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The Future of Cellular Therapies:
Targeting GPRC5D for multiple myeloma as a case study

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MIT Health Science Technologies

April 12, 2022

HARVARD MEDICAL SCHOOL

Dana-Farber Cancer Institute

Disclosures

Commercial Interest(s)	Nature of Relationship
BMS	Licensed patents/royalties for CAR T cell therapies for MM, including, stemming from my lab work currently under clinical investigation: -Orvacabtagene autoleucel (BCMA, formerly JCARH125), -BCMA NEX-T (CC-98633), -MCARH171, -FCARH143, -JWCAR129, -MCARH109 (GPRC5D), -CC-95266 (GPRC5D) Research Funding
Sanofi	Licensed patents/royalties for GPRC5D targeted Antibodies/Bi-Specifics to treat MM Research Funding
Novartis; Chimeric Therapeutics; BMS	Scientific Advisory Board
Chroma Medicine; ImmuneBridge; Secura Bio; Clade Therapeutics; Eureka Therapeutics; Sana Biotech	Consulting

Approved Indications

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Vaccines, Blood & Biologics / Cellular & Gene Therapy Products

Axicabtagene ciloleucel (Gilead/Kite) anti-CD19/CD28z

- Adults, R/R FL after 2+ lines (ZUMA-1; Neelapu S *NEJM* 2017)
- Adults, R/R large B-cell lymphoma after 1+ line (ZUMA-7; Locke F *NEJM* 2022)

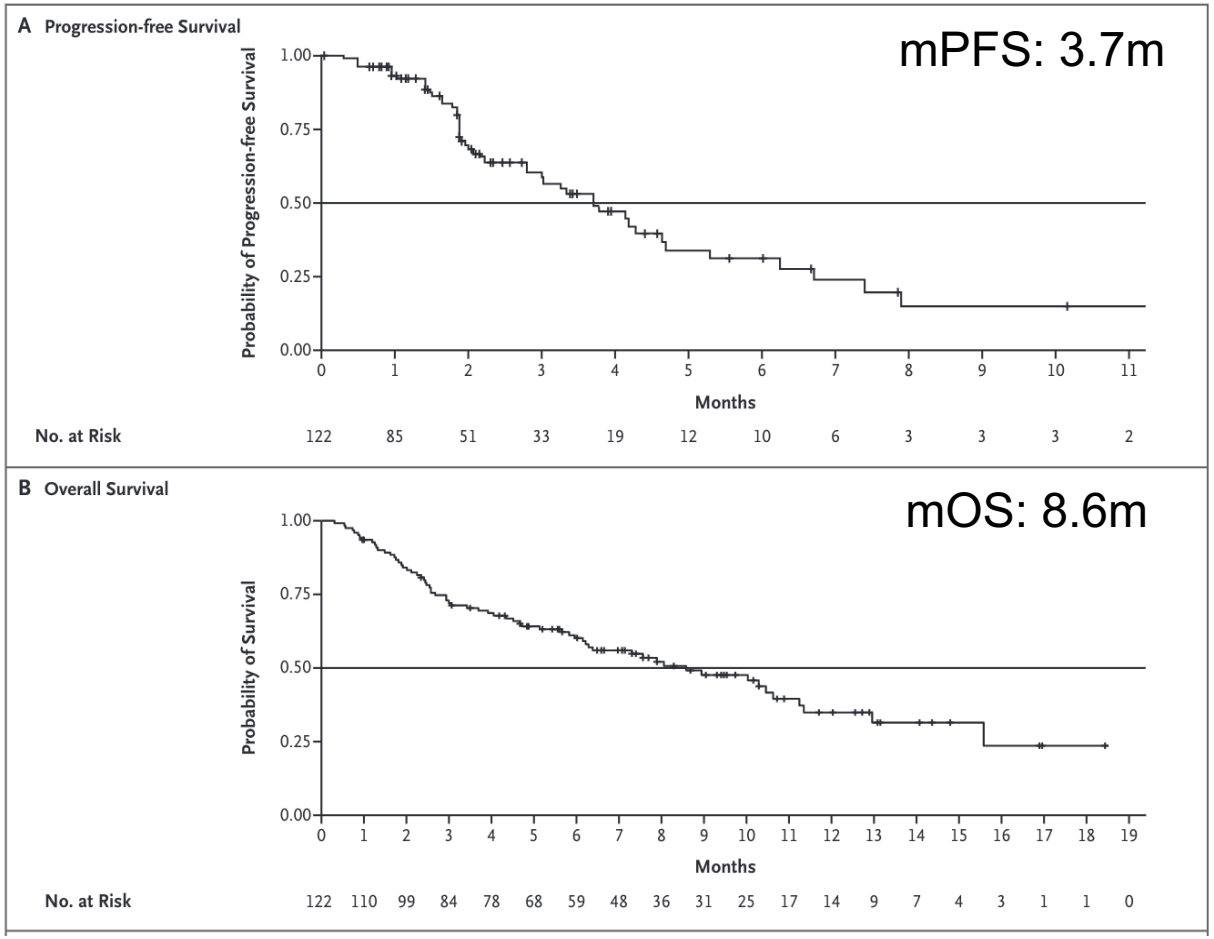
- **Tisagenlecleucel** (Novartis) anti-CD19/4-1BBz
  - </= 25yo, B-ALL primary refractory or 2+ relapses (ELIANA, Maude S *NEJM* 2018)
  - Adults, R/R large B-cell lymphoma 2+ lines (JULIET; Schuster S *NEJM* 2019)
- **Brexucabtagene autoleucel*** (Gilead/Kite) anti-CD19/CD28z
  - Adults, R/R mantle cell lymphoma (ZUMA-2; Wang M *NEJM* 2020)
- **Lisocabtagene maraleucel** (BMS/Juno) anti-CD19/4-1BBz
  - Adults, R/R large B-cell lymphoma; FL 2+ lines (TRANSEND; Abramson J *Lancet* 2020)
- **Idecabtagene vicleucel** (BMS/Bluebird) anti-BCMA/4-1BBz
  - Adults, R/R multiple myeloma 4+ lines (KarMMa; Raje N *NEJM* 2019, Munshi N *NEJM* 2021)
- **Ciltacabtagene autoleucel** (Janssen/Legend) anti-BCMA/4-1BBz
  - Adults, R/R multiple myeloma 4+ lines (CARTITUDE-1; Berdeja J *Lancet* 2021)

