PERSPECTIVE ON RESISTANCE TO CAR-T: LESSONS FROM BLOOD CANCER

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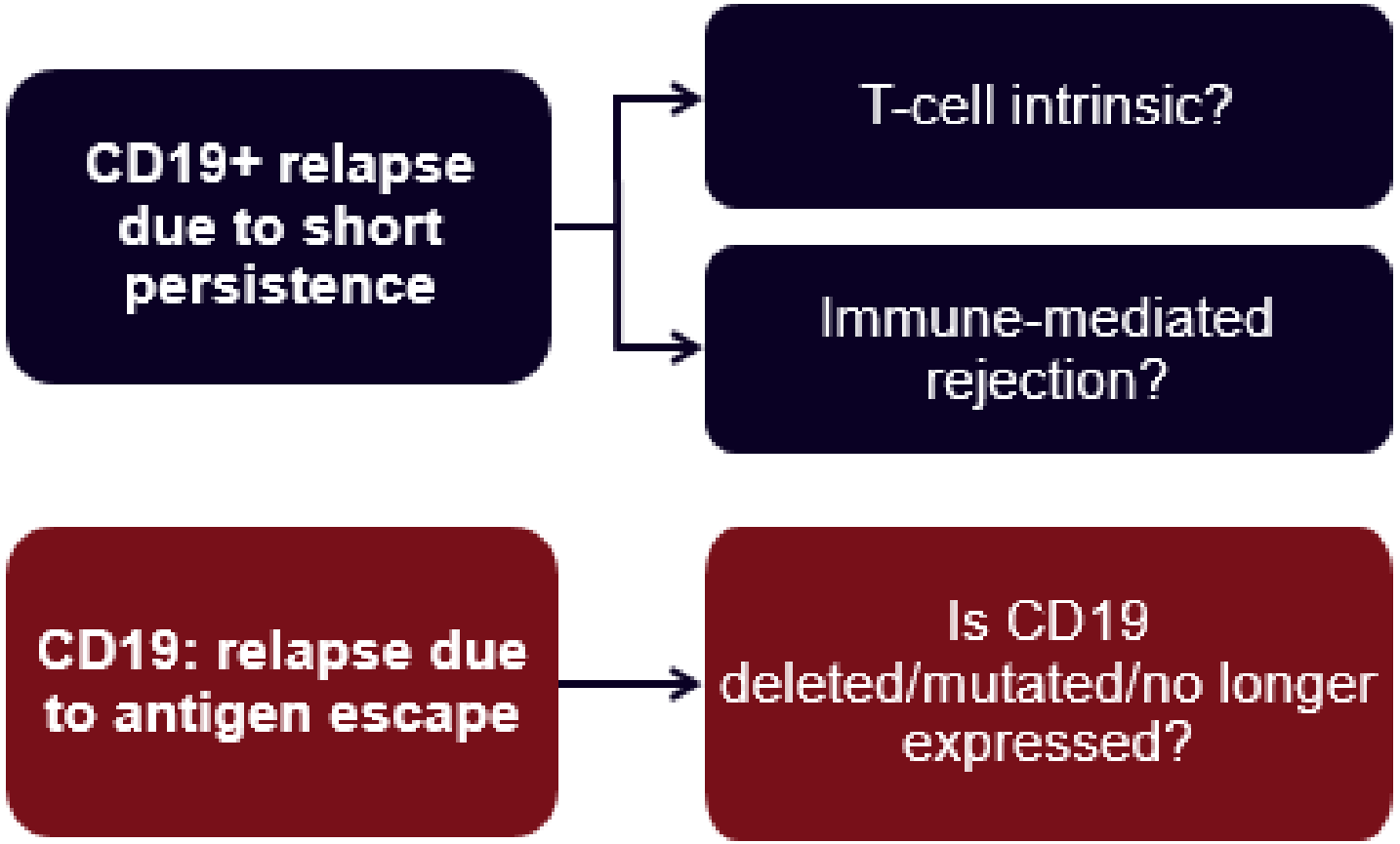
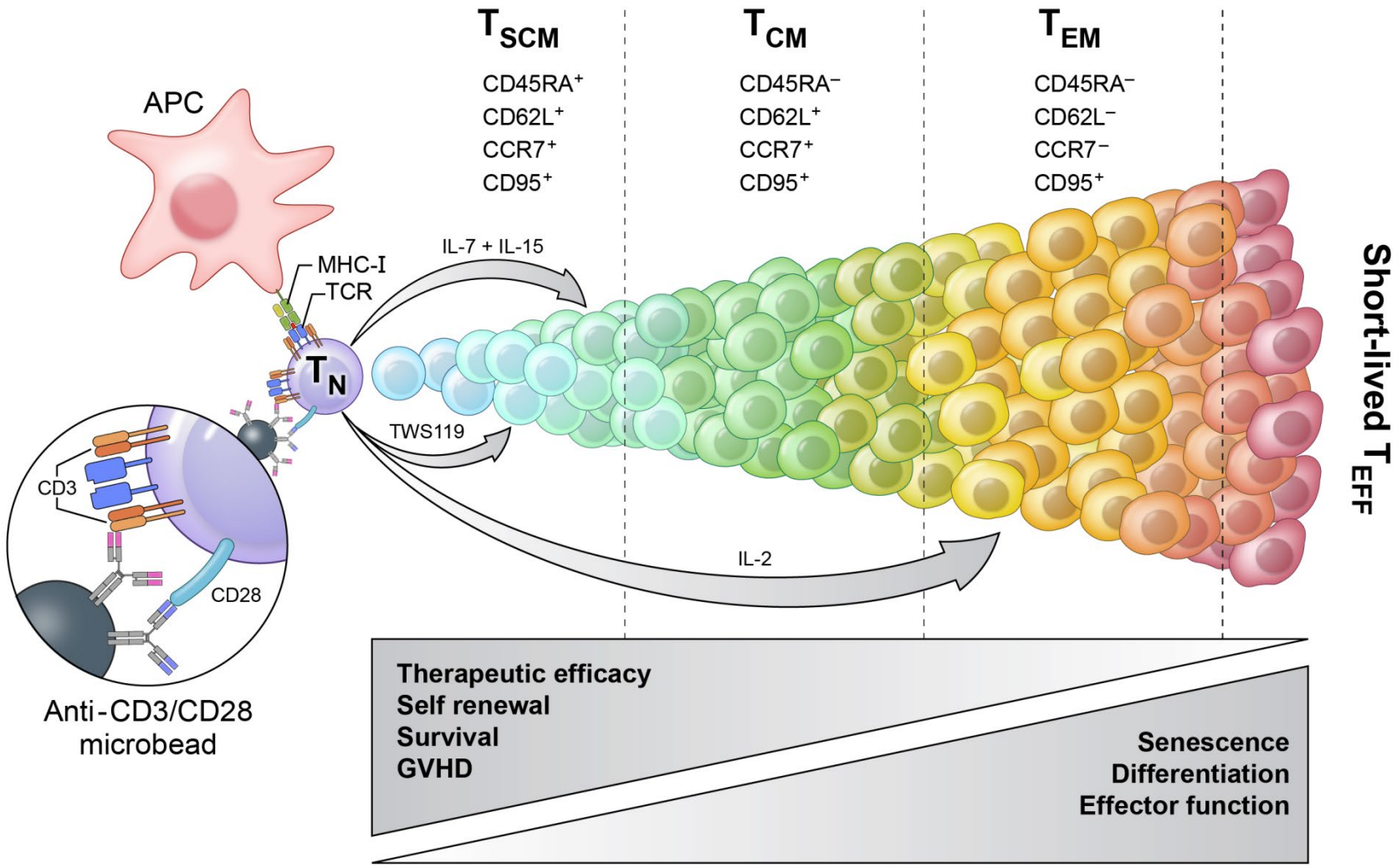
DISCLOSURES

