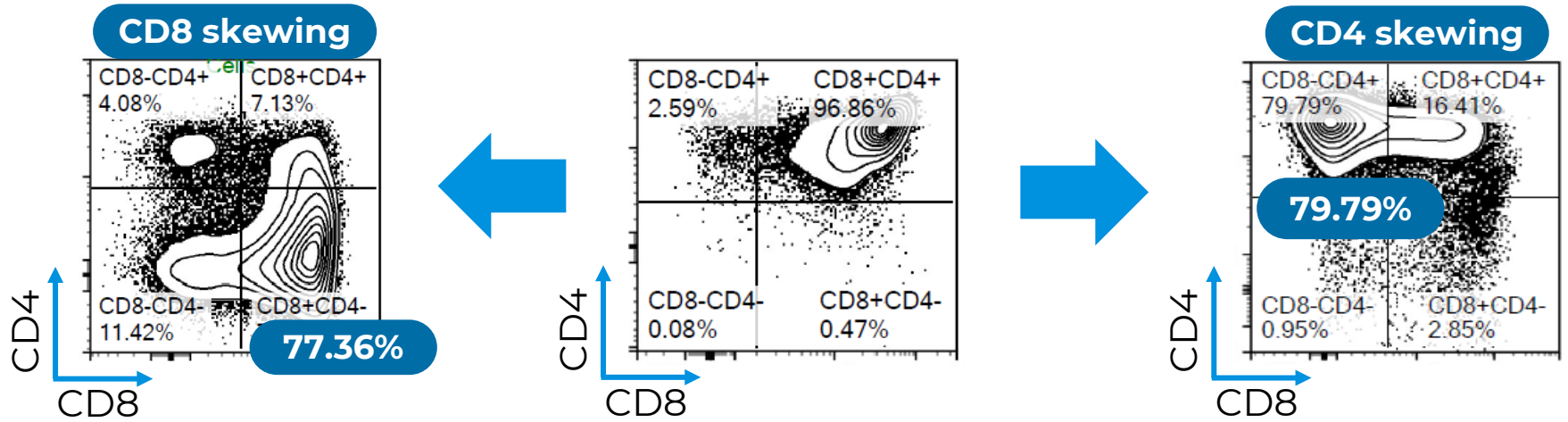




Controlled generation of CD4+ and CD8+ adaptive T cells in CAR engineered cells that don't express an αβTCR.

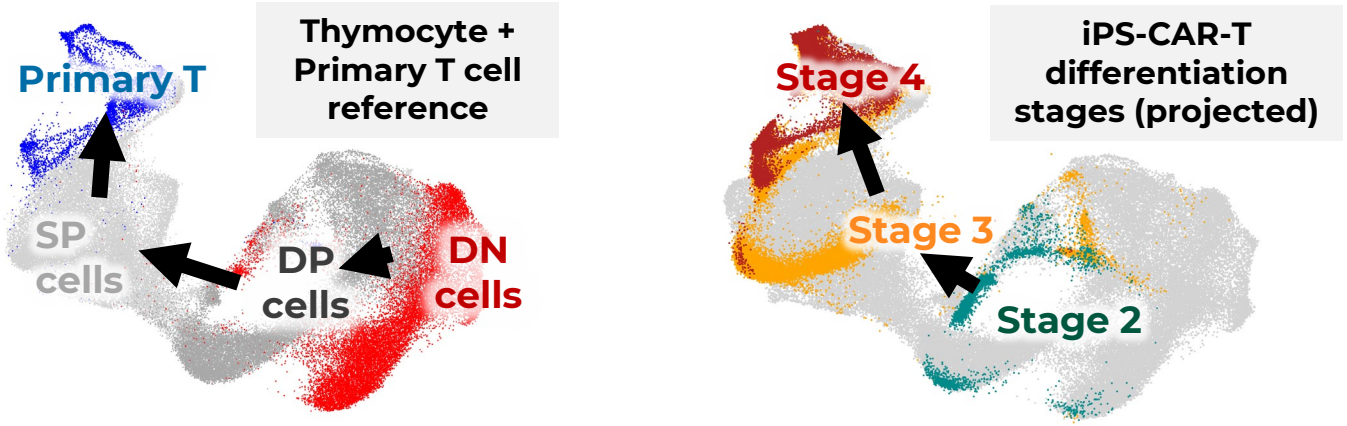


Stage	Fold change from iPSCs	Ending Viability
HSPC	3	90%
CD4+/CD8+ DP	54,000	48%
Maturation	860,000	80%

