The next-generation of cancer immunotherapies

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Cancer Immunotherapy Indications

Table 1. Summary of FDA-approved immunotherapies.

Mechanism	FDA-approved therapies	Disease indication (year of approval)
Anti-CTLA4	Ipilimumab	•Melanoma (2011) •Renal cell carcinoma (2018) •MSI-H or dMMR colorectal cancer (2018) •Hepatocellular carcinoma (2020)
Anti-PD1	Nivolumab	•Melanoma (2014) •Non-small cell lung cancer (2015) •Renal cell carcinoma (2015) •Hodgkin lymphoma (2016) •Squamous cell of the head and neck (2016) •Urothelial carcinoma (2017) •MSI-H or dMMR colorectal cancer (2017) •Hepatocellular carcinoma (2017) •Small cell lung cancer (2018)
	Cemiplimab	•Cutaneous squamous cell carcinoma (2018)
	Pembrolizumab	•Melanoma (2014) •Non-small cell lung cancer (2015) •Head and neck squamous cell carcinoma (2015) •Hodgkin lymphoma (2017) •Urothelial carcinoma (2017) •MSI-H cancer (2017) •Gastric cancer (2017) •Cervical cancer (2018) •Primary mediastinal large B-cell lymphoma (2018) •Merkel cell carcinoma (2018) •Renal cell carcinoma (2019) •Esophageal cancer (2019) •Hepatocellular carcinoma (2019) •Endometrial carcinoma (2019)
Anti-PD-L1	Atezolizumab	•Urothelial cancer (2016) •Non-small cell lung cancer (2016) •Triple-negative breast cancer (2018) •Small cell lung cancer (2019)
	Avelumab	•Merkel cell carcinoma (2017) •Urothelial cell carcinoma (2017) •Renal cell carcinoma (2019)
	Durvalumab	•Urothelial cell carcinoma (2017) •Non-small cell carcinoma (2018) •Small cell lung cancer (2020)
CAR-T cell therapy	Axicabtagene ciloleucel	•Large B-cell lymphoma (2017)
	Tisagenlecleucel	•B-cell precursor acute lymphoblastic leukemia (2017) •Large B-cell lymphoma (2018)
Cytokine modulation	Interferon	Interferon Alfa-2B: •Hairy cell leukemia (1986) •AIDS-related Kaposi's sarcoma (1988) •Melanoma (1995) •Follicular lymphoma (1997)
	Interleukin	Interleukin-2: •Renal cell carcinoma (1992) •Melanoma (1998)
Dendritic cell vaccine	Sipuleucel-T	•Prostate cancer (2010)
Oncolytic viruses	Talimogene laherparepvec	•Melanoma (2015)

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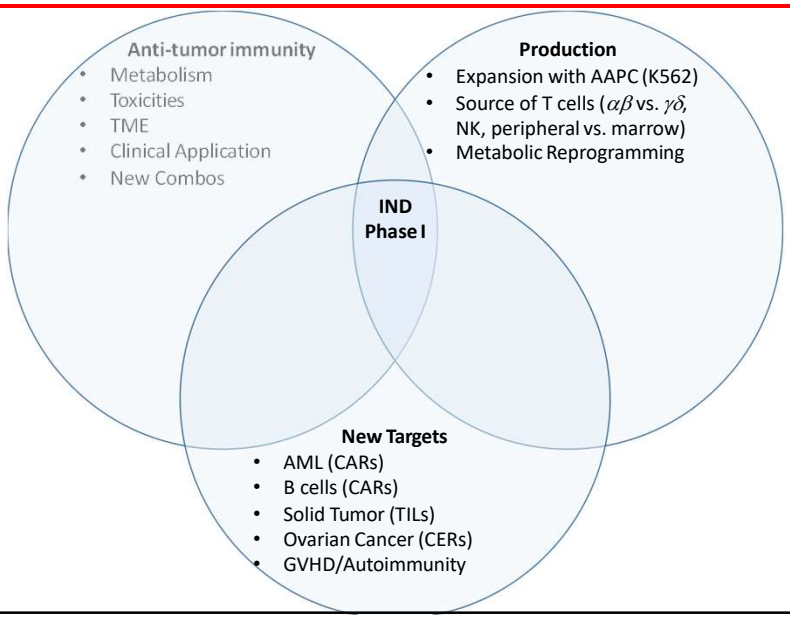
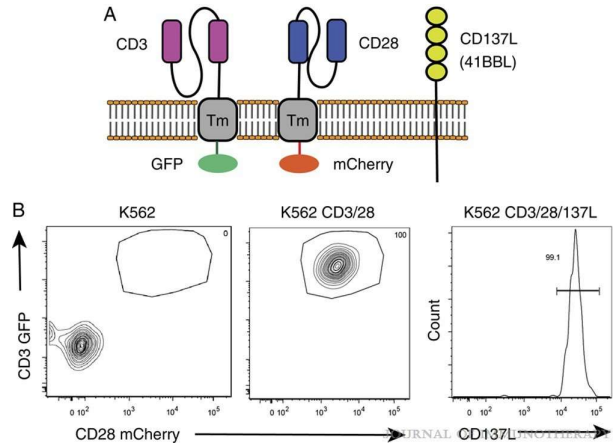
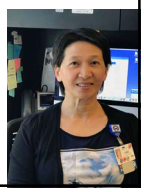
Cancer Immunotherapy Future Research Directions



