Multi-targeted CAR T cells

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SITC Annual Meeting

National Harbor, MD

November 6, 2019

Disclosure Information
Updated November 6, 2019
Marcela V. Maus, MD, PhD

- I have the following relevant financial relationships to disclose:

  Consultant for: *Adaptimmune, Arcellx, Cellectis (SAB), CRISPR therapeutics, Incysus (SAB), GSK, Kite Pharma, Micromedicine, Novartis, TCR2 (SAB), and WindMIL (SAB)*

  Speaker's Bureau for: none

  Grant/Research support from: CRISPR therapeutics, Kite Pharma

  Stockholder in: Century Therapeutics, TCR2

  Honoraria from: listed under Consultant

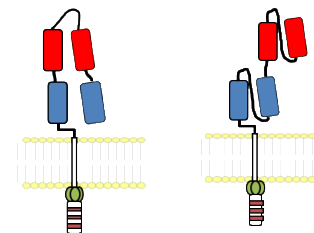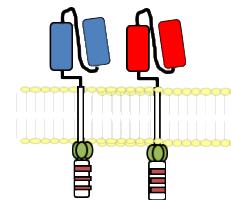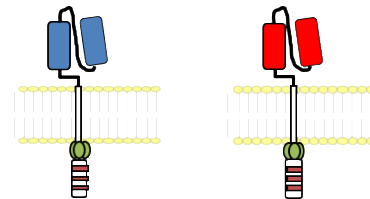 Employee of: Massachusetts General Hospital

  - AND –

- I may discuss the following off label use and/or investigational use in my presentation: new CAR T cells
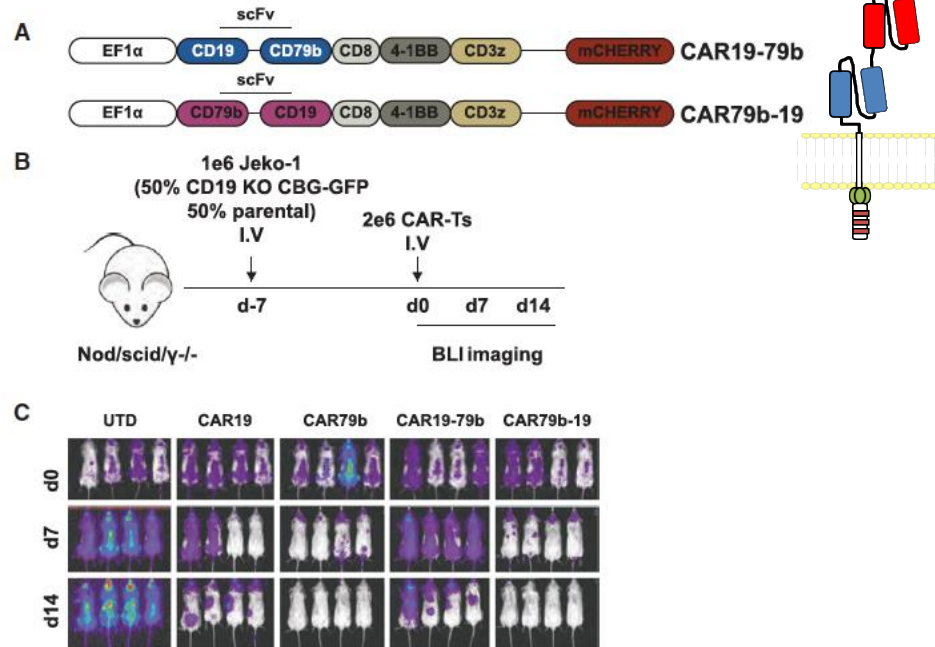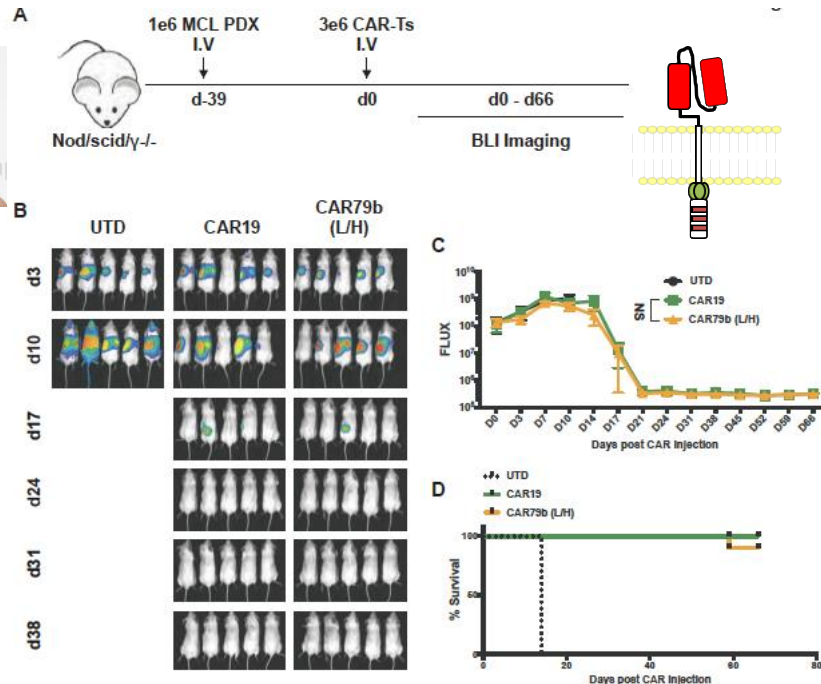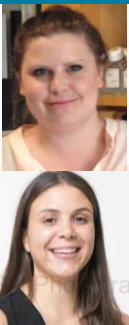
  - AND -