- Research and/or clinical trial support from Novartis, Servier, Vertex, and Kite
- Study steering committees, consulting, DSMBs, or scientific advisory boards: Novartis, Allogene, Adaptimmune, Juno, CBMG, GlaxoSmithKline, Cellectis, J&J/Janssen, CRISPR/Vertex, Jazz, TCR2, and Cabaletta
- Toxicity management patent managed by U Penn policies

MECHANISMS OF RELAPSE IN ALL AFTER PERSISTENT CD19 CAR



T CELL STATE-FUNCTION RELATIONSHIP



TCF7 gene:

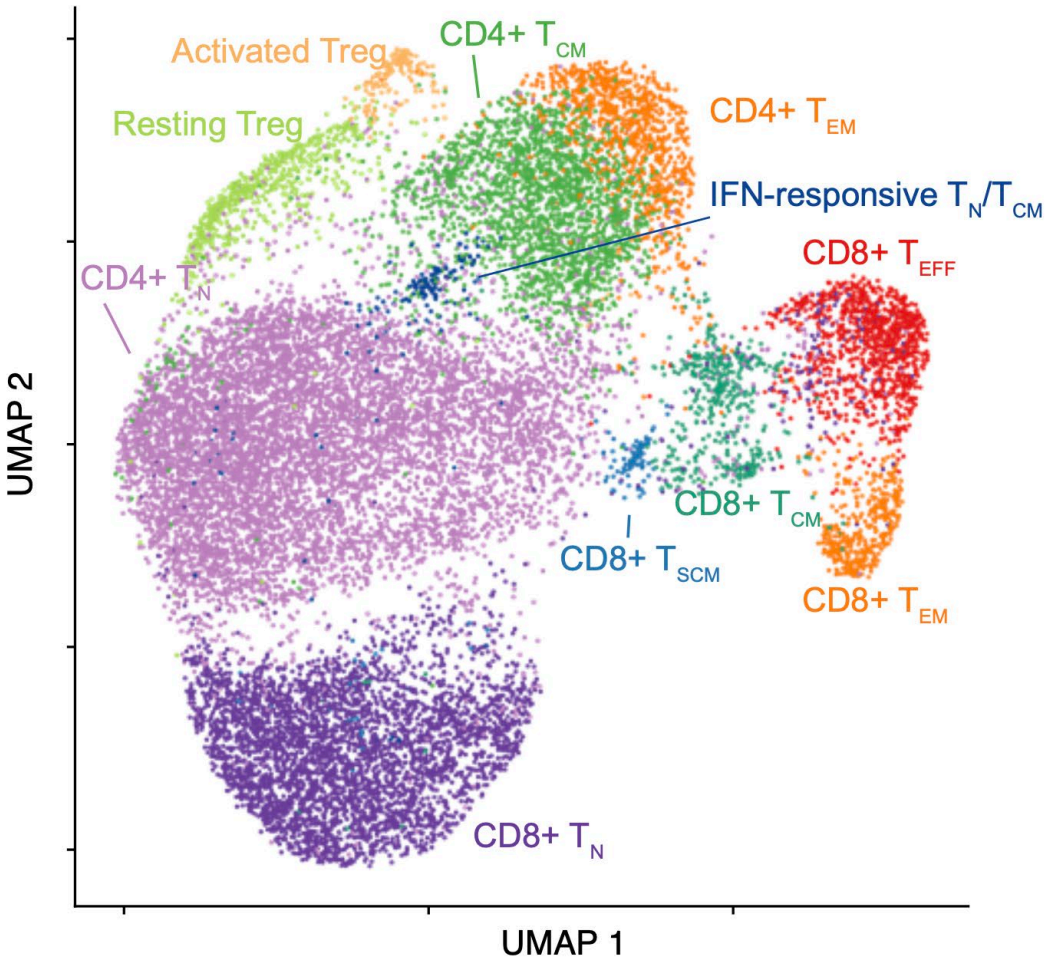
- Encodes for TCF1 transcription factor
- Key in early thymocyte development
- Highly expressed in Tn and Tscm cells
- Role in maintaining stemness in exhausted T cells

IFNg signaling and response genes:

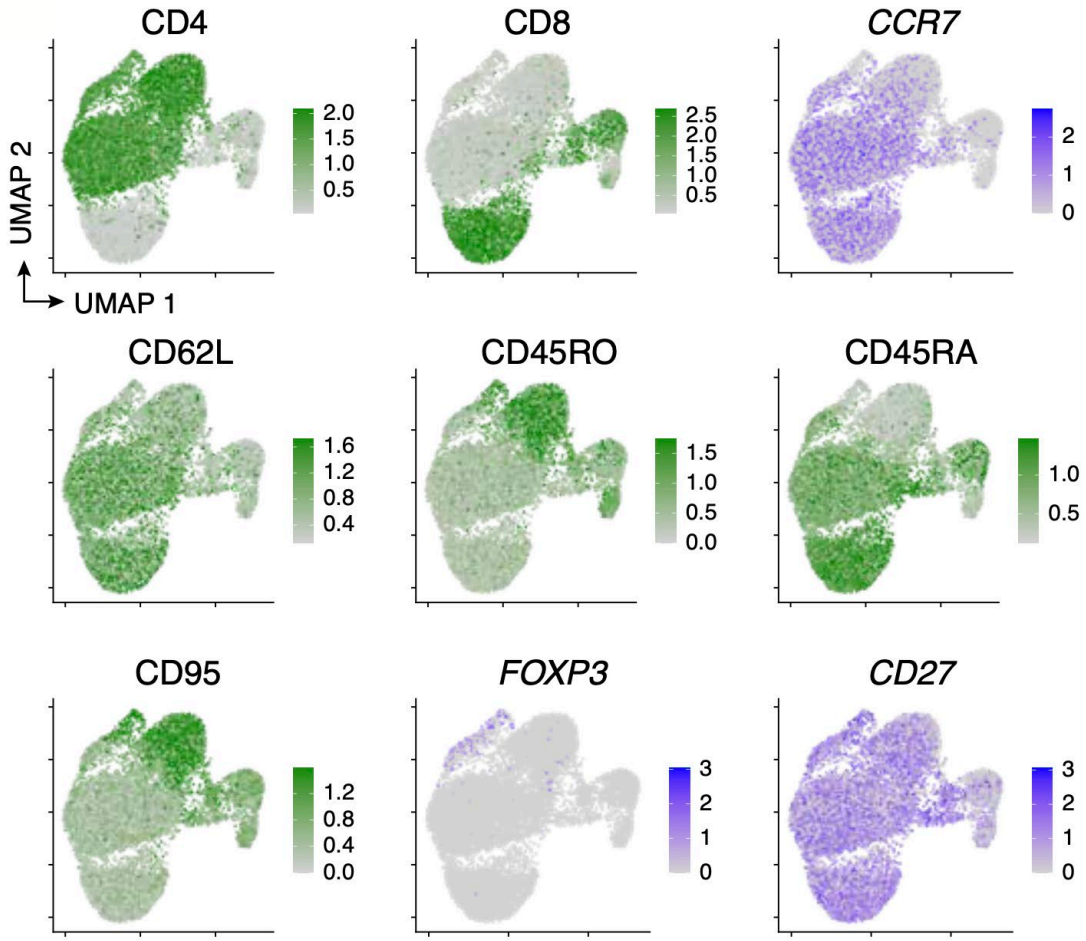
- Short term stimulation of T cell responses
- Chronic IFNg may drive T cell exhaustion (Wherry)
- IRF7 is an important regular of type 1 IFN response

Gattinoni Nat Med 2011, Cieri et al., Blood 2013, Gattinoni Inside Blood 2013

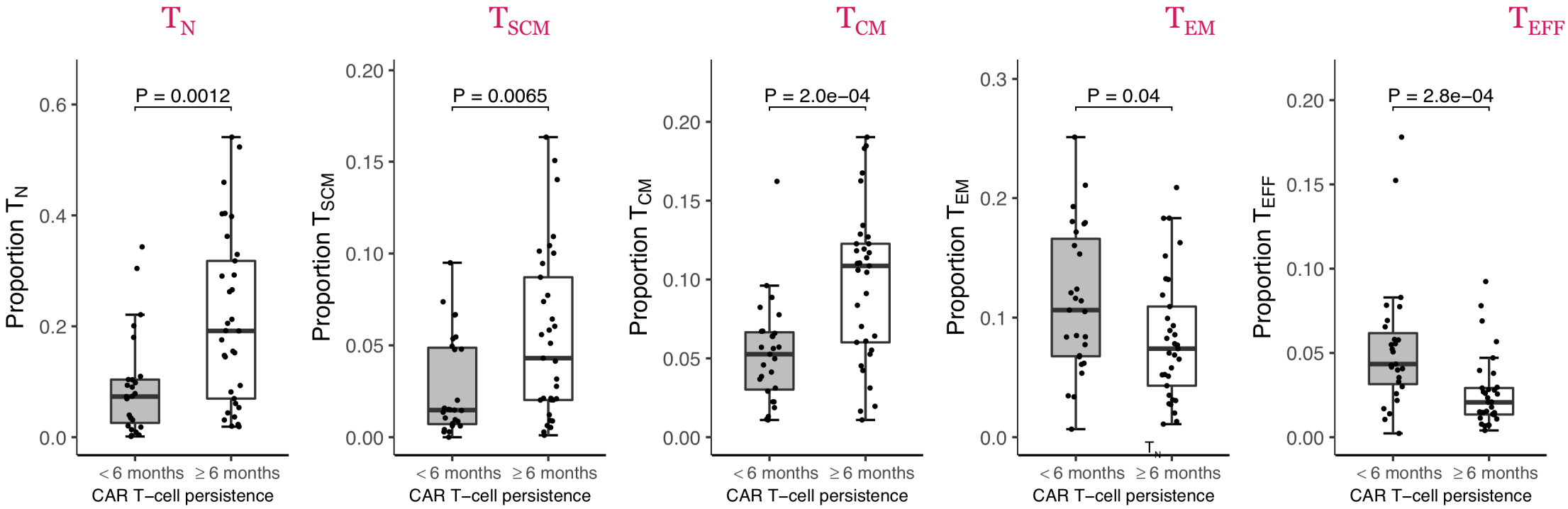
CITE-SEQ OF PRE-MANUFACTURE T-CELLS FROM SIX PATIENTS CAPTURES MAJOR CD4+ AND CD8+ T-CELL SUBTYPES