Safe targets

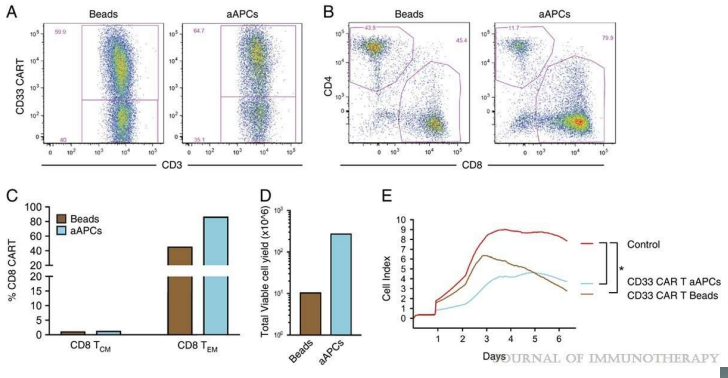
AAPC for T cell engineering

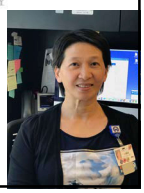




Bishwas Shrestha
Bin Yu
Journal of Immuotherapy 2019

AAPC for T cell engineering





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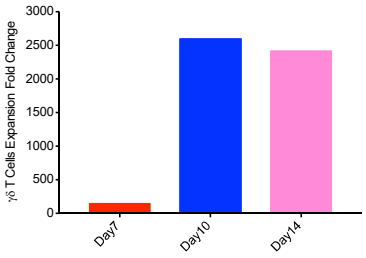
Moving beyond $\alpha\beta$ T cells

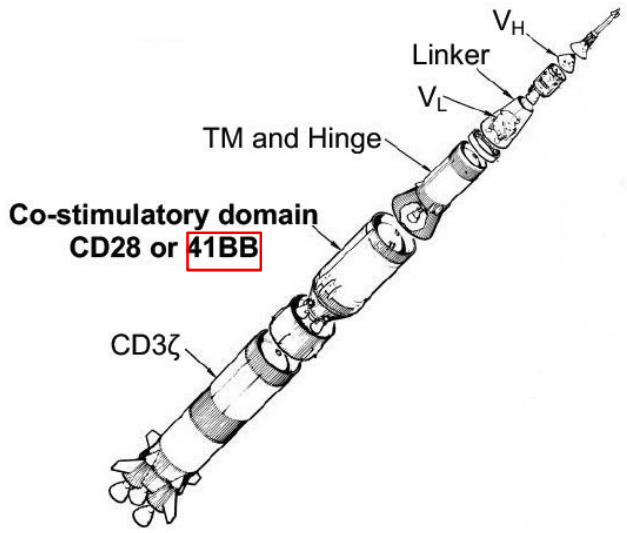
- Expansion of T cells up to 3000-fold in 2 weeks
- Gene-transfer at levels similar to beads + retronectin
- Renewable cell line replaces 2 critical reagents
- Scalable
- Adaptable to MILs, TILs, Gamma-Delta T cells
  - **Basis for a Bankhead Coley Award to fund a clinical trial in collaboration with Nelli Bejanyan. Will treat patients with MDS or AML post-allo SCT at risk for relapse**



Bin Yu
Nelli Bejanyan

Next-generation CAR designs

How does CAR design contribute to T cell function?