- My career is intricately tied to CAR T cells now
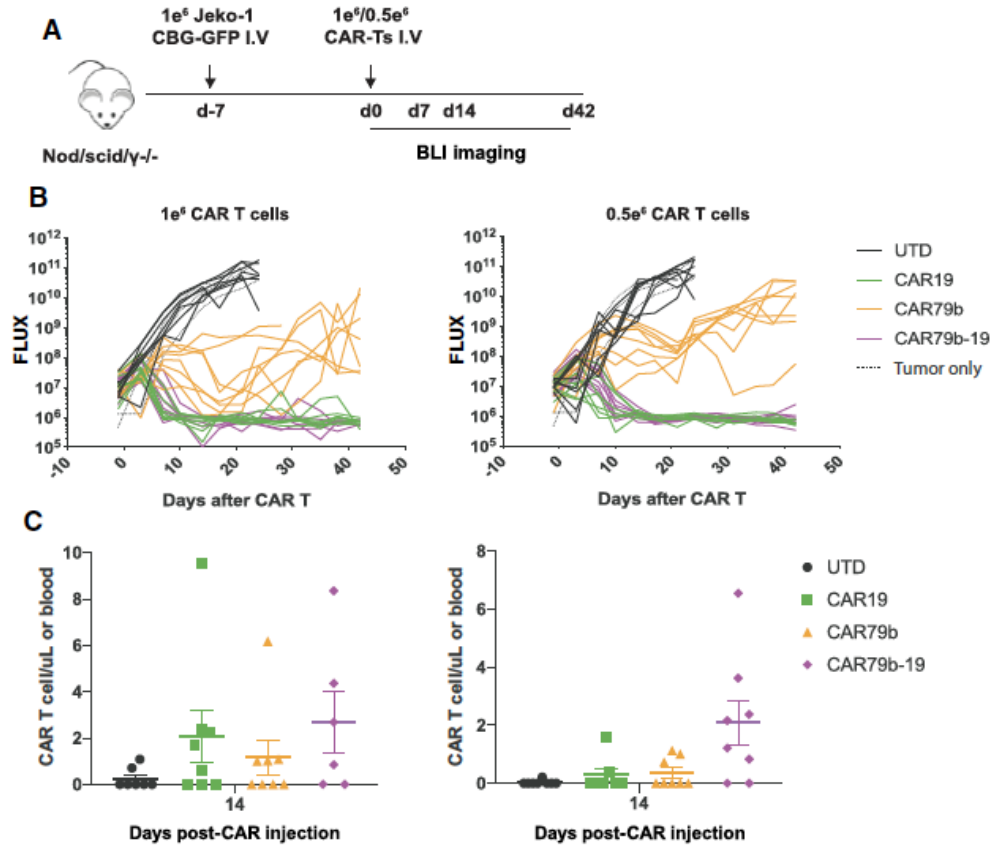
Approaches to multi-targeted CAR T cells

- ## Transduce 2 different cell populations with 2 different vectors

  - Savoldo JCI 2011 used this method to demonstrate 28z > z

- ## Transduce 1 cell population with 2 vectors

  - Ruella JCI 2016 used this method to show that 1 cell population > pooled cell populations

- ## Transduce 1 cell population with 1 "tandem" CAR

  - (Zah/Chen CIR 2016 with CD19/20; Qin/Fry Mol Ther Onc CD19/22)

A new CAR for the CD79b B cell antigen works in CD19+ and CD19- lymphoma as single and tandem CAR with CD19

Ormhoj et al, Clin Canc Res, 2019

Tandem 1979 CARs are preferable in a stress test of "upfront" CD19+ CD79b lymphoma models