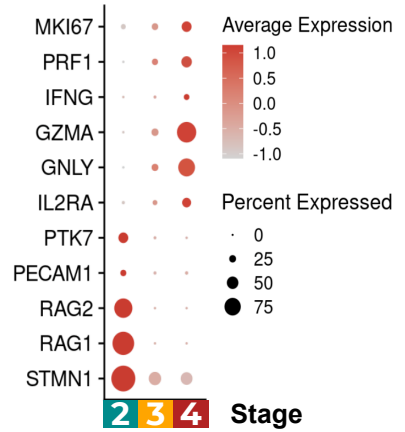


Century iPSC-CAR-T cells traverse thymocyte development

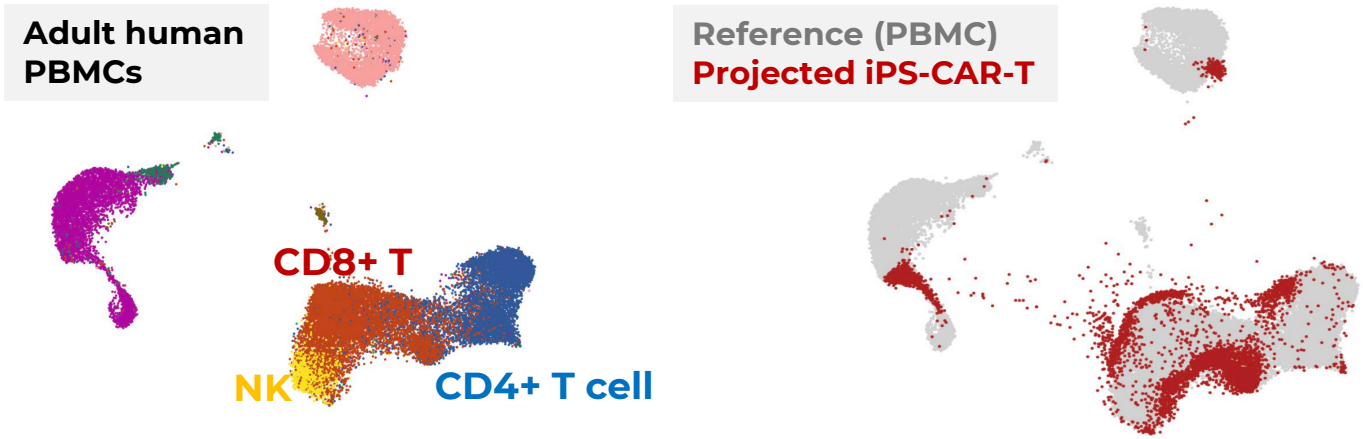
iPSC-CAR-T differentiation projected onto human thymocytes



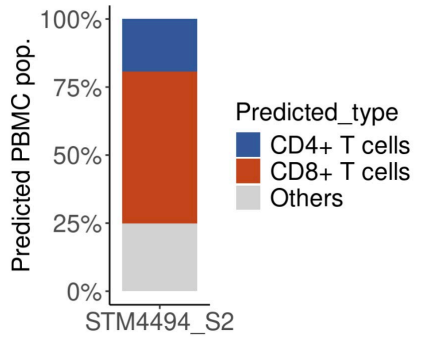
Gene expression by differentiation stage