Green = single-cell protein expression (CITE antibody-derived tag)
Blue = single-cell RNA expression



HIGHER PROPORTIONS OF NAIVE AND EARLY MEMORY T-CELLS ARE ASSOCIATED WITH LONGER CAR T-CELL PERSISTENCE

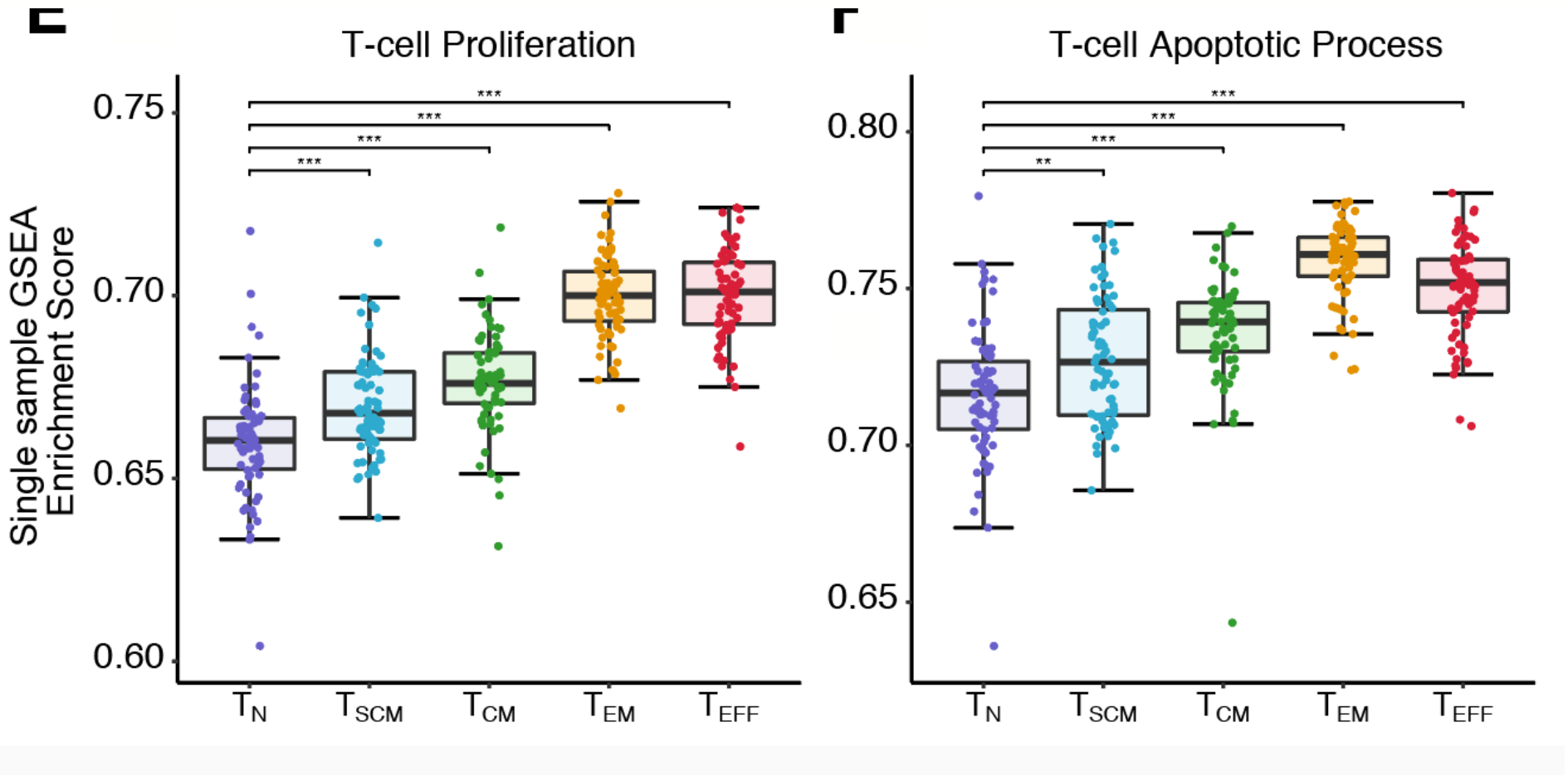


N=60, non-censored patients

Patients with failure of CAR T-cell persistence (<6 months)