Ormhoj et al, Clin Canc Res, 2019

Clinical trials of CAR T cells in multiple myeloma
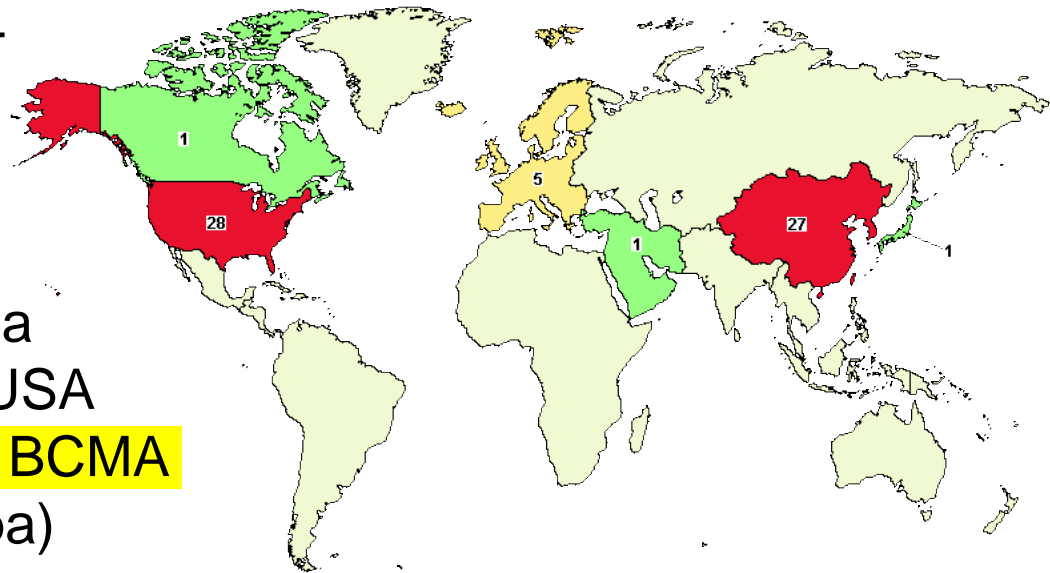
Multiple myeloma and CAR-T