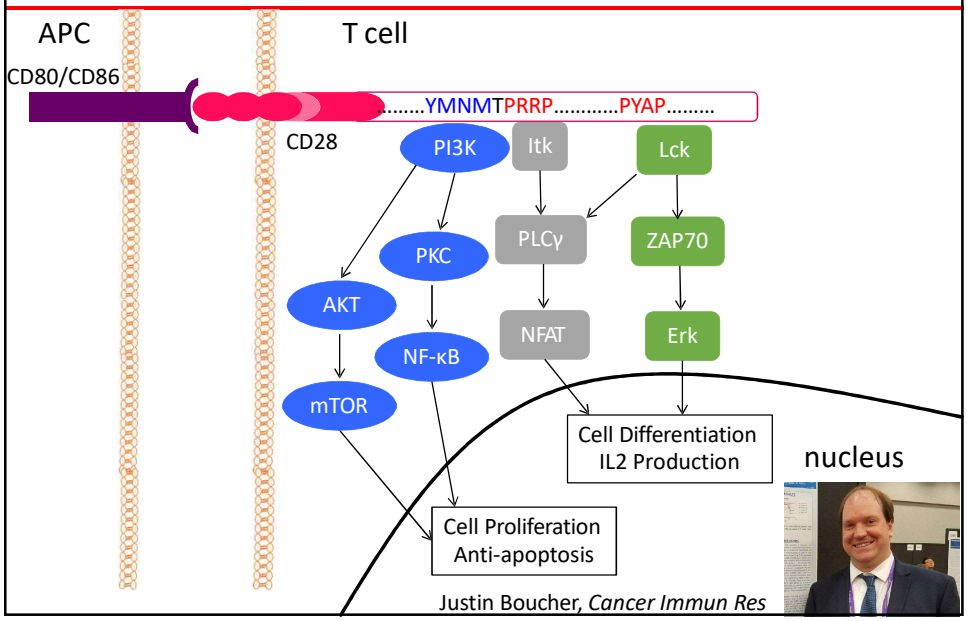


How does 4-1BB and CD28 drive CAR T function?

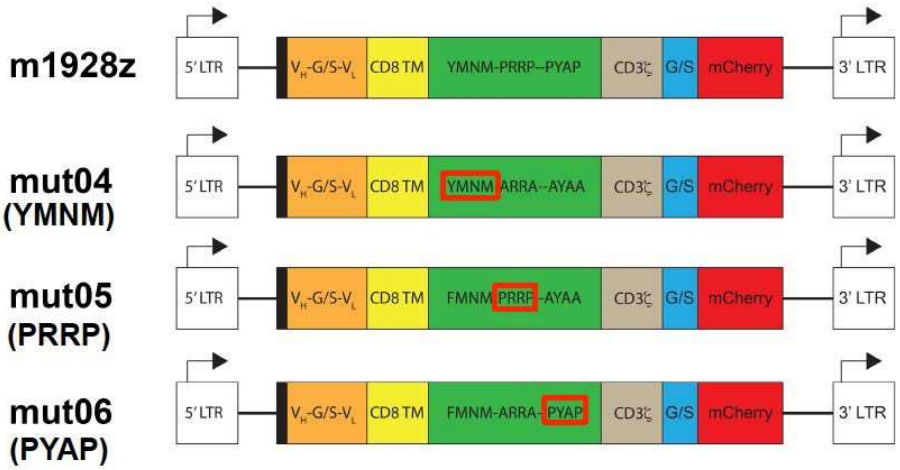
- 4-1BB drives CAR T cells towards a metabolic phenotype that resembles central memory T cells
- Metabolism with CD28 co-stimulation in CAR T cells is more similar to effector memory T cells
- 4-1BB is critical for reversing or preventing an exhaustion phenotype in human CAR T cells
- CAR expression impacts tonic signaling of CD28 co-stimulatory domain
- CARs with a 41BB endodomain can have improved cytotoxicity by over-expressing LCK

Long et al *Nat Med* 2015
Kawalekar et al *Immunity* 2015
Zhao et al *Cancer Cell* 2015
Eyquem et al *Nature* 2017
Dotti *Cancer Cell* 2020

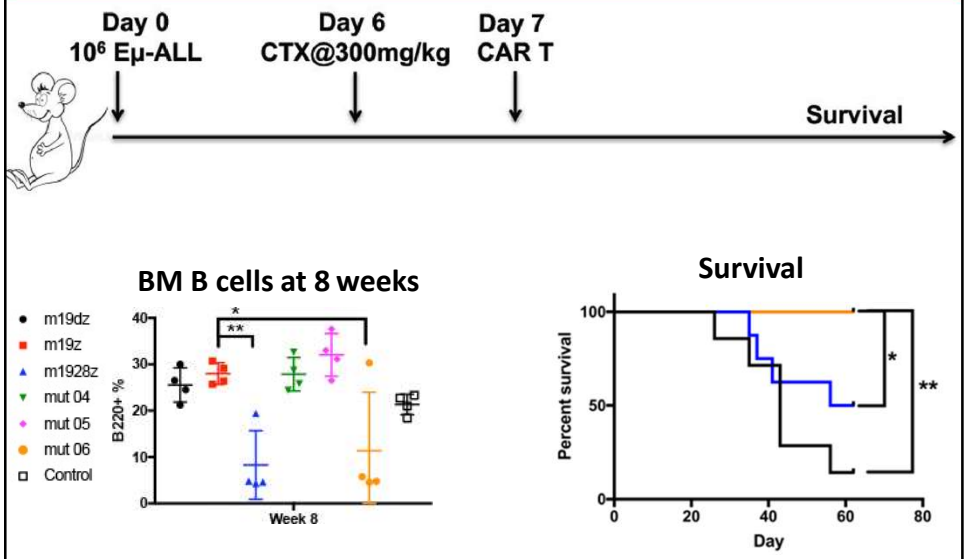
How does CD28 contribute to exhaustion?