iPSC-CAR-T projected onto human PBMC



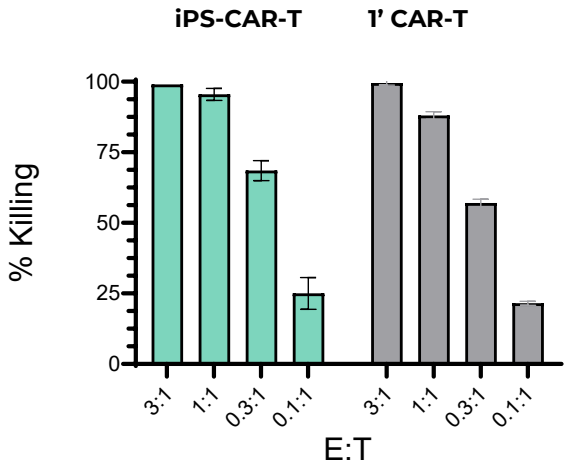
iPS-CAR-T predicted PBMC identity



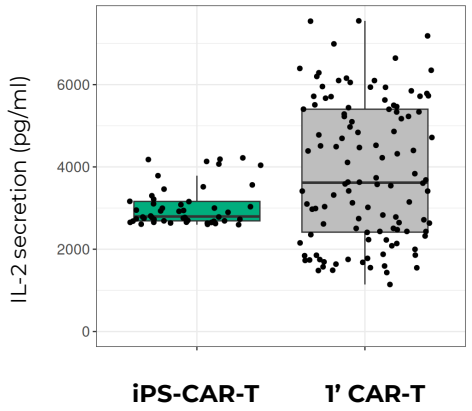
Century's iPSC-CAR-T cells display the functional characteristics of adult primary T cells: In vitro activity

Therapeutic efficacy requires:

1. Cytotoxicity Effector function

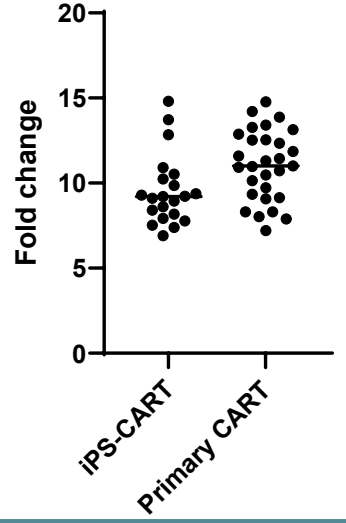


2. Cytokine (IL2) production

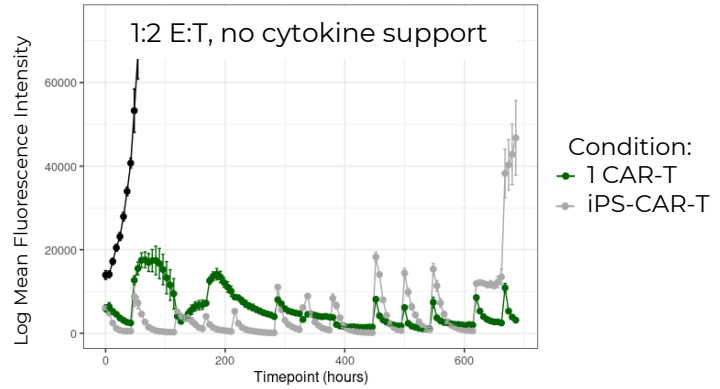


3. Cell expansion and persistence

Proliferation on target engagement



Repeat Killing



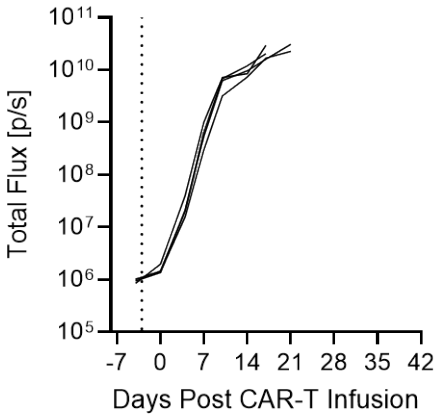
Effective T cell therapies require the generation of iPSC-CAR-T cells with three key in vitro cell functions

A single infusion of iPSC-CAR-Ts consistently controls NALM6 tumors

In vivo experimental details

- Disseminated Nalm6 model (1e5 cells infused)
- Effectors added 3 days post-tumor infusion
- 1’ CAR-T dose: 5e6 cells
- iPSC-CAR-T dose: 30e6 cells
- No added cytokine or small molecule support

Representative PBS control



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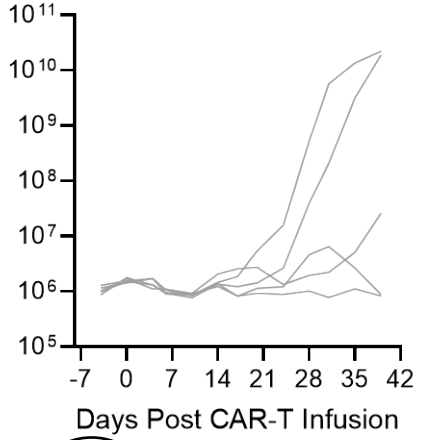

