Emerging and personalized cellular therapy approaches for myeloid diseases

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DISCLOSURES

Consulting Fees: Celyad, Kite/Gilead, Novartis, Servier, Precision Biosciences, CBMG

Stock Options: Adaptive Biotechnologies, Precision Biosciences

Research Funds: Atara Biotherapeutics, Celgene, Novartis

Licensing Fees: Atara Biotherapeutics

Strategies to enhance safety targeting diseased myeloid cells

Safe targets

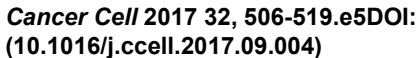# Adaptable to other immune cells ($\gamma\delta$ T cells)

- Expansion of T cells up to 3000-fold in 2 weeks

- Gene-transfer at levels similar to beads + retronectin

- Renewable cell line replaces 2 critical reagents

- Scalable

- Adaptable to MILs, TILs, <u>Gamma-Delta T cells</u>
  - **<u>Basis for a Bankhead Coley Award to fund a clinical trial in collaboration with Nelli Bejanyan. Will treat patients with MDS or AML post-allo SCT at risk for relapse</u>**
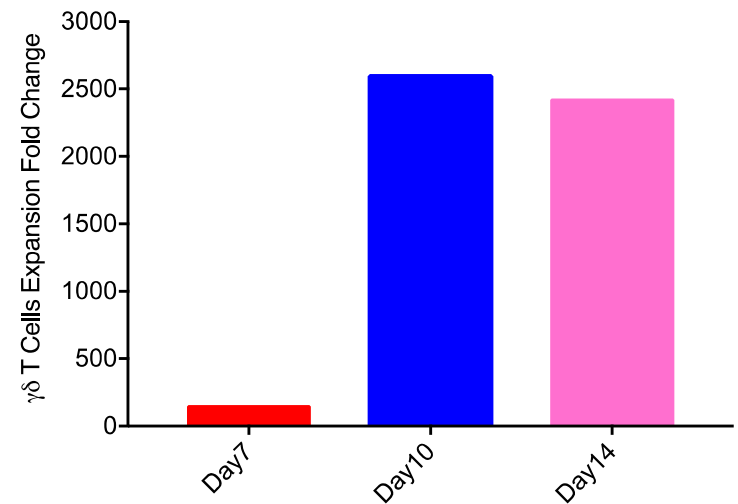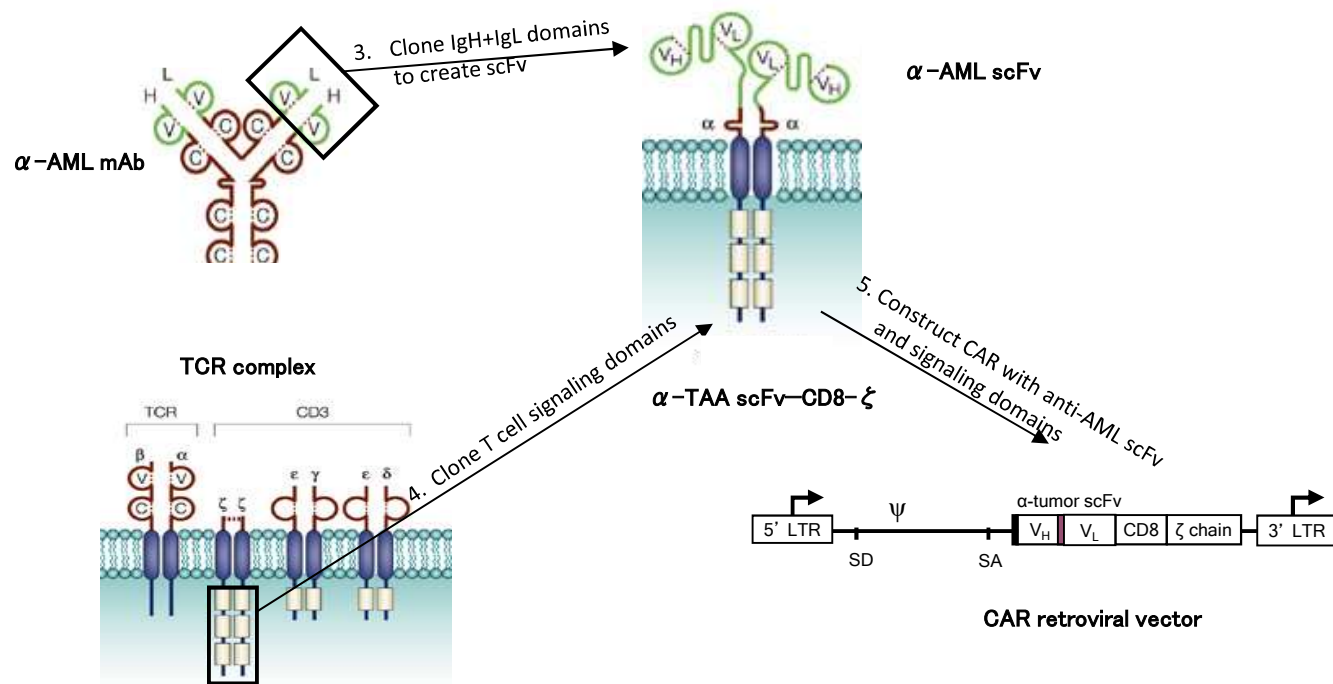
Bin Yu
Nelli Bejanyan