59 trials worldwide
38 trials recruiting worldwide
   27 trials recruiting in China
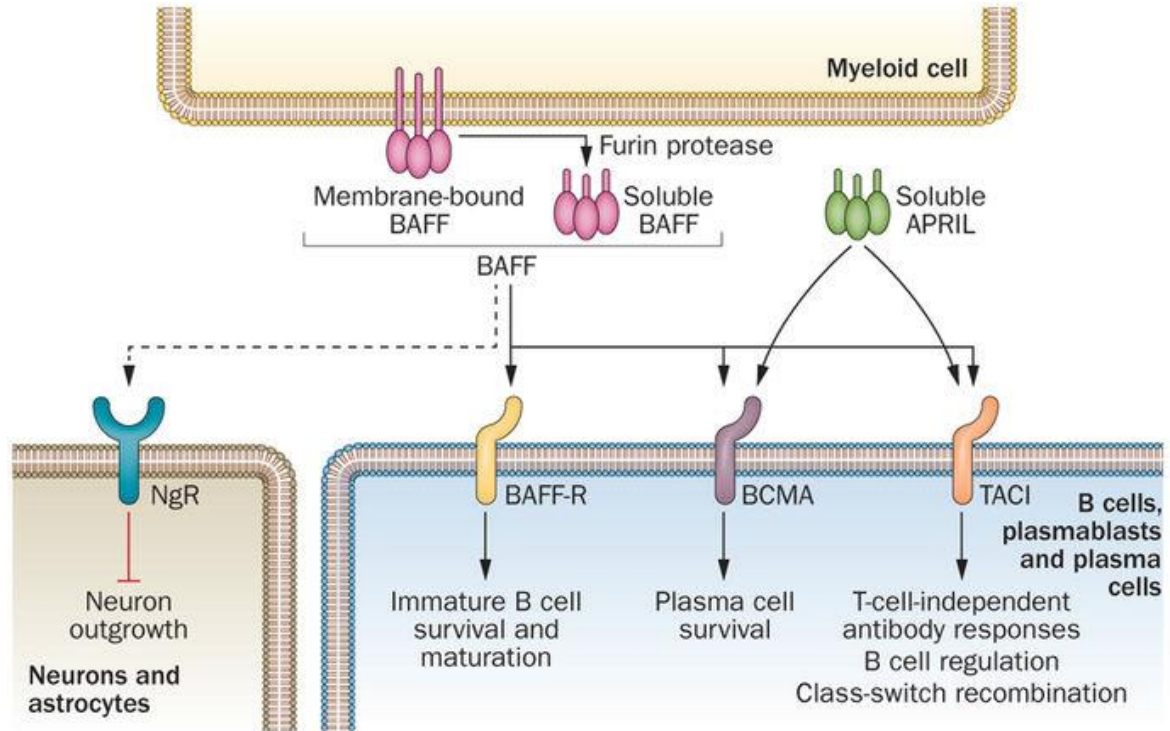   18 trials recruiting in the USA
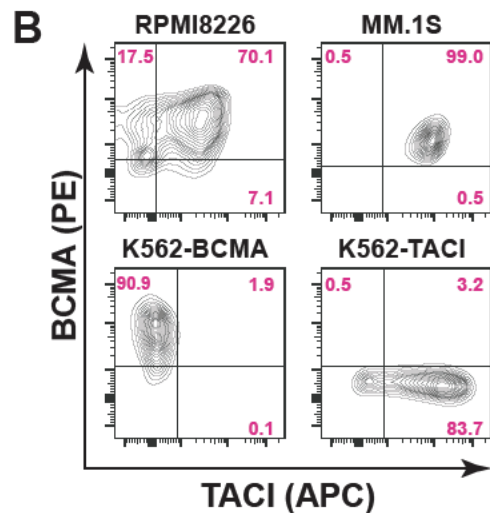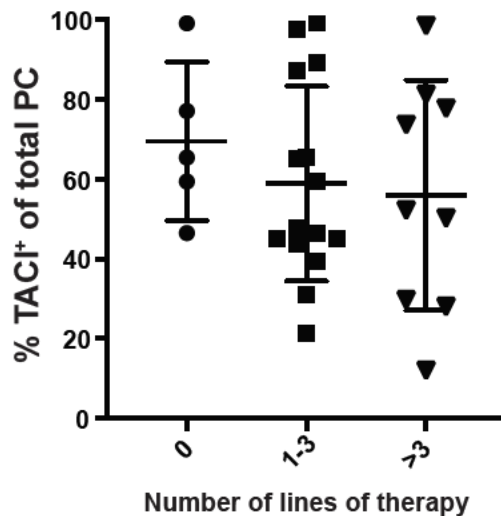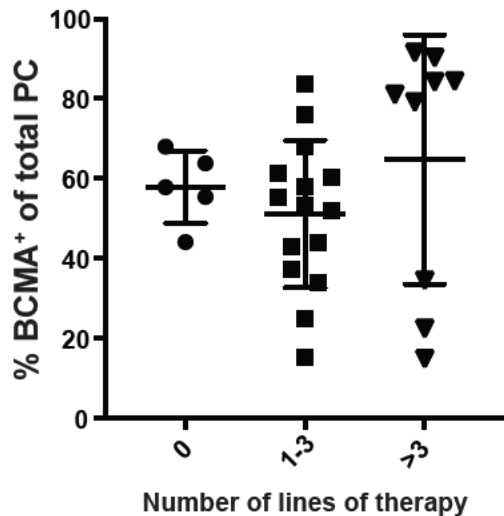   all but 3 are targeting BCMA