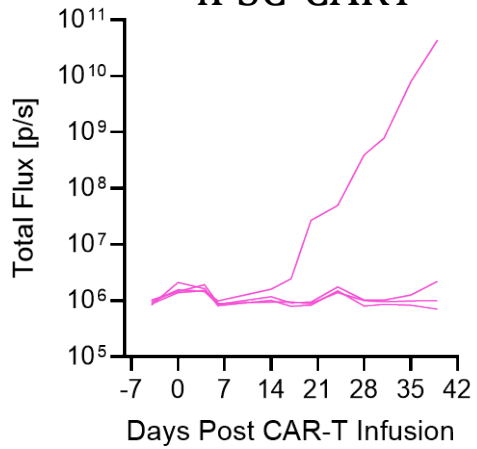

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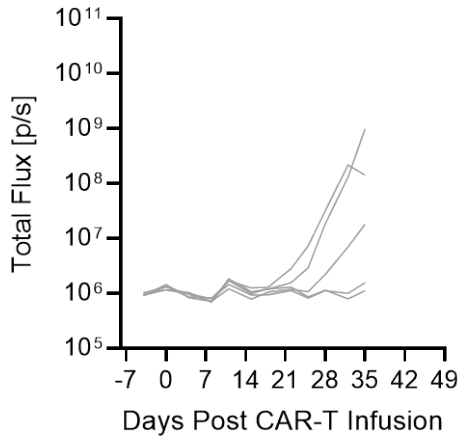

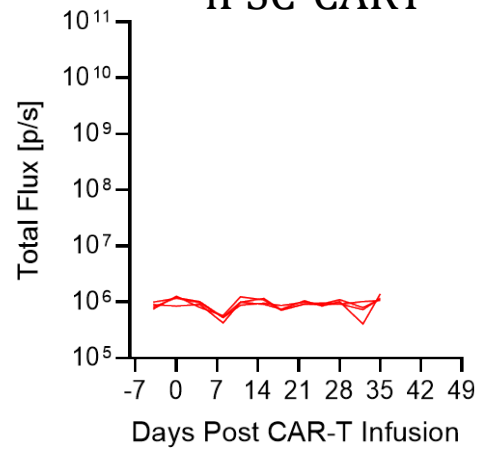

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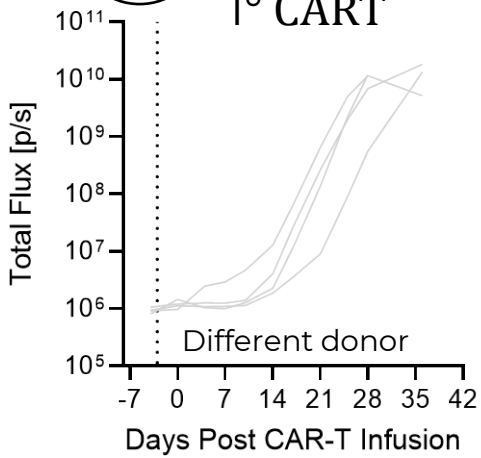