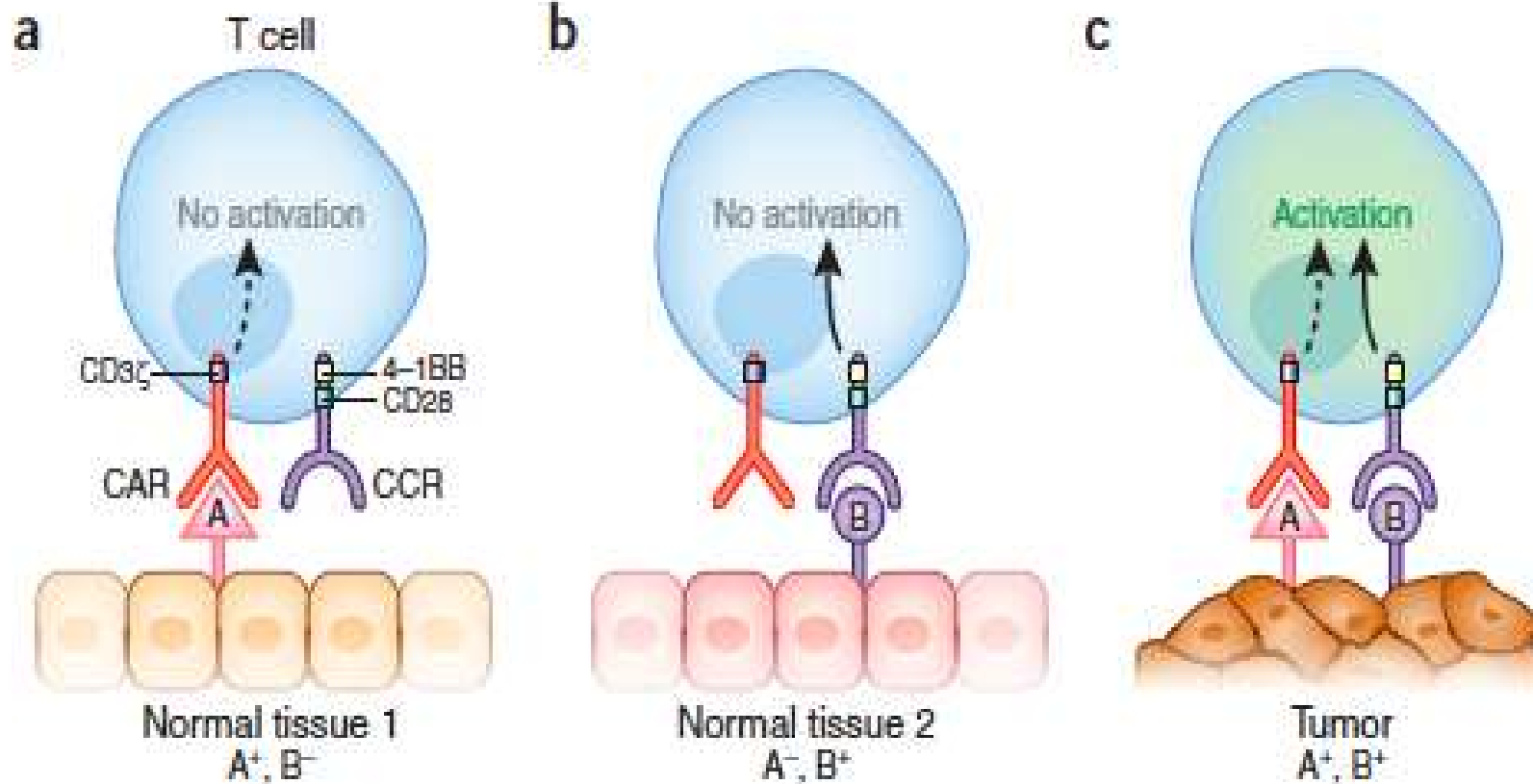# Gating strategy to focus T cells on myeloid cells not HSC