     (NKG2D, CD38, kappa)
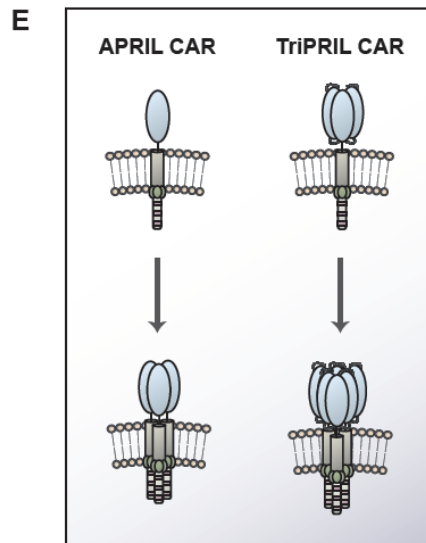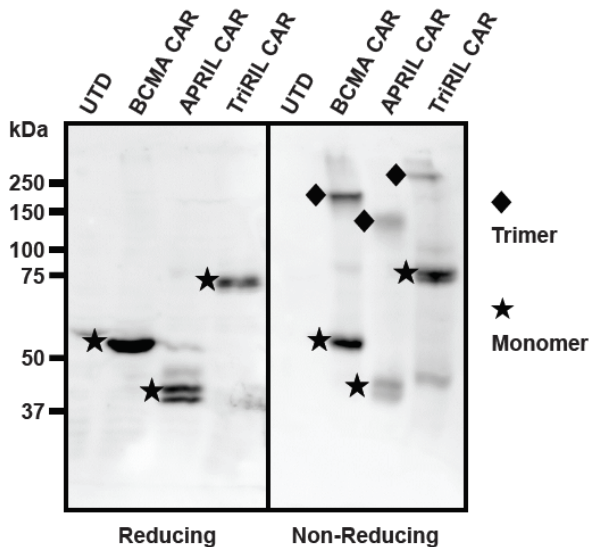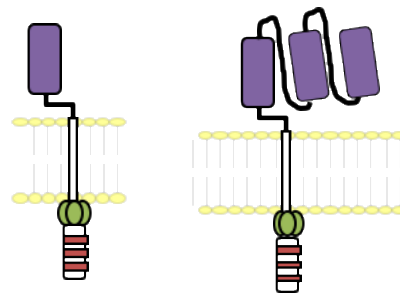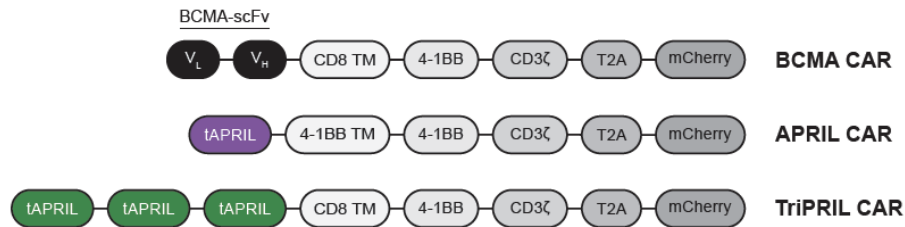
Targeting BCMA and TACI on multiple myeloma