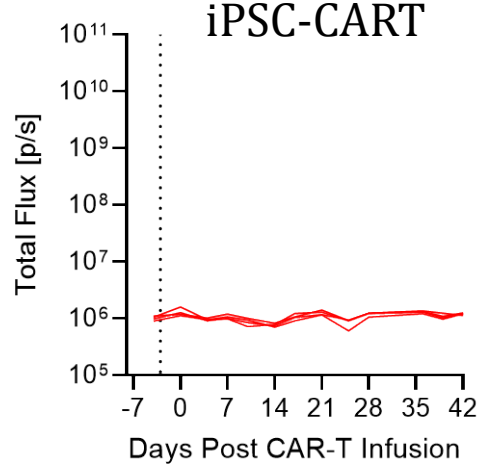

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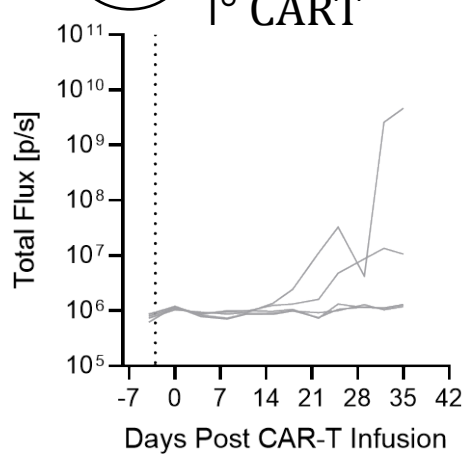