Expression of AML targets on patients BM

Develop a CAR for AML

1. Immunize mice with AML antigens
2. Screen for anti-AML antibodies

3. Clone IgH+IgL domains to create scFv

α−AML mAb

α−AML scFv

TCR complex

4. Clone T cell signaling domains

5. Construct CAR with anti-AML scFv and signaling domains

α−TAA scFv—CD8−ζ

α-tumor scFv

5' LTR | ψ | V$_H$ V$_L$ | CD8 | ζ chain | 3' LTR

SD | SA

CAR retroviral vector

Multi-antigen targeting by AND gating

Kloss et al, *Nat Biotech*

In vitro function
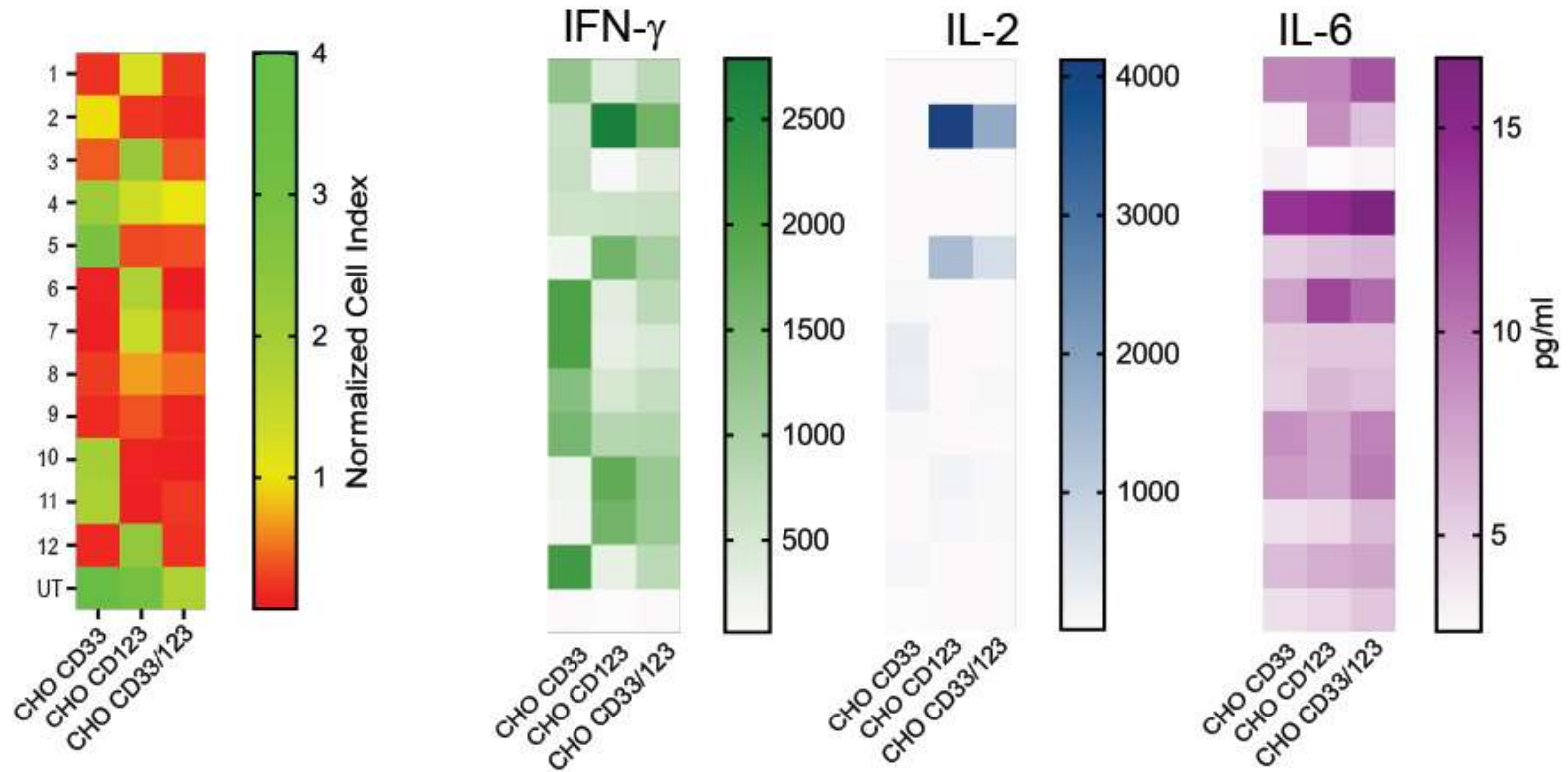
In vivo function
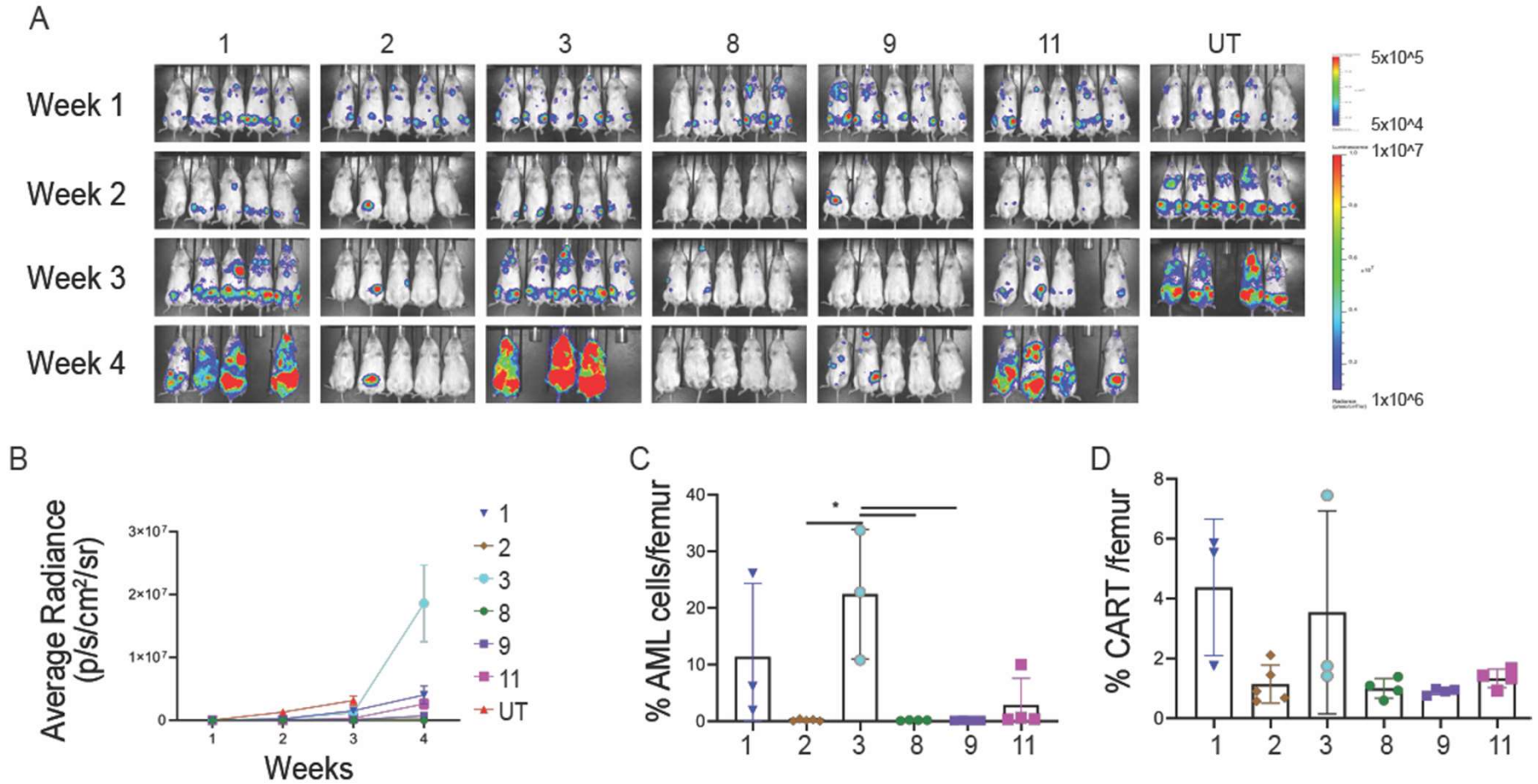
HSC toxicity assay (CFU assay)
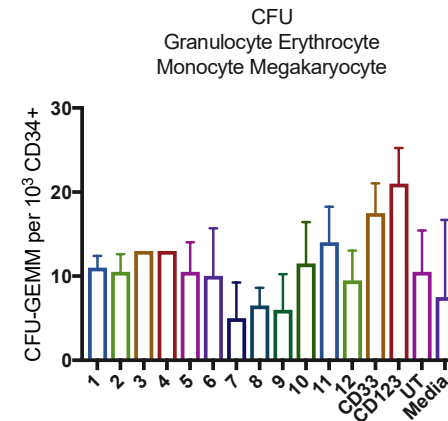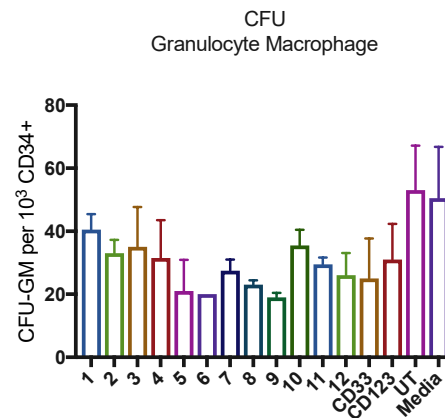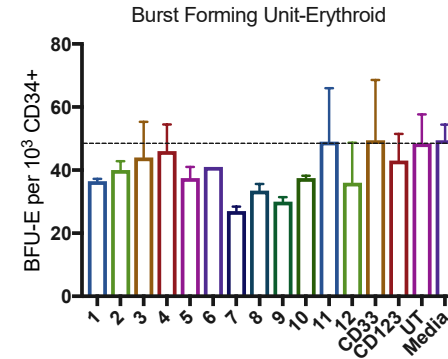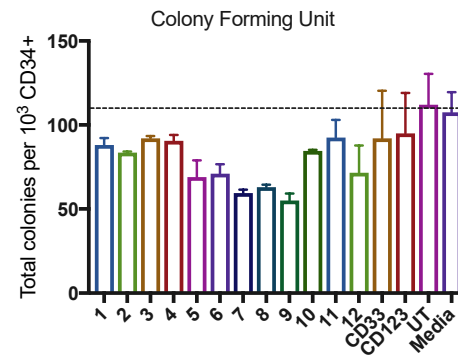
Novel targets that can be used for dual purposes