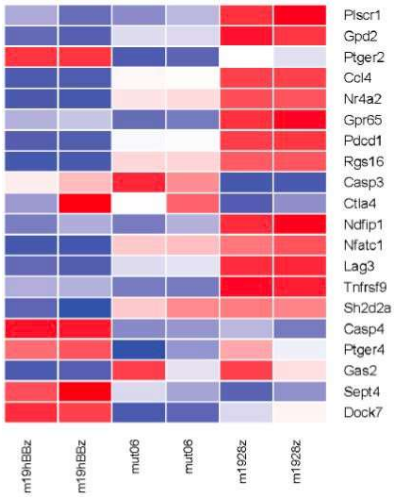
Mouse CD19-targeted CAR constructs with CD28 null mutations



Targeted CD28 mutations that disrupt signaling preserve anti-leukemia in vivo efficacy



Mut06 supports signaling that is associated with less upregulation of exhaustion related genes

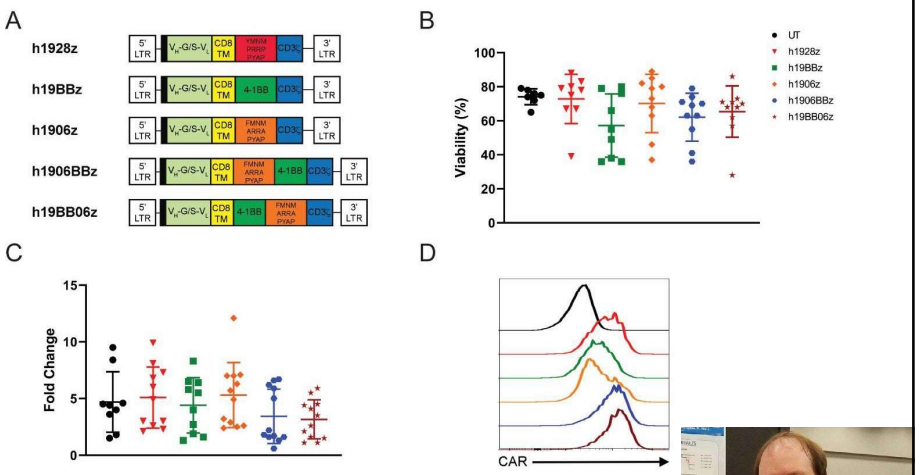


How does co-stimulation regulate CAR T cell function in relevant pre-clinical models

- Mouse T cells modified with a CD19-targeted CAR containing a CD28 endodomain have functional characteristics of exhaustion.
- Mutation of CD28 subdomains preserve in vitro and in vivo function, while reducing exhaustion
- Modulating signaling, TF, and gene regulation can modulate CD28 or 41BB enhancement of CAR T cell function.
- Adapt mut06 to a CD19-targeted CAR
- New roles for TF in CAR T cell function now being explored such as TOX, JUN

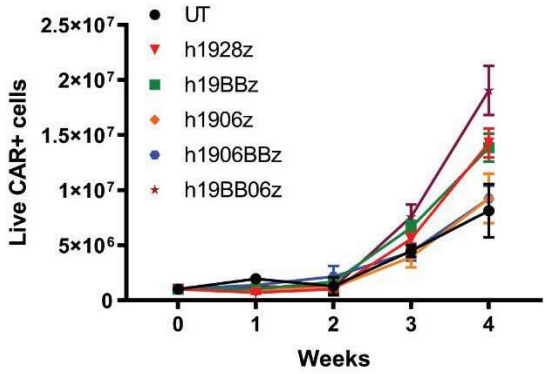
Justin Boucher, Gongbo Li, *Cancer Immunology Research in press*