*same CAR vector as Axi-cel, manufacturing now includes T cell enrichment

CAR T cell therapies provide historic advance for patients with relapsed/refractory hematologic malignancies

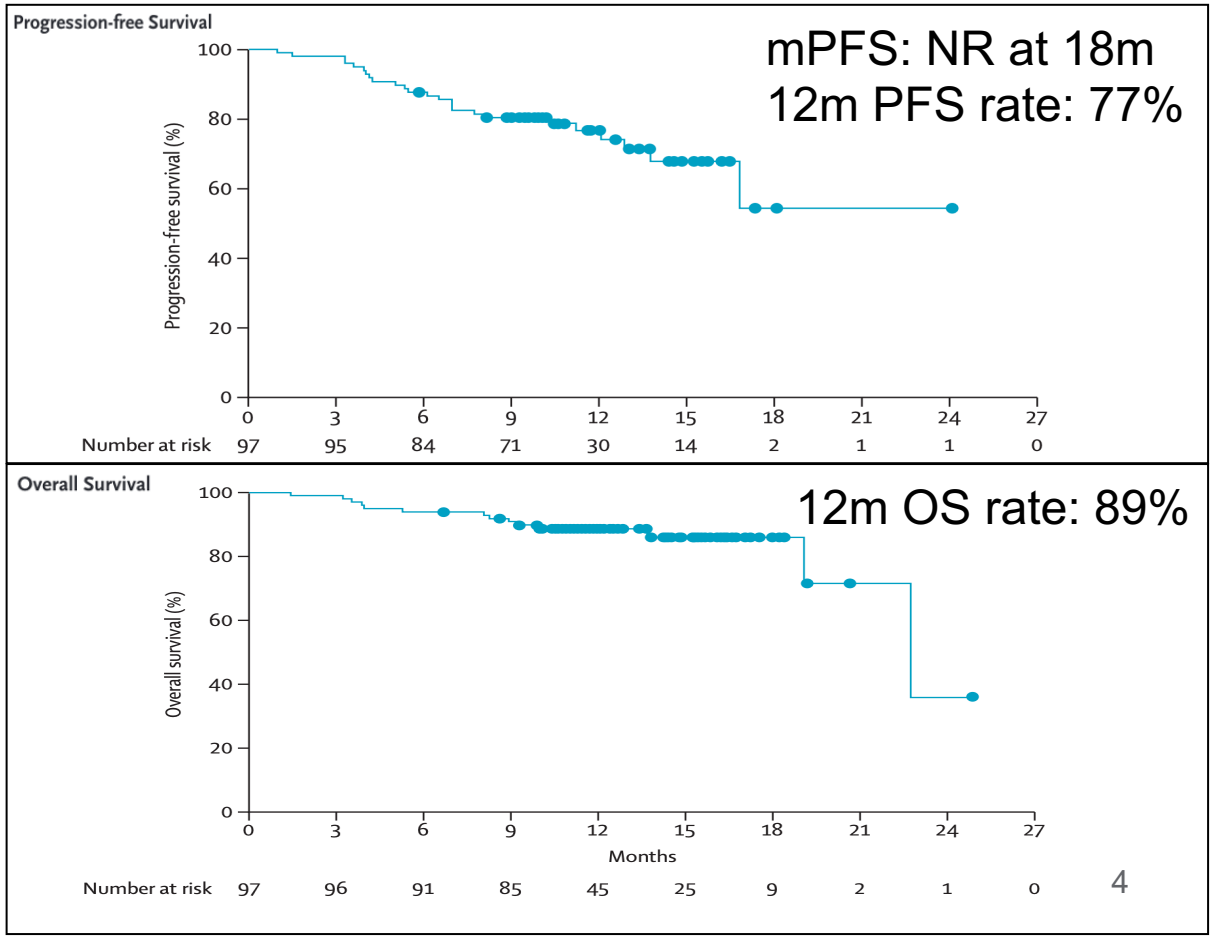
Selinexor

N ENGL J MED 381;8 NEJM.ORG AUGUST 22, 2019

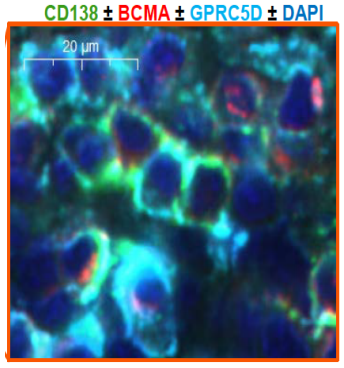


Cilta-cel