# CD83 as a target for GVHD and myeloid diseases

- For **over 3 decades**, GVHD prophylaxis has included calcineurin inhibitors (CNI) such as tacrolimus
- CD83 is a member of immunoglobulin superfamily
- Maturation marker expressed on mature DCs
- Interestingly, sCD83 is immune suppressive
- An anti-CD83 mAb, 3C12C, reduces GVHD
- CD83 is highly expressed on myeloid cells including MDS/AML

Heilingloh CS. JMB. 2017.
Horvatinovich JM. JI. 2017.
Li Z. Haematologica. 2018.

Brian Betts, UMN
*Shrestha et al JCI in press*

Designing a CD83-targeted CAR T cell
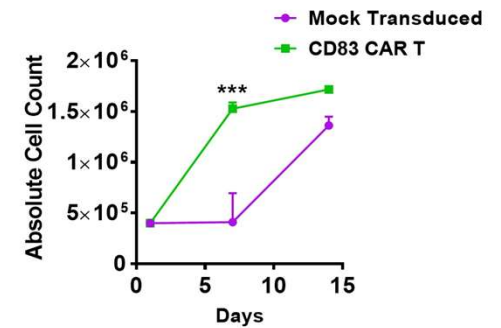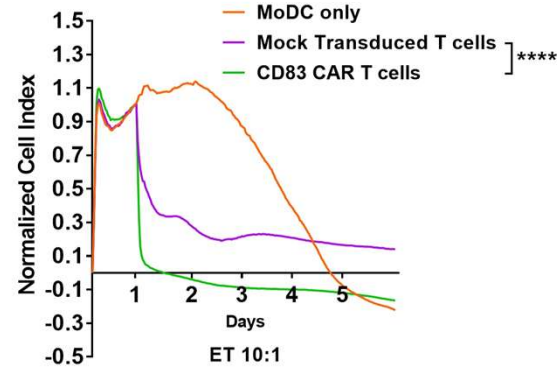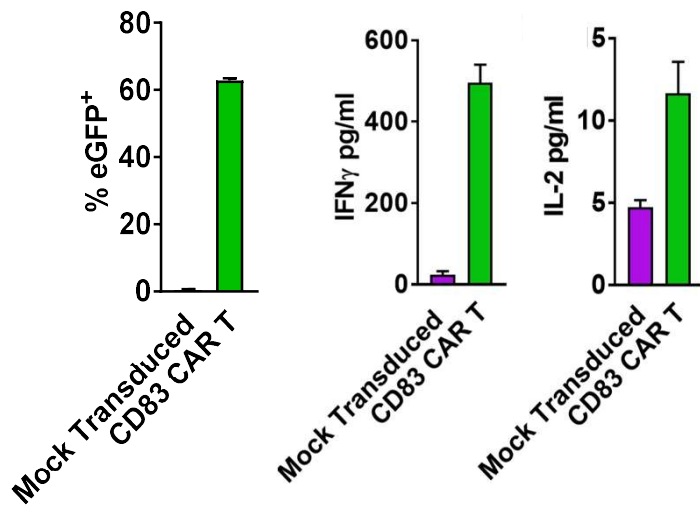
CD83 expression on alloantigen-stimulated T cells

- CD83 is significantly expressed on CD4$^+$ Tconv, compared to Tregs or CD8$^+$ T cells

- CD4$^+$ Tconv CD83 expression is rapid, within 4-8 hours of interaction with alloantigen