Combining mut06 with 41BB



Justin Boucher

Combining mut06 with 41BB



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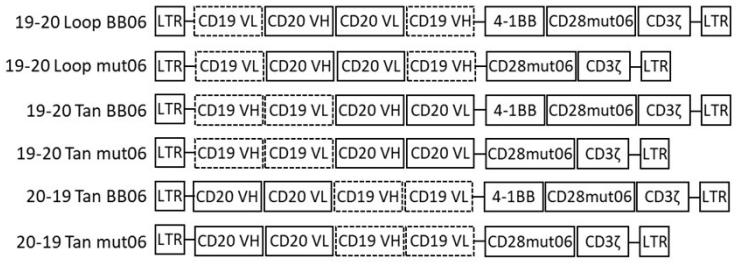
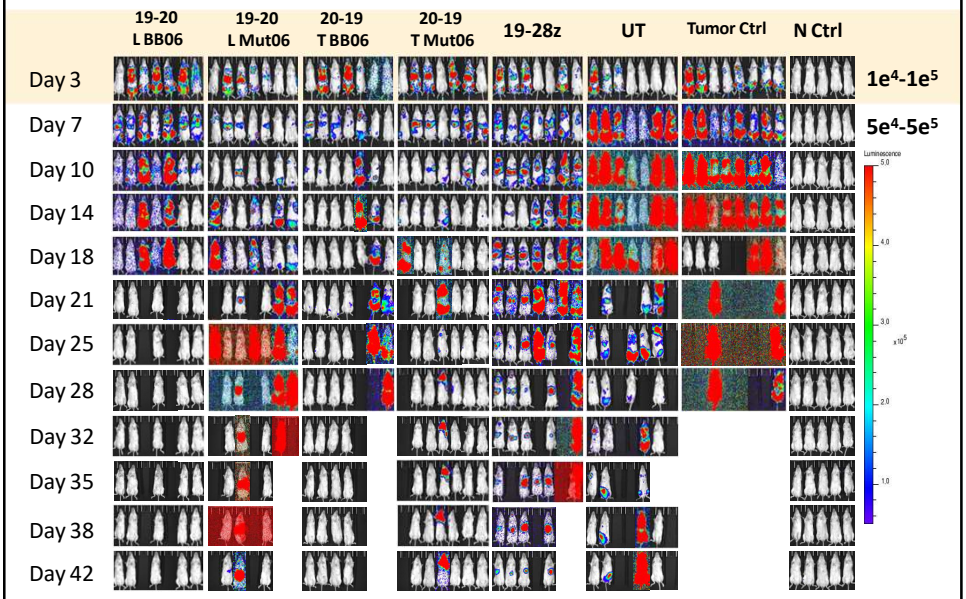
Creating a bi-specific CD19/CD20 CAR (to address antigen-escape)



Emiliano Roselli

Bi-specific CD19/CD20 CAR in vivo efficacy



Emiliano Roselli

Novel indications

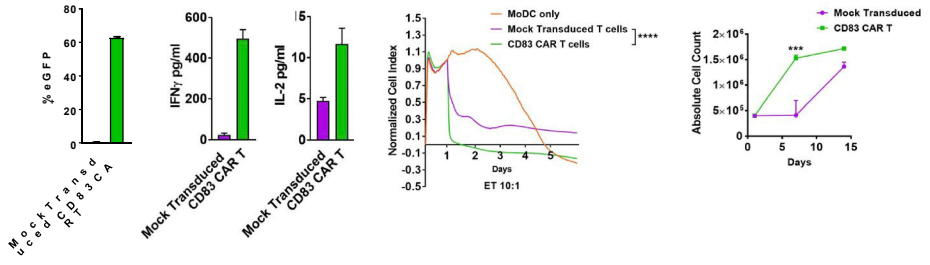
CD83 as a target for GVHD and myeloid diseases

- 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

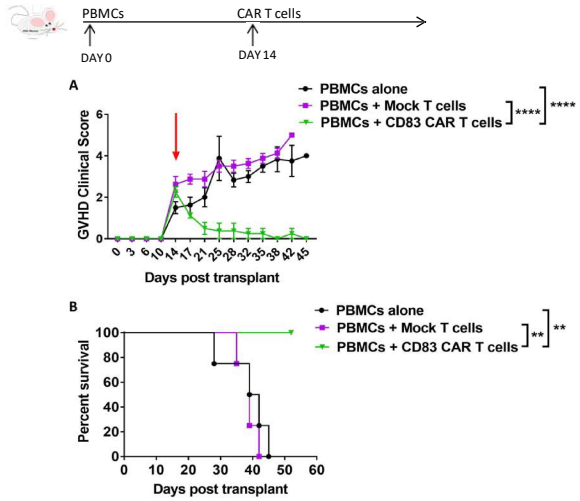
Heilingloh CS. JMB. 2017.
Horvatinovich JM. JI. 2017.
Li Z. Haematologica. 2018.

Brian Betts, UMN
Shrestha et al JCI in press

Designing a CD83-targeted CAR T cell

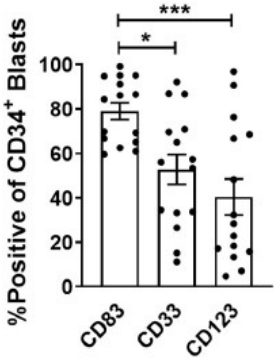


CD83 CAR T cells can also treat GVHD



Effects of CD83 CAR T cells on leukemia versus normal hematopoiesis

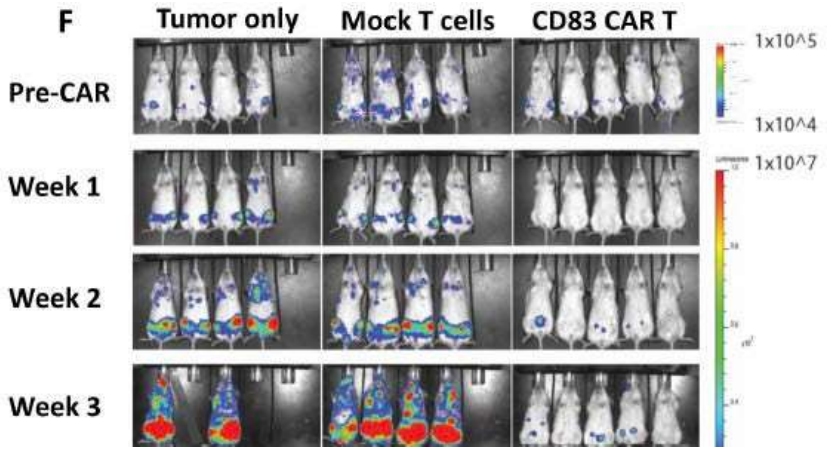
- Over 8,000 allo-HCT procedures are performed annually in the United States
- In adults, AML is the primary indication for allo-HCT
- Disease relapse and GVHD are the leading causes of mortality after allo-HCT
- CD83 is expressed on human AML blasts



Majhail NS. BBMT. 2015.