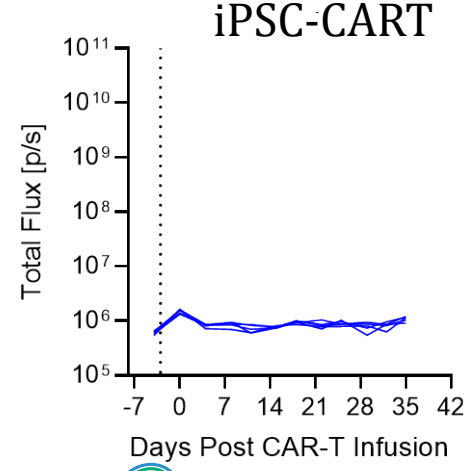
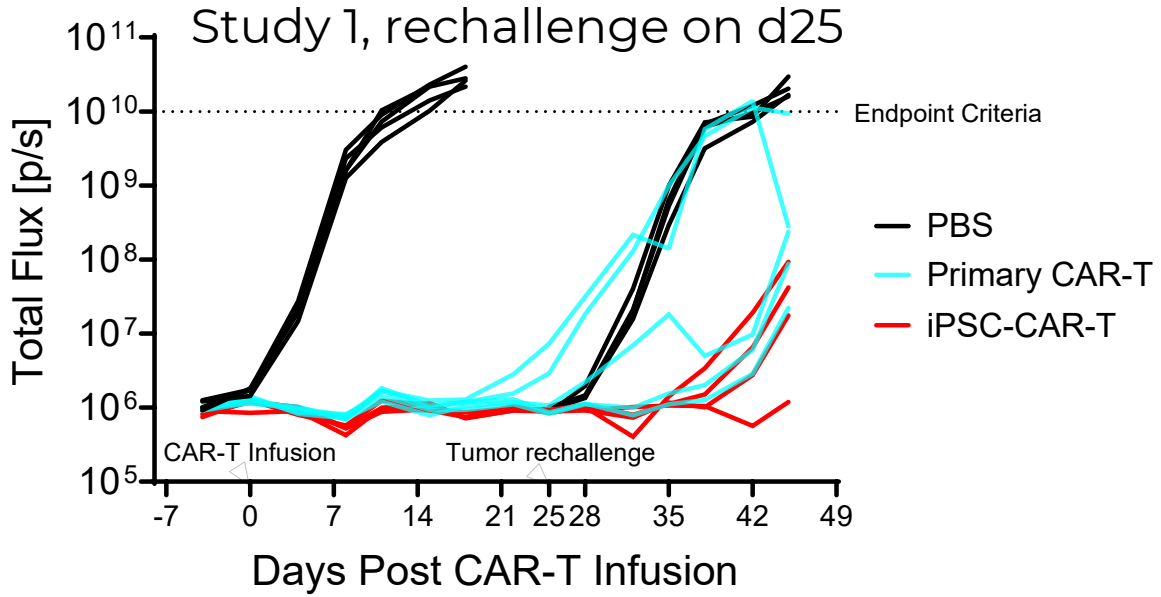
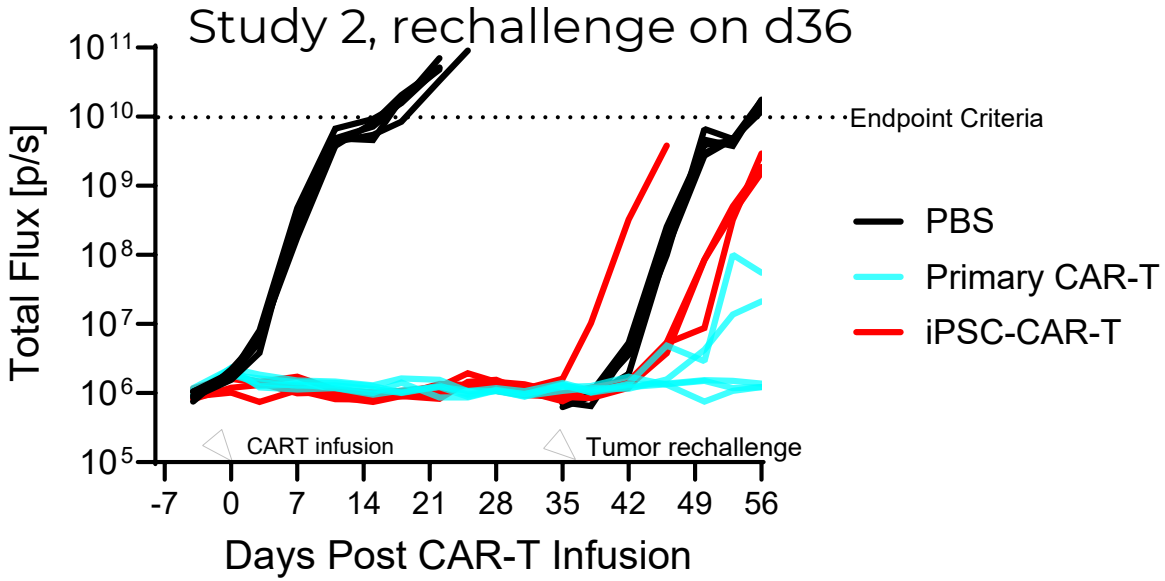
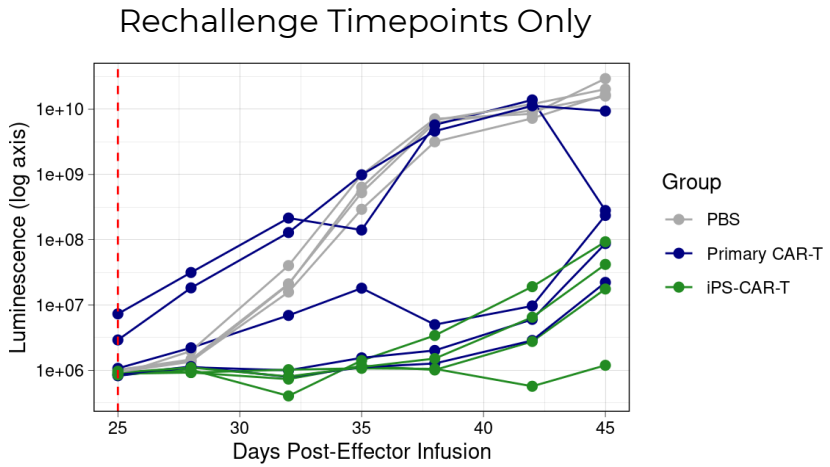