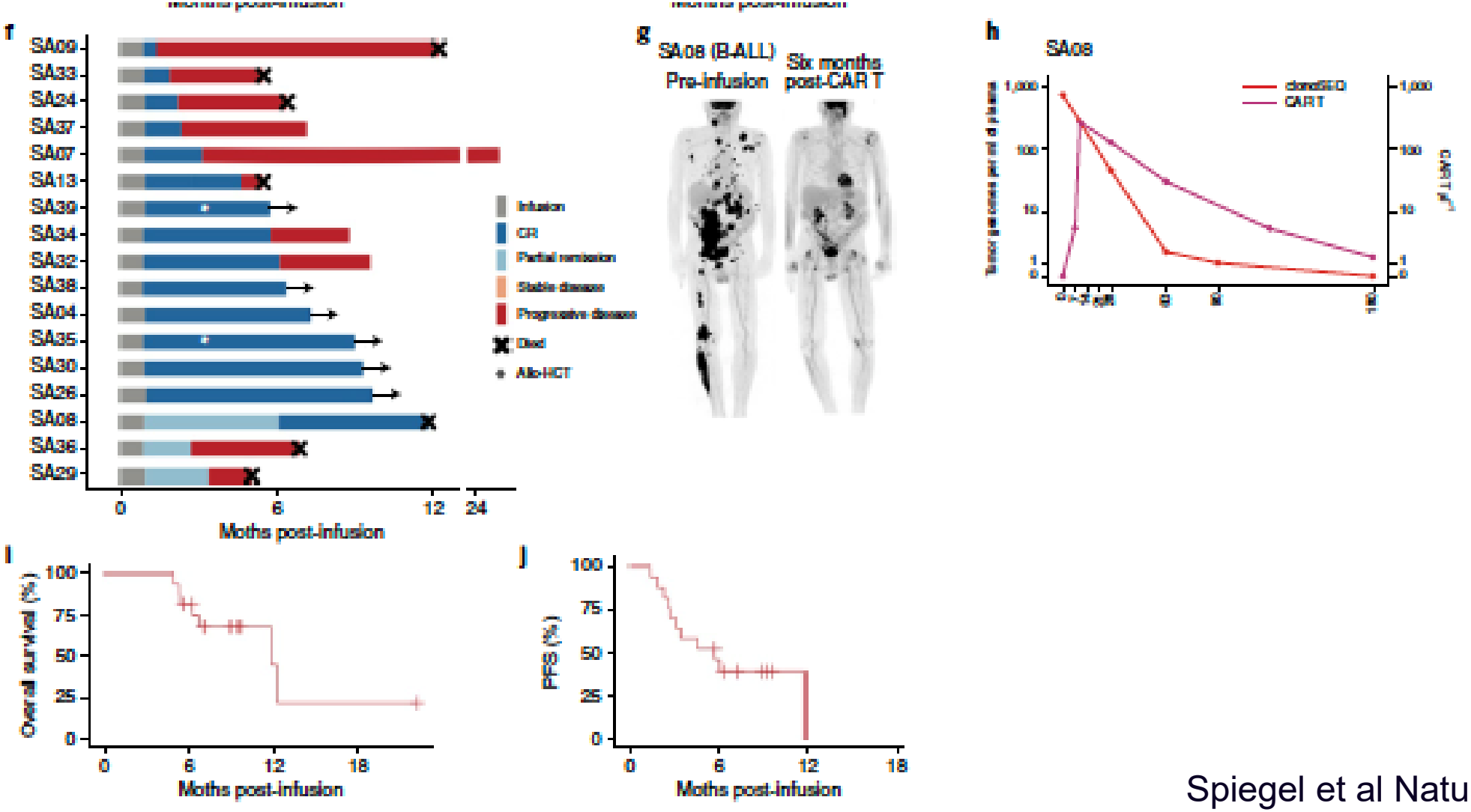
Patients with long-term (≥ 6 months) CAR T-cell persistence