D'Souza A. BBMT. 2017.

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



Mechanisms of immune resistance

The Moffitt Experience: Using patient samples to investigate CAR T cell biology

- 100 patients with R/R LBCL treated with axi-cel were available for evaluation
- Patient-level and laboratory data, as well as clinical outcomes
- Pre-treatment and post-treatment serum and/or CSF
- Pre-treatment and post-treatment PBMC
- Pre-treatment and post-treatment LN biopsies

Faramand et al, Clinical Cancer Research in press
Jain, Locke, et al, Re-submitted

Study Sample Schema

- **Baseline** sample collection (ANG1&2, IFNγ, IL1β,IL2, IL6, IL15, TNFα, GM-CSF, CRP and Ferritin)
- Fludarabine/Cyclophosphamide (Days -5,-4,-3)
- **Day 0** sample collection (ANG1&2, IFNγ, IL1β,IL2, IL6, IL15, TNFα, GM-CSF, CRP and Ferritin)
- Infusion of CAR T cells
- Daily sample collection while hospitalized(ANG1&2, IFNγ, IL1β,IL2, IL6, IL15, TNFα, GM-CSF, CRP and Ferritin)
- Daily grading of CRS and NT during hospitalization using ASTCT Consensus Guidelines

Baseline Patient Characteristics

	Current study (n=75)	Zuma 1 (n=101)
Age - Median (Range) yrs	63 (23-79)	58 (23-76)
Male Sex – no. (%)	50 (67)	68 (67)
Histology – no. (%)		
de Novo DLBCL	50 (67)	77 (76)
Transformed Indolent lymphoma	25 (33)	24(24)
Ann Arbor Stage III/IV – no. (%)	58 (77)	86 (85)
IPI ≥ 3 at apheresis – no. (%)	52 (69)	48 (48)
Lines of therapy ≥ 3 — no. (%)	46 (61)	70 (69)
Bridging therapy – no. (%)	46 (61)	0
Not eligible for Zuma 1 – no. (%)	56 (75)	---

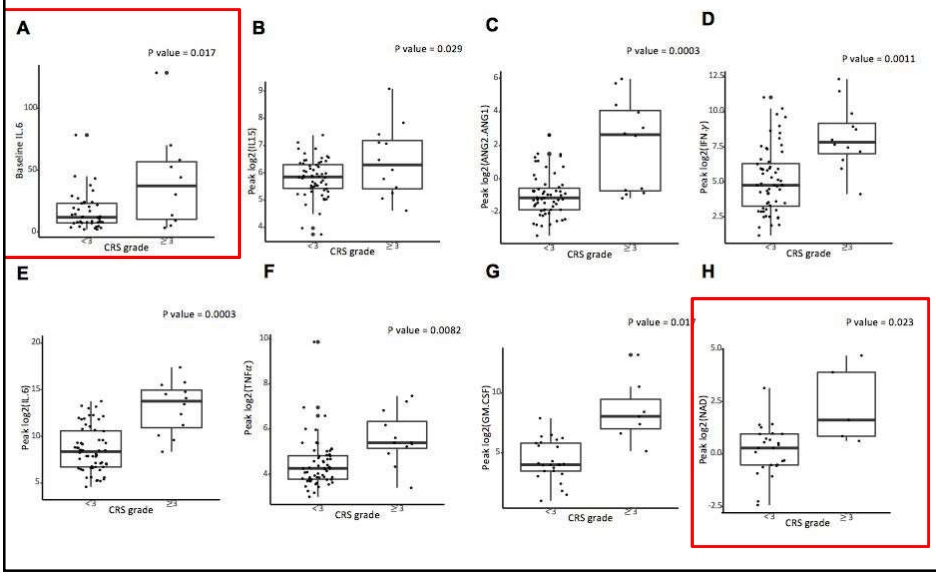
Neealapu et al, NEJM 2018
Locke et al, Lancet Oncol 2019