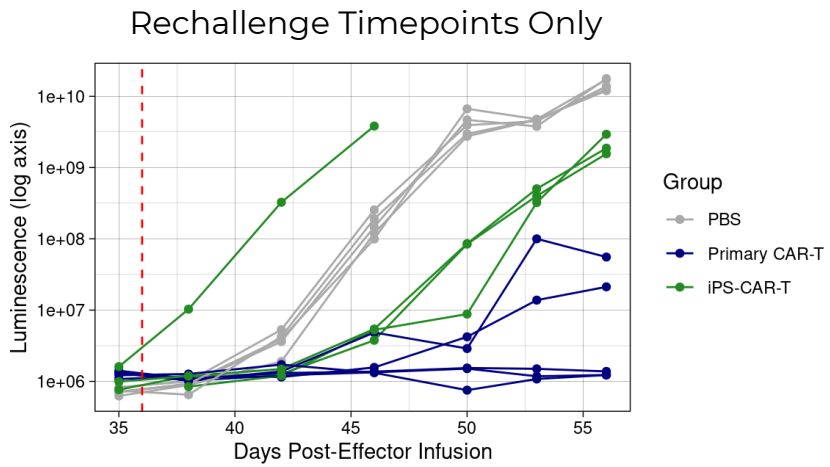


Transient response on tumor rechallenge up to 36 days after CART infusion









In vivo target-mediated expansion of iPSC-CAR-T cells

In vivo experimental details

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- iPSC-CAR-T dose: 30e6 cells
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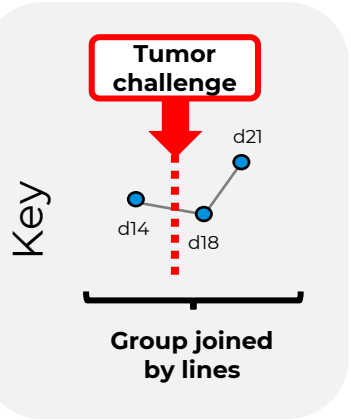
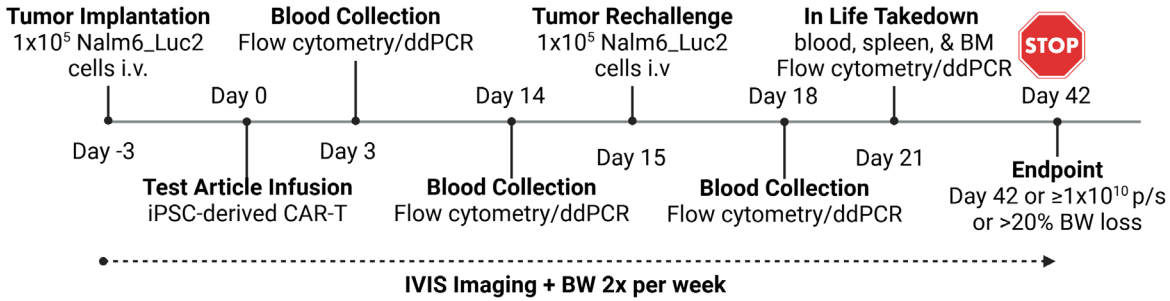
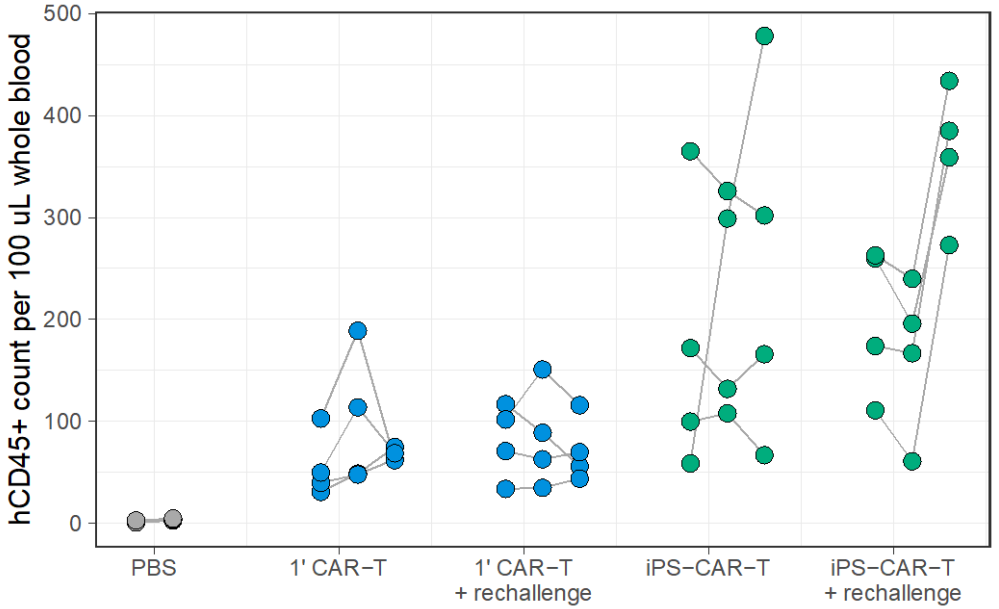
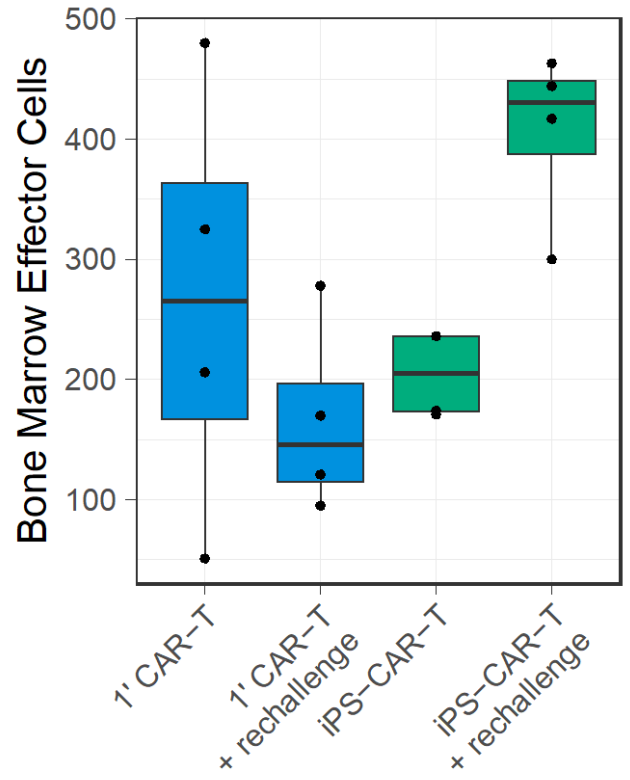