- APRIL (a proliferation-inducing ligand) is produced by myeloid cells in the BM microenvironment

- soluble APRIL binds to BCMA and TACI and promotes proliferation and survival of MM

Vincent et al. Nature Reviews Rheumatology 2014

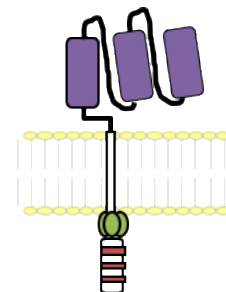# Patients with MM retain BCMA and TACI expression on their plasma cells

Design and trimerization of APRIL and Trimeric-APRIL CARs

With Wolfgang Schamel
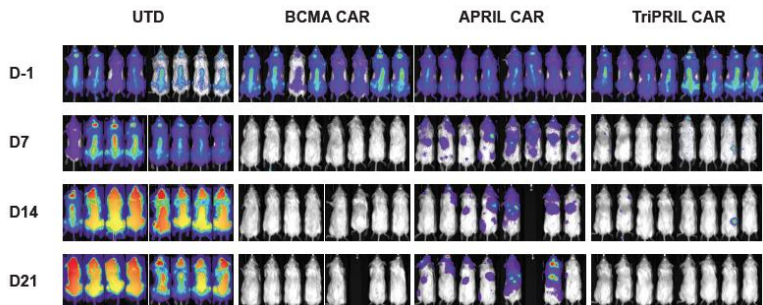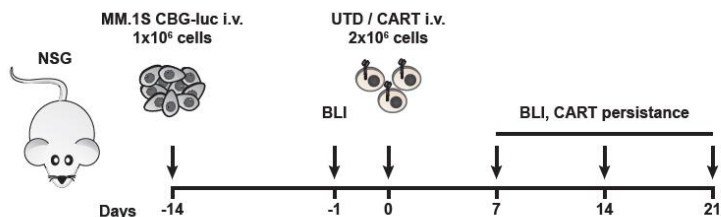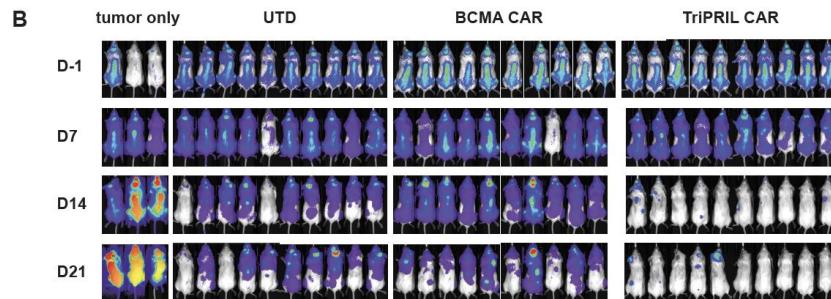
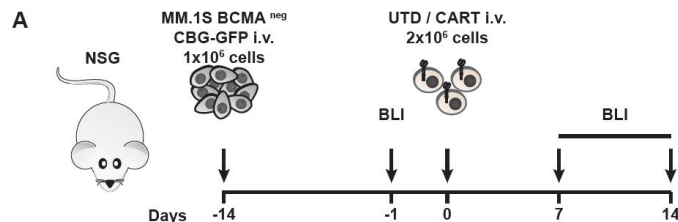# TriPRIL targets BCMA+ or BCMA- myeloma
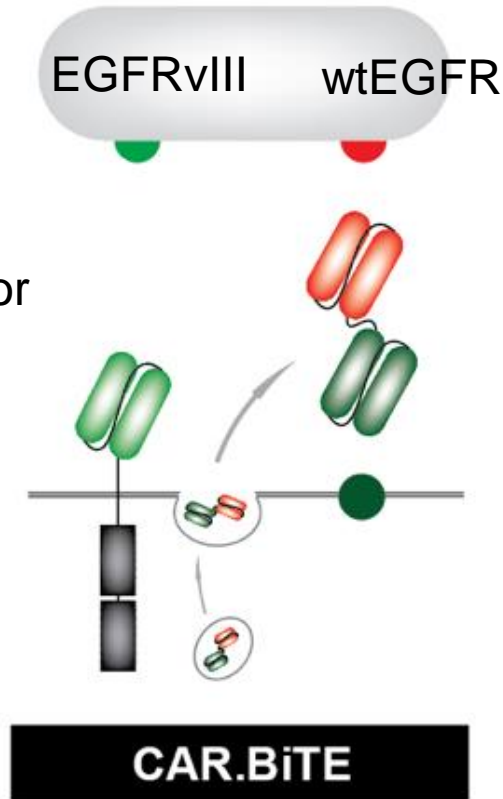