Clinical Endpoints

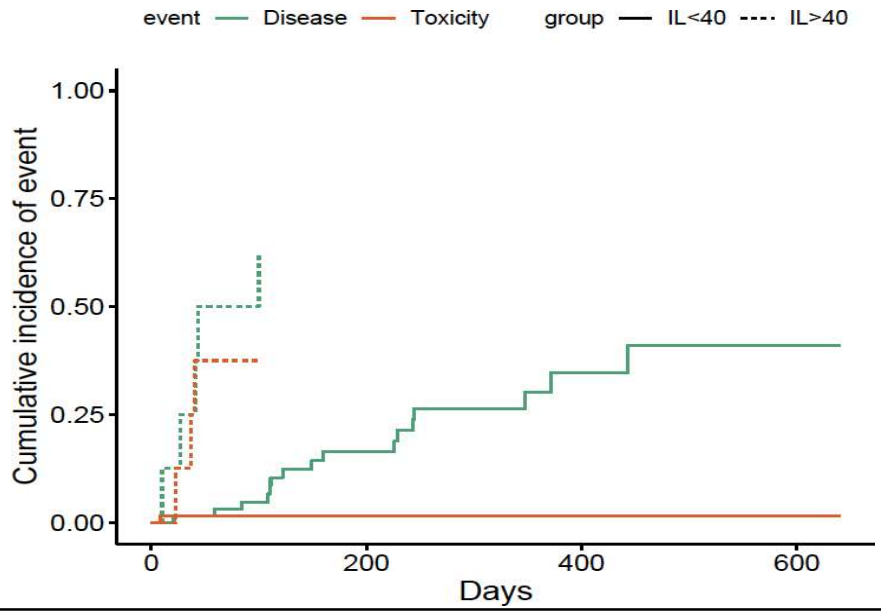
	Current study (n=75)	Zuma 1 (n=101)
CRS		
Median time to CRS	2 days	2 days
Median time to max CRS	4 days	n/a
CRS all grades – no. (%)	72 (96)	94 (93)
Grade ≥ 3 CRS – no. (%)	12 (16)	13 (13)
Use of tocilizumab – no. (%)	43 (57)	43 (43)
Use of steroids – no. (%)	41 (55)	27 (27)
Neurotoxicity		
Median time to NT	5 days	5 days
Median time to max NT	6 days	n/a
NT all grades– no. (%)	50 (67)	65 (64)
Grade ≥3 NT– no. (%)	23 (31)	28 (28)
D90 Response (N=68)		
CR + PR –no. (%)	36 (53)	5 days
Complete Response – no. (%)	29 (43)	n/a
NRM – no. (%)	4 (6)	65 (64)
Disease related mortality– no. (%)	9 (13)	28 (28)

Neealapu et al, NEJM 2018
Locke et al, Lancet Oncol 2019

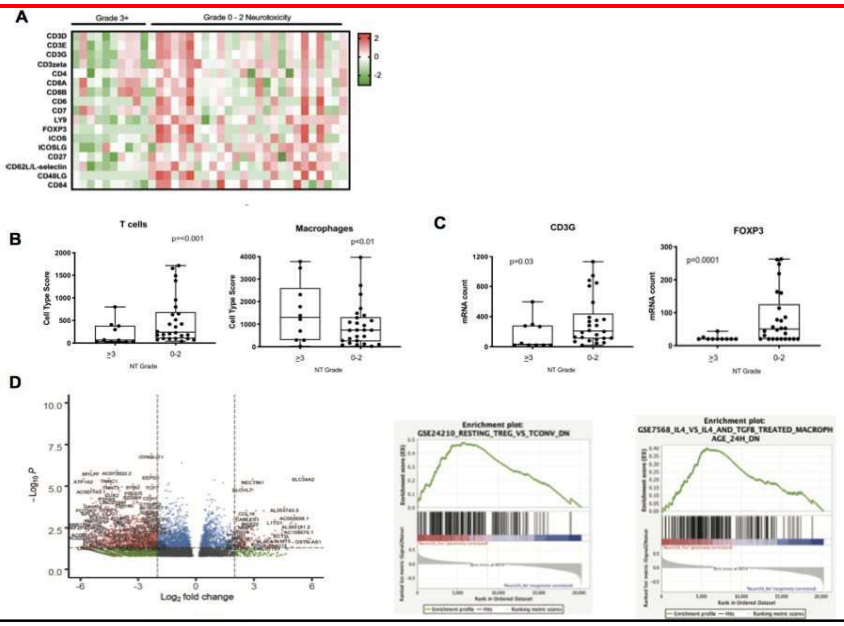
Serum Markers Associated with Severe CRS



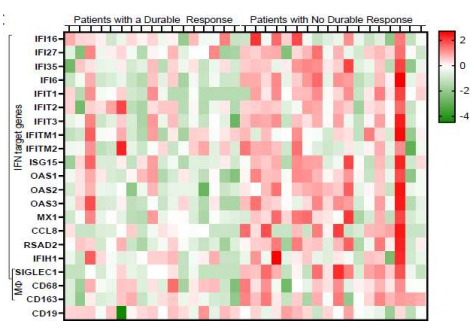
Pre-Treatment Elevated IL6 Associated with Life Threatening Events