EFFECTOR T-CELLS LIVE FAST AND DIE YOUNG



Chen et al Cancer Discovery 2021

#1 problem in ALL CAR T is CD19 escape: Stanford bispecific CD19/CD22 CAR trial – ALL results



Spiegel et al Nature Medicine 2021

Penn Medicine

American Society of Hematology: 2021 Annual Meeting

CART22-65s Co-Administered with huCART19 in Adult Patients with Relapsed or Refractory Acute Lymphocytic Leukemia

Noelle V Frey, MD, MS[1], Saar Gill, MD, PhD[1], Wei-Ting Hwang, PhD[2*], Selina M. Luger, MD, FRCPC[1], Mary Ellen Martin, MD[1], Shannon R. McCurdy, MD[1], Alison W. Loren, MD[1], Keith W. Pratz, MD[1], Alexander E. Perl, MD[1], Julie Barber-Rotenberg, PhD[3*], Amy Marshall[3*], Marco Ruella, MD[1], Simon F Lacey, PhD[3], Joseph Fraietta, PhD[3*], Andrew Fesnak, MD[3*], Megan O'Brien[3*], Theresa Schanne[3*], Jennifer L Brogdon, PhD[4*], Boris Engels, PhD[4*], Bruce L Levine, PhD[3], Carl H June, MD[3], David L Porter, MD[1] and Elizabeth O. Hexner, MD[1]

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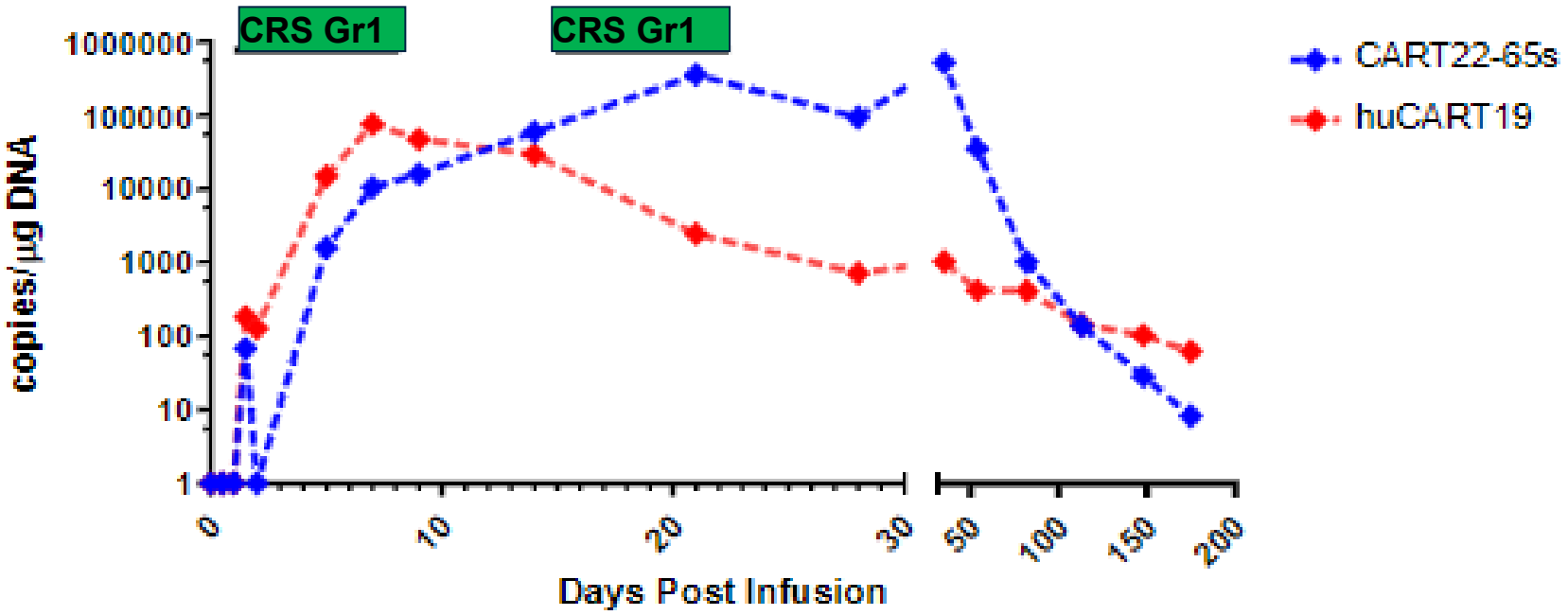
Different peak expansions correlate with distinct CRS events