Schmidts et al, Blood Advances, in press

Challenges for dual targeting CAR T cells in solid tumors

- Targeting tumor heterogeneity is desirable

- Lack of tumor-specific antigens is a challenge

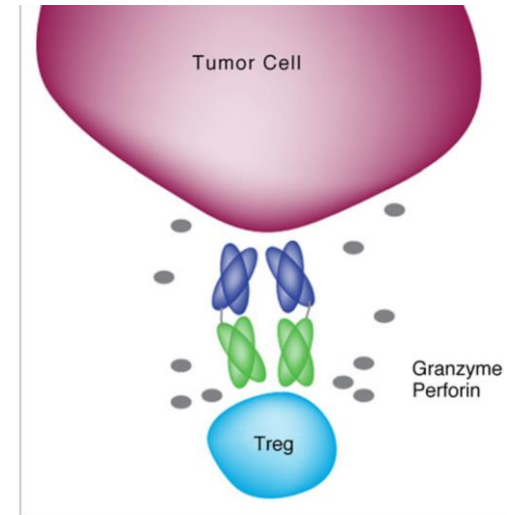- Would ideally also target or modify the tumor microenvironment

CAR T cells for solid tumors need to overcome heterogeneity and immunosuppressive environment: CAR-BiTE design

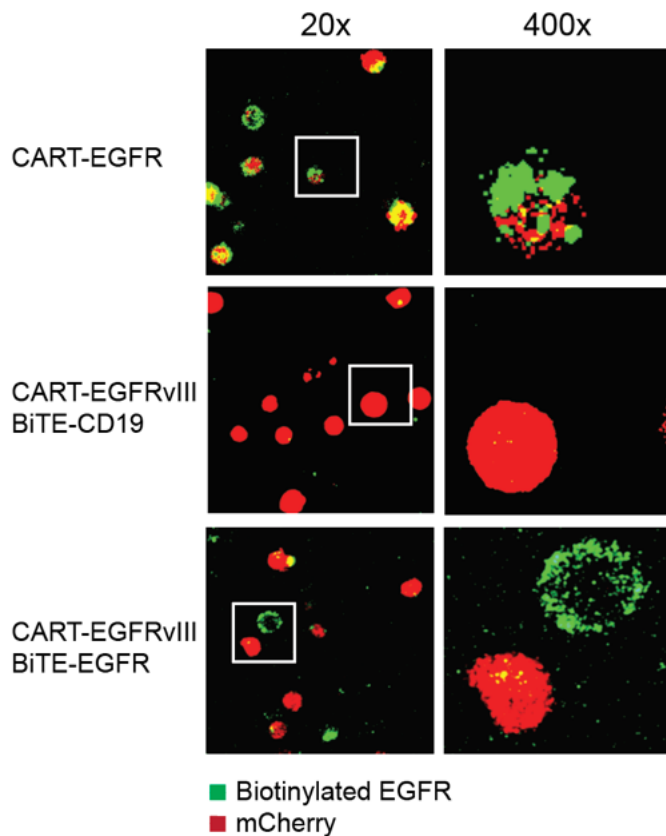EGFRvIII   wtEGFR

One tumor-specific target for the CAR

BiTE can target the "undruggable"
- Local site
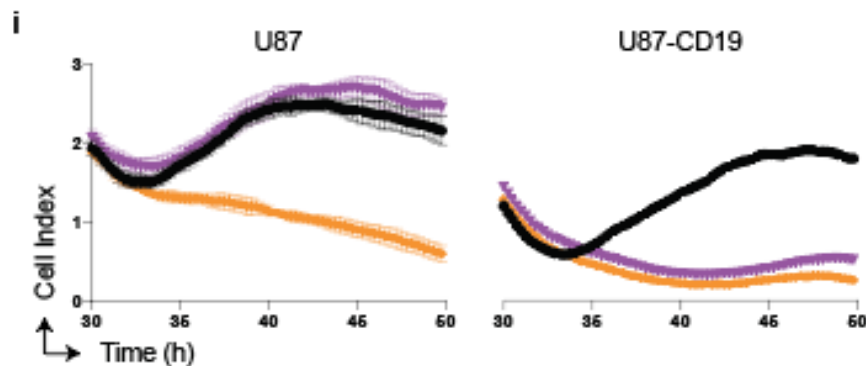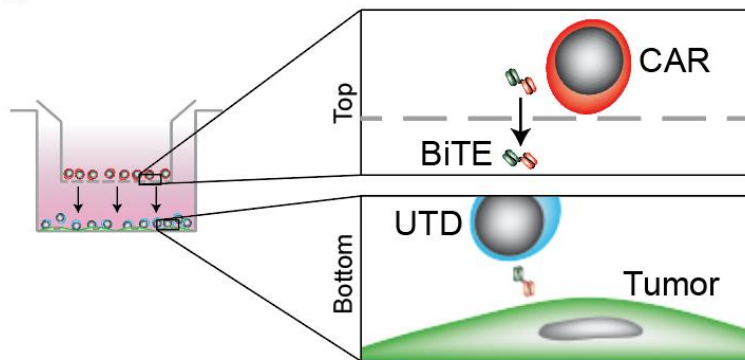- Rapid clearance
- Can re-direct Tregs