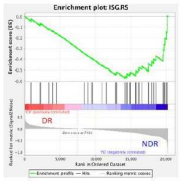


Gene expression of lymphoma tissue correlates with toxicities

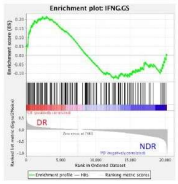


…and to CAR T cell resistance as well



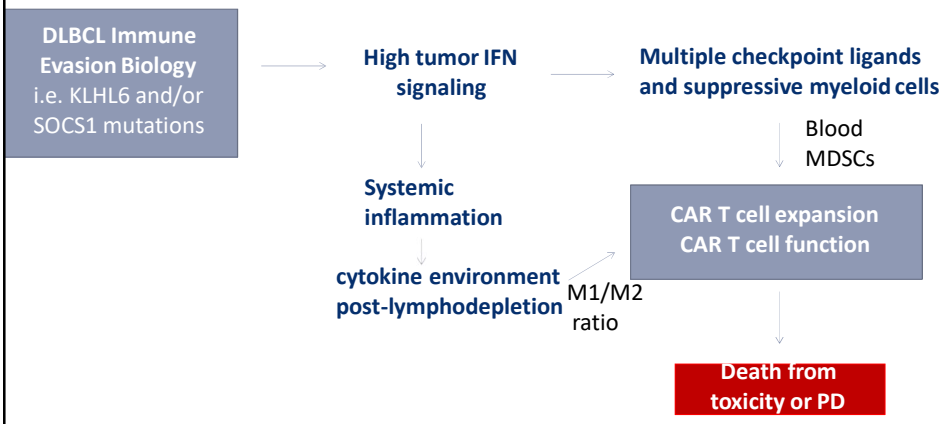


Tumor IFN gene signature associates with no durable response



T cell IFN gene signature associates with durable response

Model how tumor genomics impact CAR T cell toxicity and efficacy



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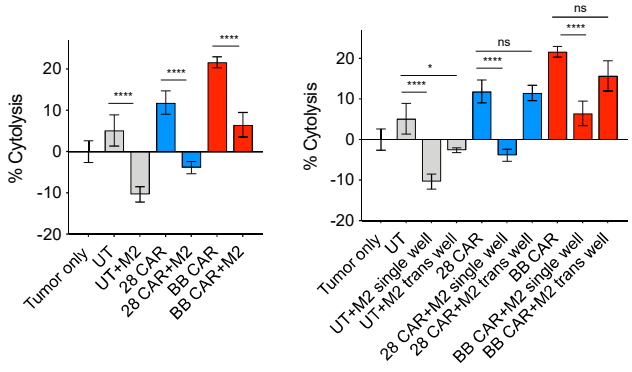
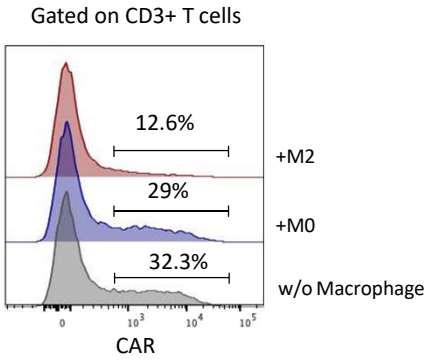
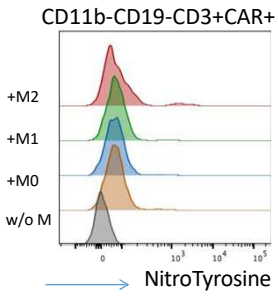
Myeloid cells inhibit CAR T cell cytotoxicity



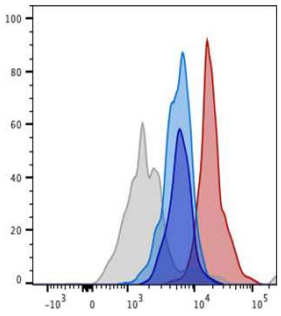
Myeloid cells reduce CAR+ T cells



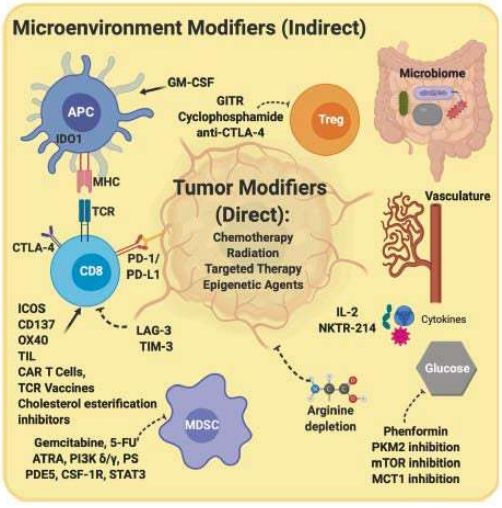
Myeloid cells nitrate CAR+ T cells



CAR T cells are nitrated in patient lymphoma samples



ICB and CAR T cells share a common enemy present in solid tumors



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