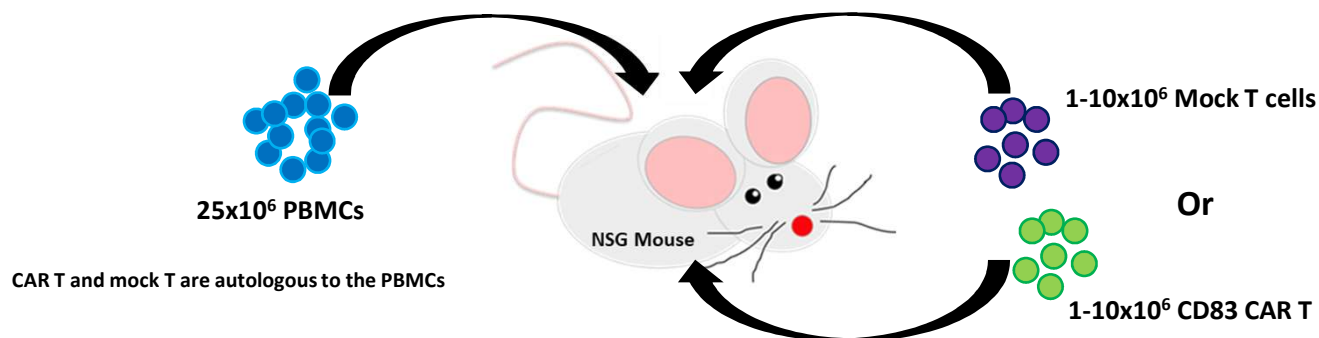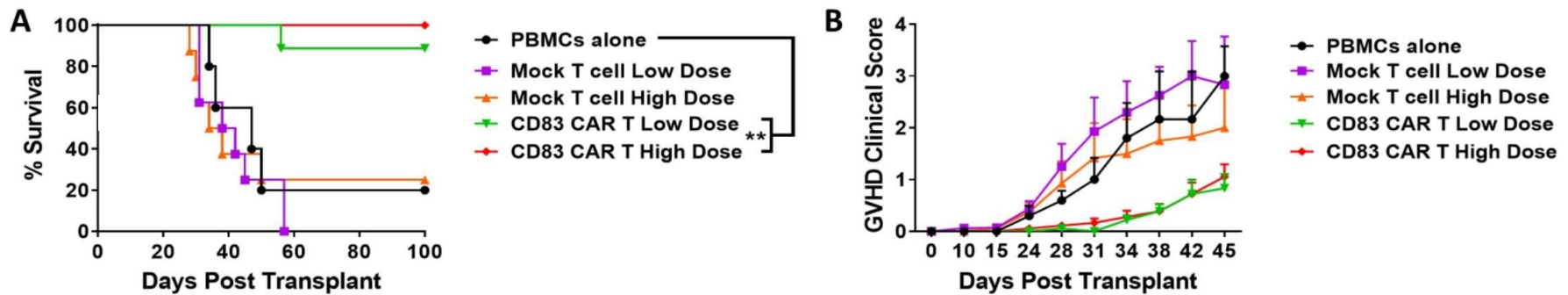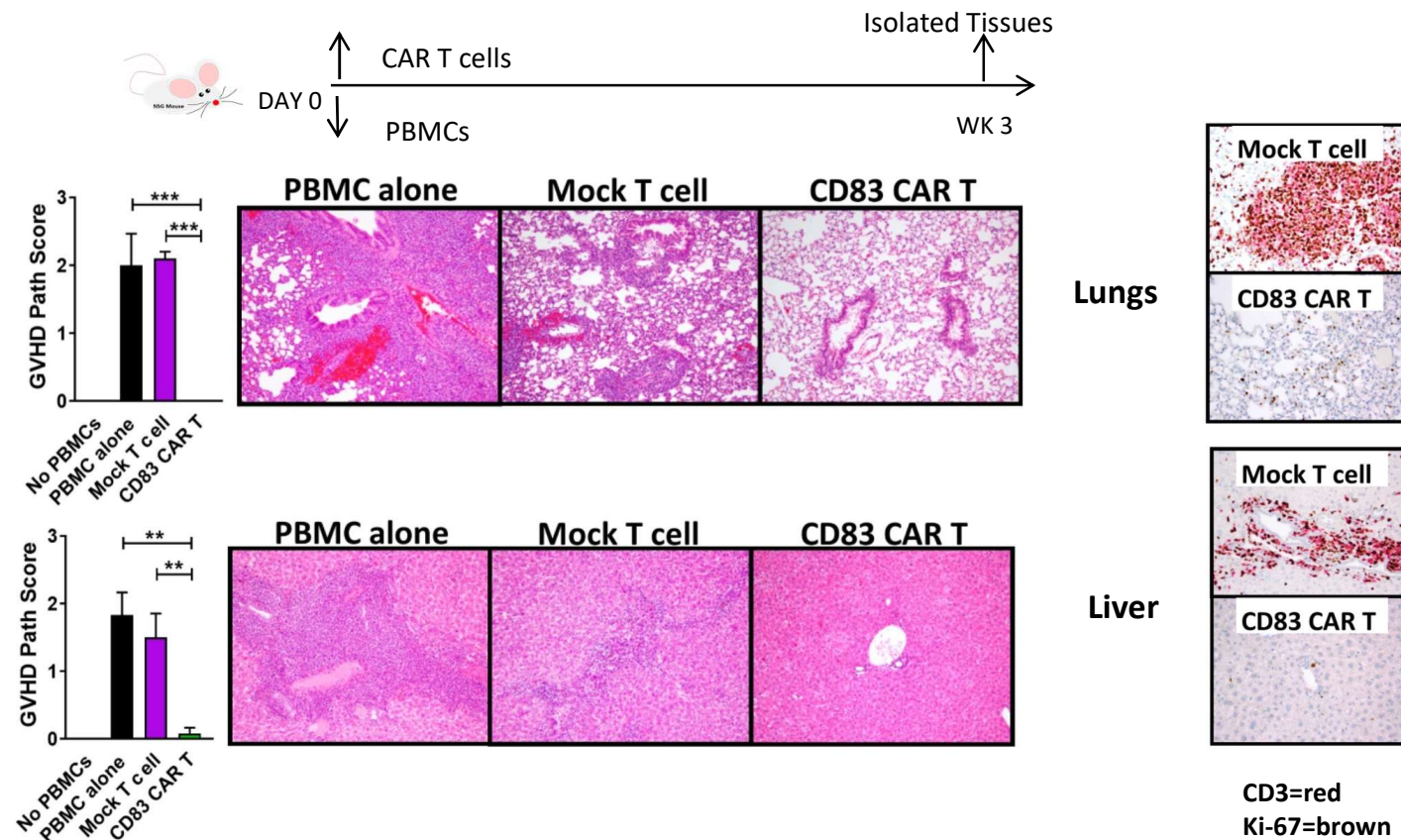- CD4$^+$ Tconv CD83 expression declines to baseline levels by 48 hours of engaging alloantigen in vitro
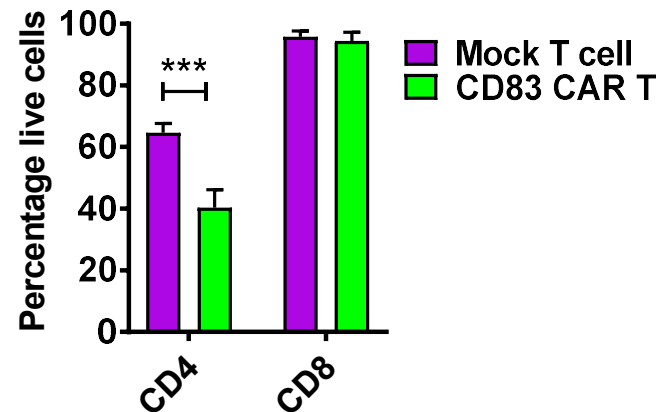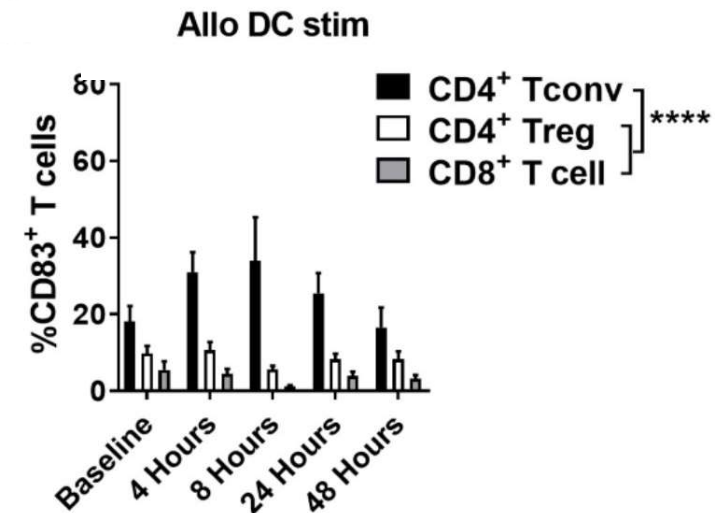