Expansion of iPS-CAR-T cells after tumor rechallenge



Expansion in Bone Marrow



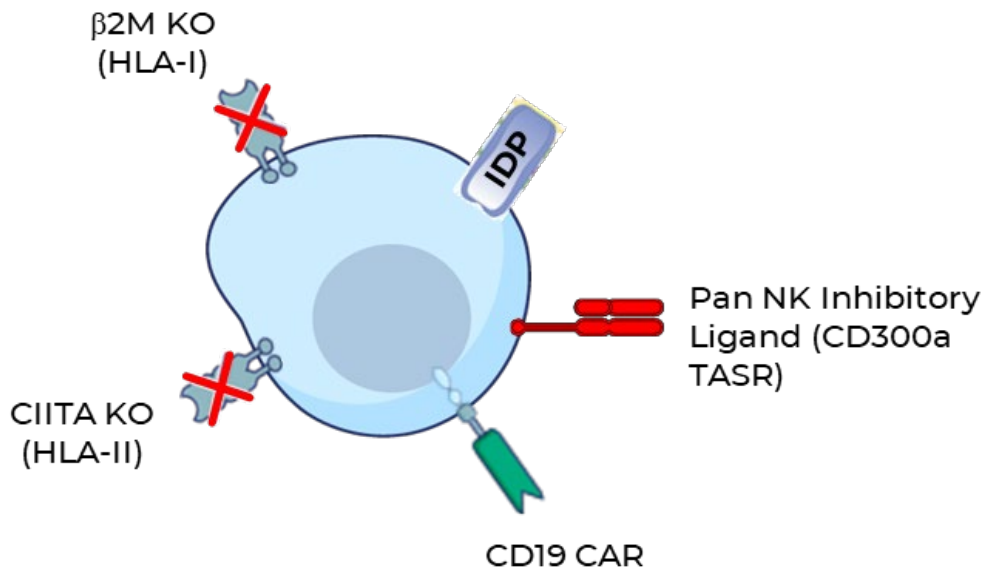
Century's iPSC CAR T cells possess key cell functions that lead to effective T cell therapies

Therapeutic efficacy requires:	Cytotoxicity: Effector function	Cytokine (IL2) production	Cell expansion and persistence
1° CAR-T	✓	✓	✓
Other iPSC CAR-T	✓	✗	✗
Century's iPSC CAR-T	✓	✓	✓

Only Century's iPSC CAR-T cells display the functional characteristics of adult primary T cells

CNTY-308 is an iPSC-derived CD19-targeted CAR-iT with preclinical efficacy comparable to autologous CD19 CAR-T cells

CNTY-308



CD4+/CD8+ αβ iT-cell

- CD19-targeted CAR to target B-cells for cytotoxic depletion
  - 4-1BB and CD3z co-stim domain to stimulate expansion on target engagement
- Allo-Evasion™ 5.0 edits include protection from host T cell, NK cell, and humoral response; αβ TCR KO to prevent GvHD
- Displays characteristics of autologous CAR-T cells[1]
  - Highly proliferative upon target engagement
  - Secretes cytokines (e.g., IL-2, IFNγ, and TNFα)
  - Cytotoxic effector function rapidly eliminates tumor cells
  - Long-term persistence *in vivo*

1. https://www.centurytx.com/wp-content/uploads/ASH_Heinze_iPSC-Derived-CD4-CD8-Final.pdf

CENTURY
THERAPEUTICS

Thank you for your attention!

This work was only possible because of the whole Century team!