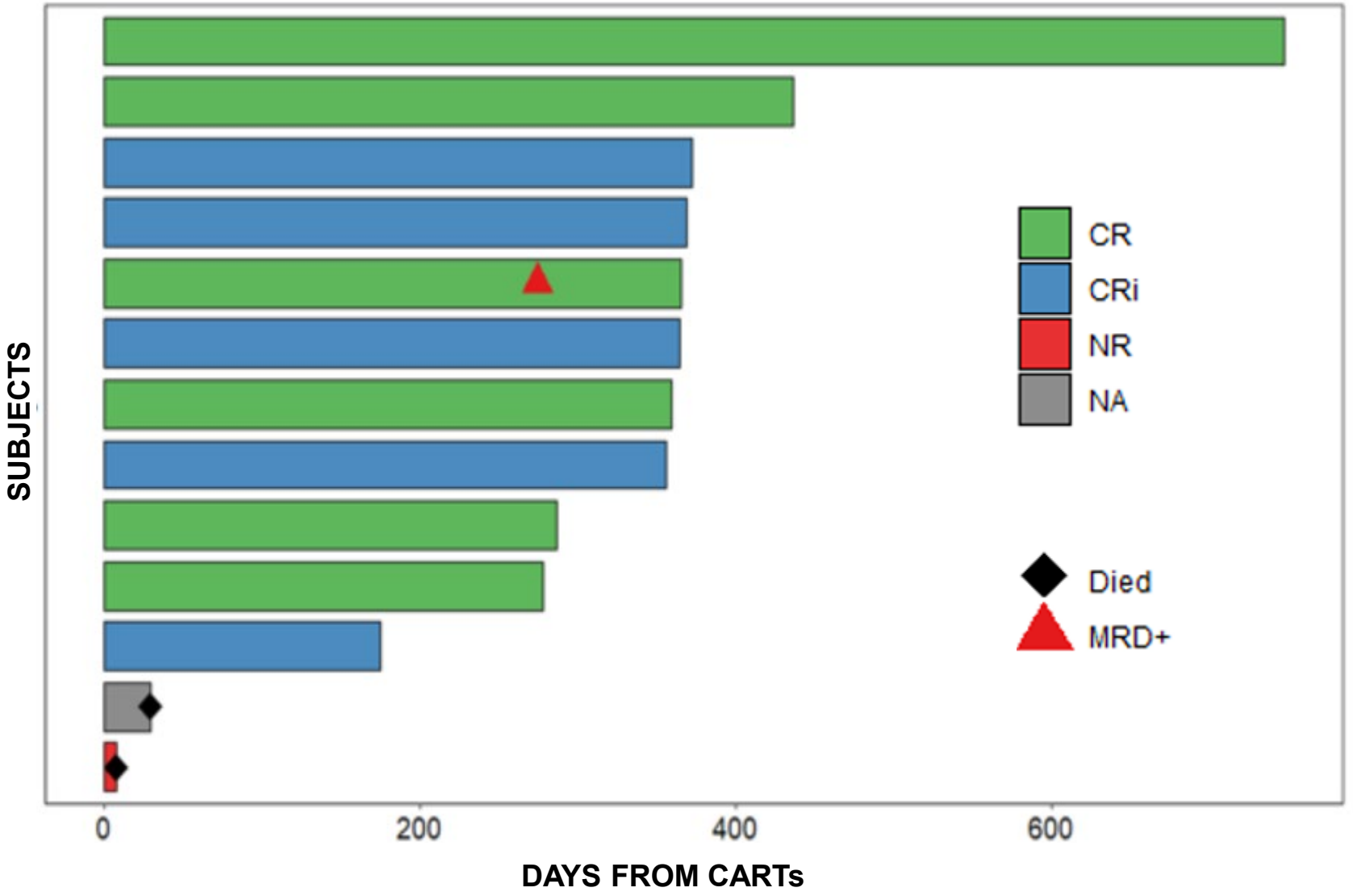
Response

CART19 and CART22: (N=13)

- 13 pts infused
- 11 pts evaluable D28
- 11 CR/CRi (MRD -)

Med follow up 11.8 mo:

- One pt with molecular recurrence
- 10 with ongoing CR/CRi



Penn Medicine

CELL THERAPY & TRANSPLANT

From: **Antitumor Activity Associated with Prolonged Persistence of Adoptively Transferred NY-ESO-1 ^{c259}T Cells in Synovial Sarcoma**

Cancer Discov. 2018;8(8):944-957. doi:10.1158/2159-8290.CD-17-1417