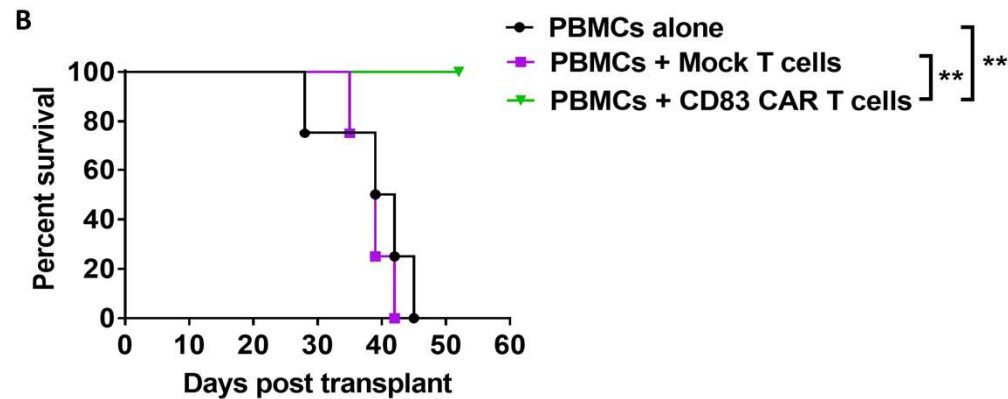# CD83 CAR T cells shut down proliferative T cells in allo-MLRs
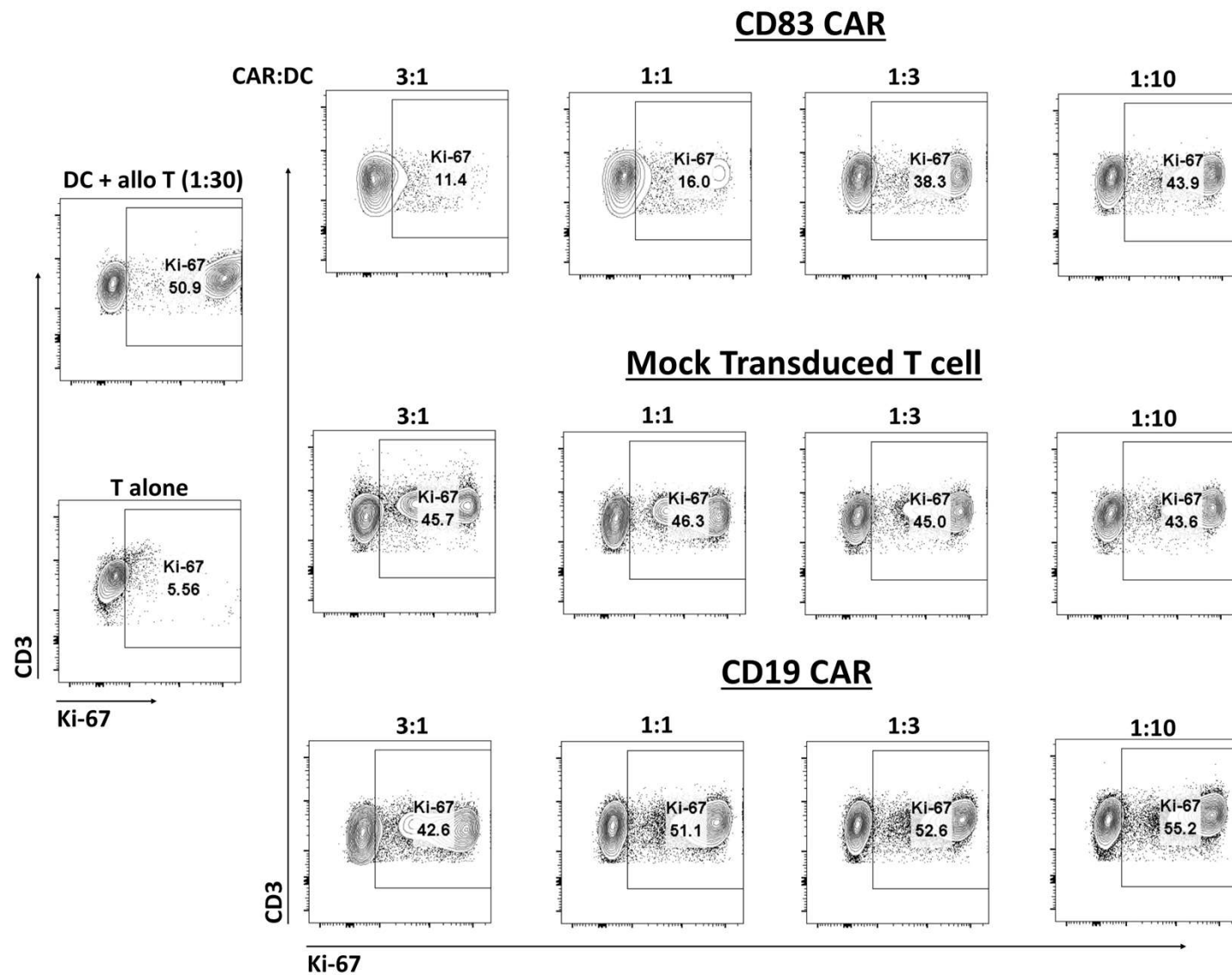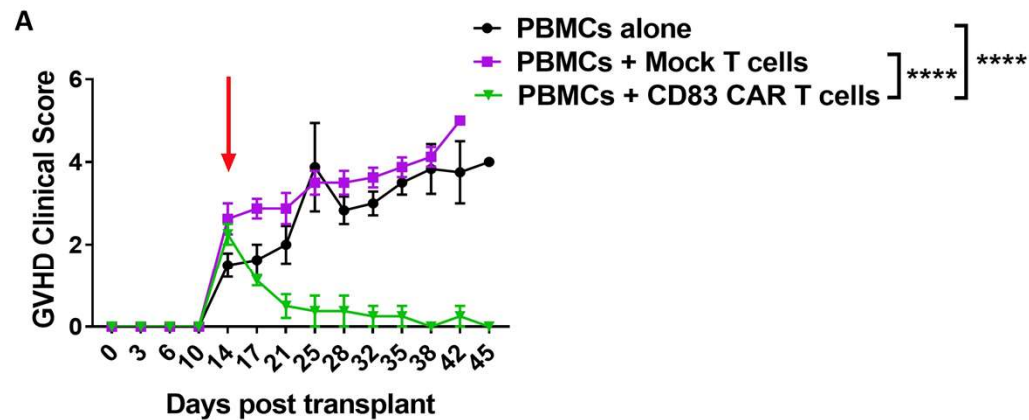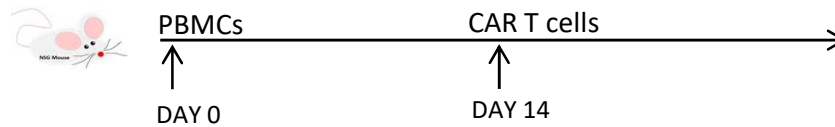
CD83 CAR T cells provide durable protection from GVHD mediated by human T cells