CAR.BiTE

Choi et al, CIR 2013

BiTEs (green) bind to both CAR+ (red) and bystander T cells

Choi et al, Nature Biotechnology 2019

Secreted BiTEs bind CART but also redirect bystander T cells

Choi et al, Nature Biotechnology 2019

Choi et al, Nature Biotechnology 2019

No evidence of EGFR (BiTE)-related toxicity in skin graft model
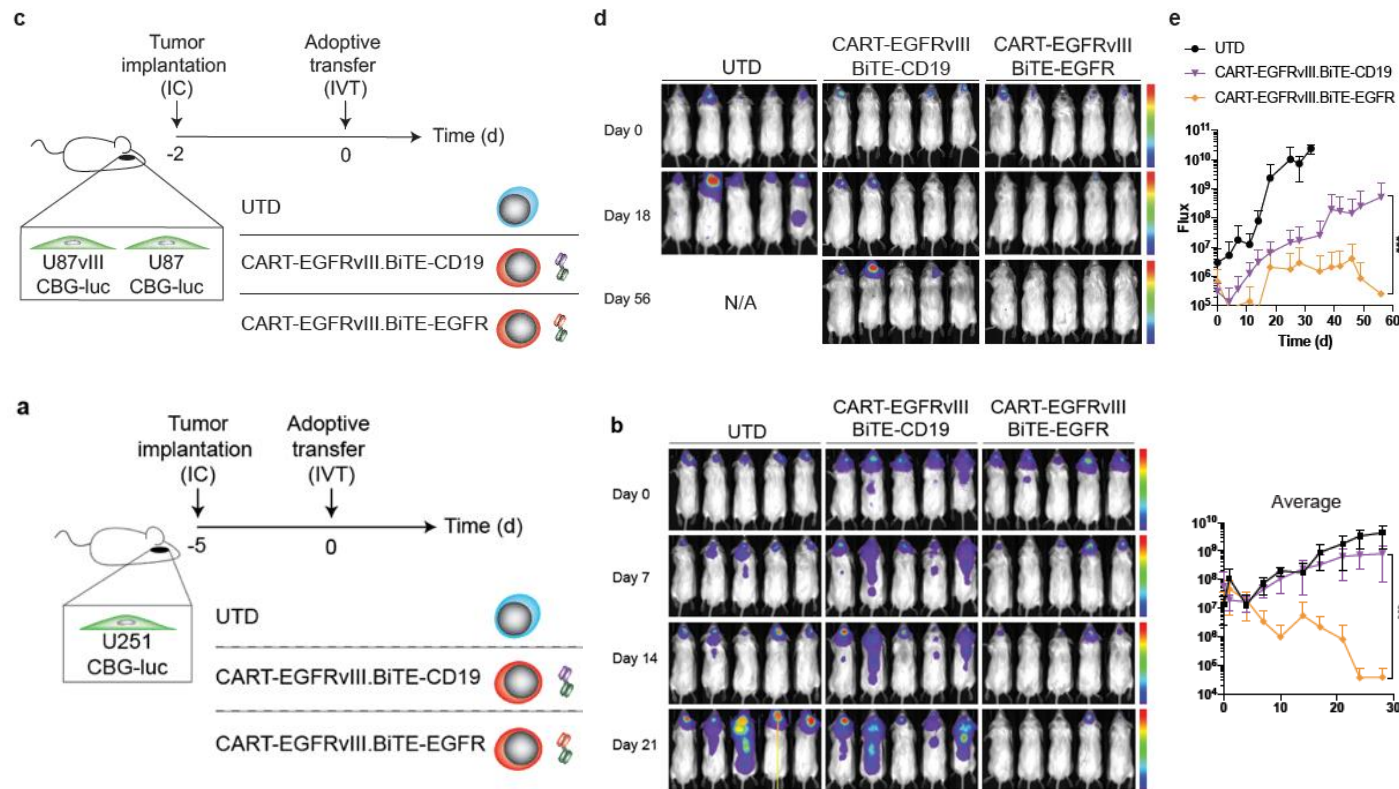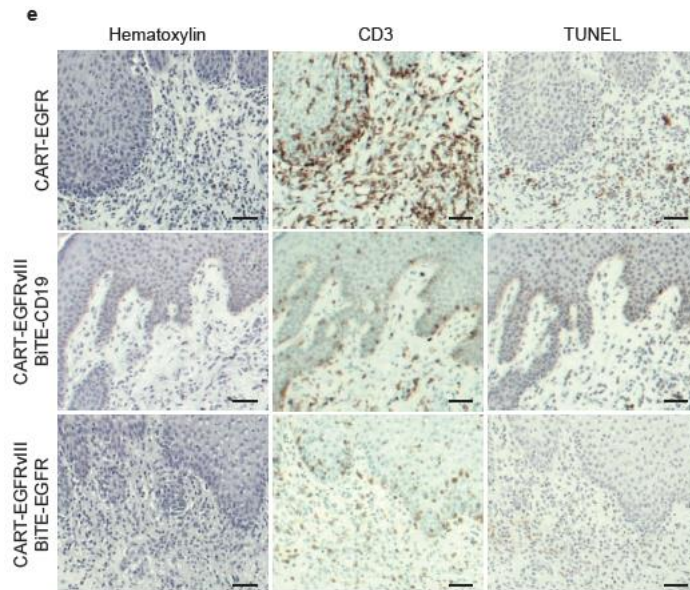

Choi et al, Nature Biotechnology 2019

Conclusions

- There are multiple ways to target more than one antigen with a CAR T cell

- Using one vector/one cell population may be most effective (and most cost-effective)

- Creative approaches are needed depending on expression profile of each antigen

Acknowledgements

Maus Lab

Science CAR T team
Irene Scarfo
Mark Leick
Stefanie Bailey
Andrea Schmidts
Becca Larson
Korneel Grauwet
Max Jan
Amanda Bouffard
Maria Cabral
Bryan Choi
Emily Silva
Mike Kann
Sonika Vatsa
Aarti Srivastava
Alex Pourzia

Immune Monitoring
Kathleen Gallagher
Fred Preffer

Clinical
Matthew Frigault
Yi-bin Chen

Manufacturing
Jerry Ritz

Collaborators
Hiroaki Wakimoto
David Weinstock
Joren Madsen
Daniel Irimia
Ben Ebert

Job openings in our group for Immunology PhD's who are done pipetting

- ## Science/Medical Writer

  - Participate in writing manuscripts, grants, IND's, clinical protocols

- ## Translational Operations

  - Make bench-to-bedside happen

  - Interact with FDA, regulatory committees, physicians, and clinical and correlative data

  - Participate in business development, strategy, contracts

- ## Please email me: mvmaus@mgh.harvard.edu if interested

  - Posted on SITC job board