# CD83 CAR T cells ameliorate GVHD target organ damage

CD3=red
Ki-67=brown

CD83 CAR T cells can also treat GVHD

Effects of CD83 CAR T cells on leukemia versus normal hematopoiesis

- Over 8,000 allo-HCT procedures are performed annually in the United States

- In adults, AML is the primary indication for allo-HCT

- Disease relapse and GVHD are the leading causes of mortality after allo-HCT
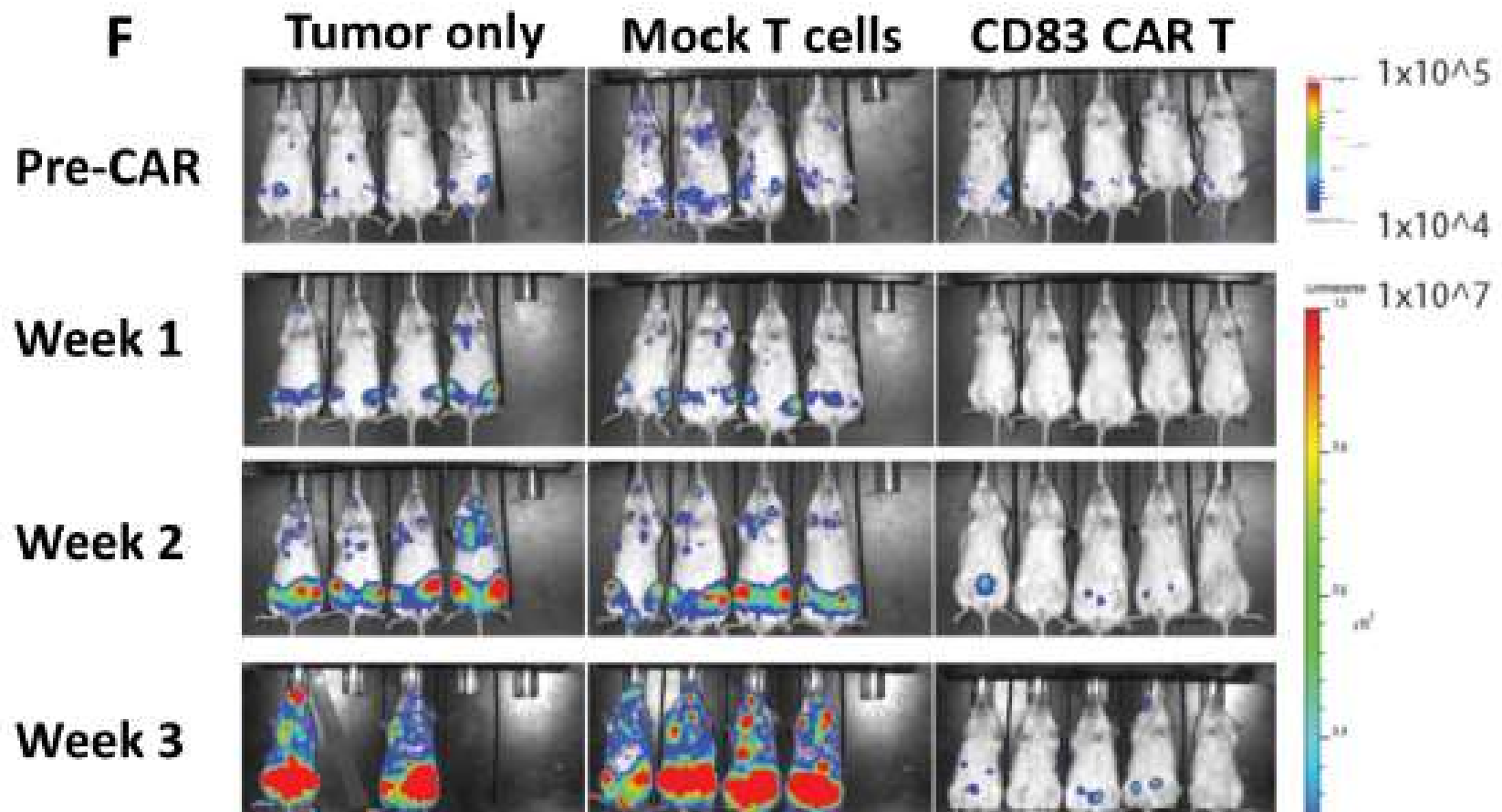
- CD83 is expressed on human AML blasts
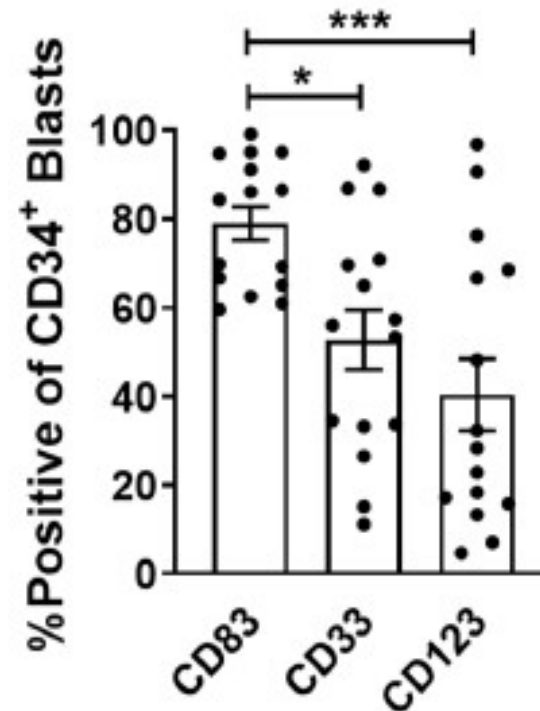
Majhail NS. BBMT. 2015.
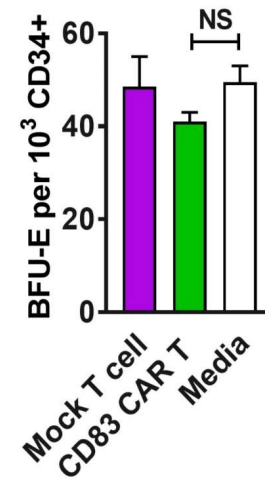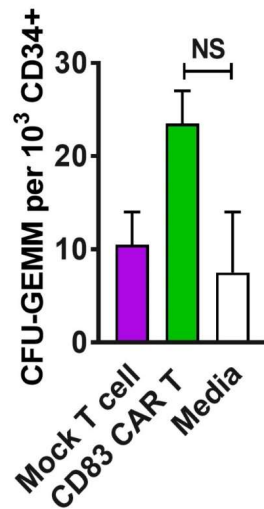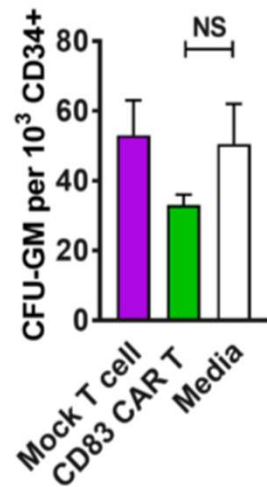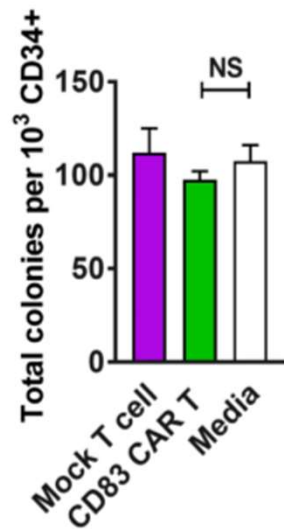
D'Souza A. BBMT. 2017.

CD83 is expressed on AML and can be targeted by CD83 CAR T

CD83 CAR T cells do not impair normal hematopoietic cells

Myeloid Progenitors: G-Granulocytes   E-Erythrocytes,   M-Monocytes   BFU-BURST Forming Units

Acknowledgements