Lancet 2021; 398: 314–24 July 24, 2021



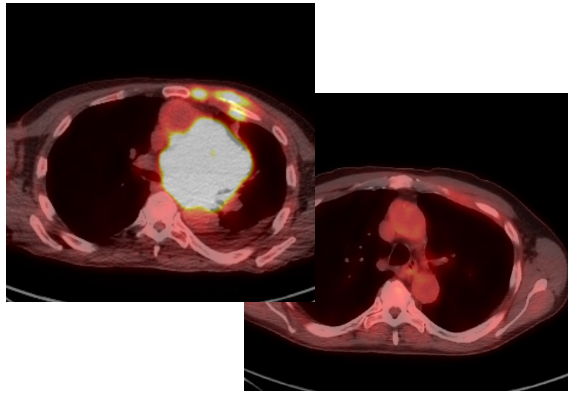
- New targets and logic gating



GPRC5D as target for MM

Mette Staehr

>>



GPRC5D CAR T clinical trial

Sham Mailankody

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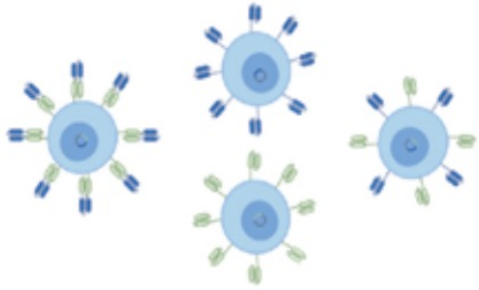
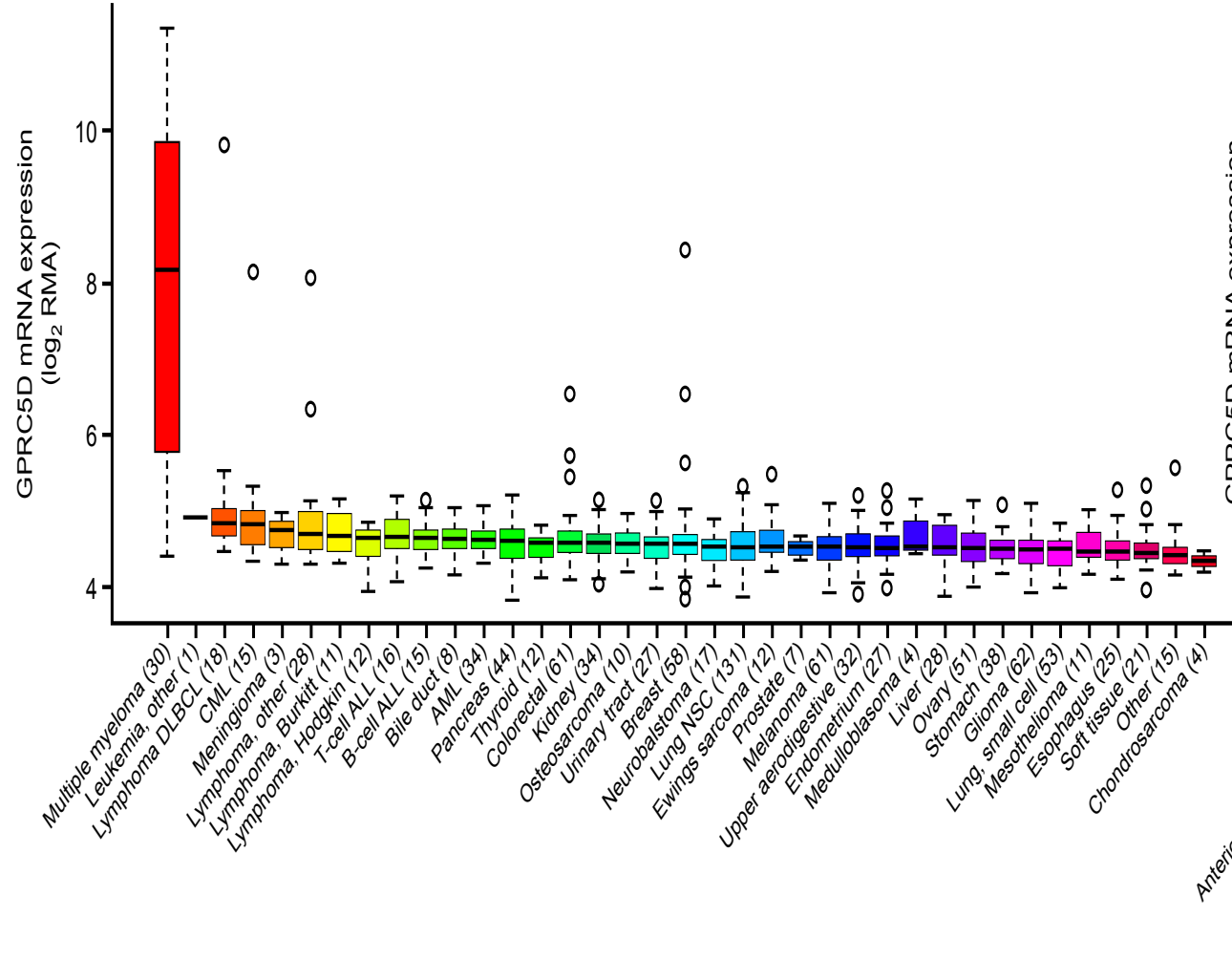


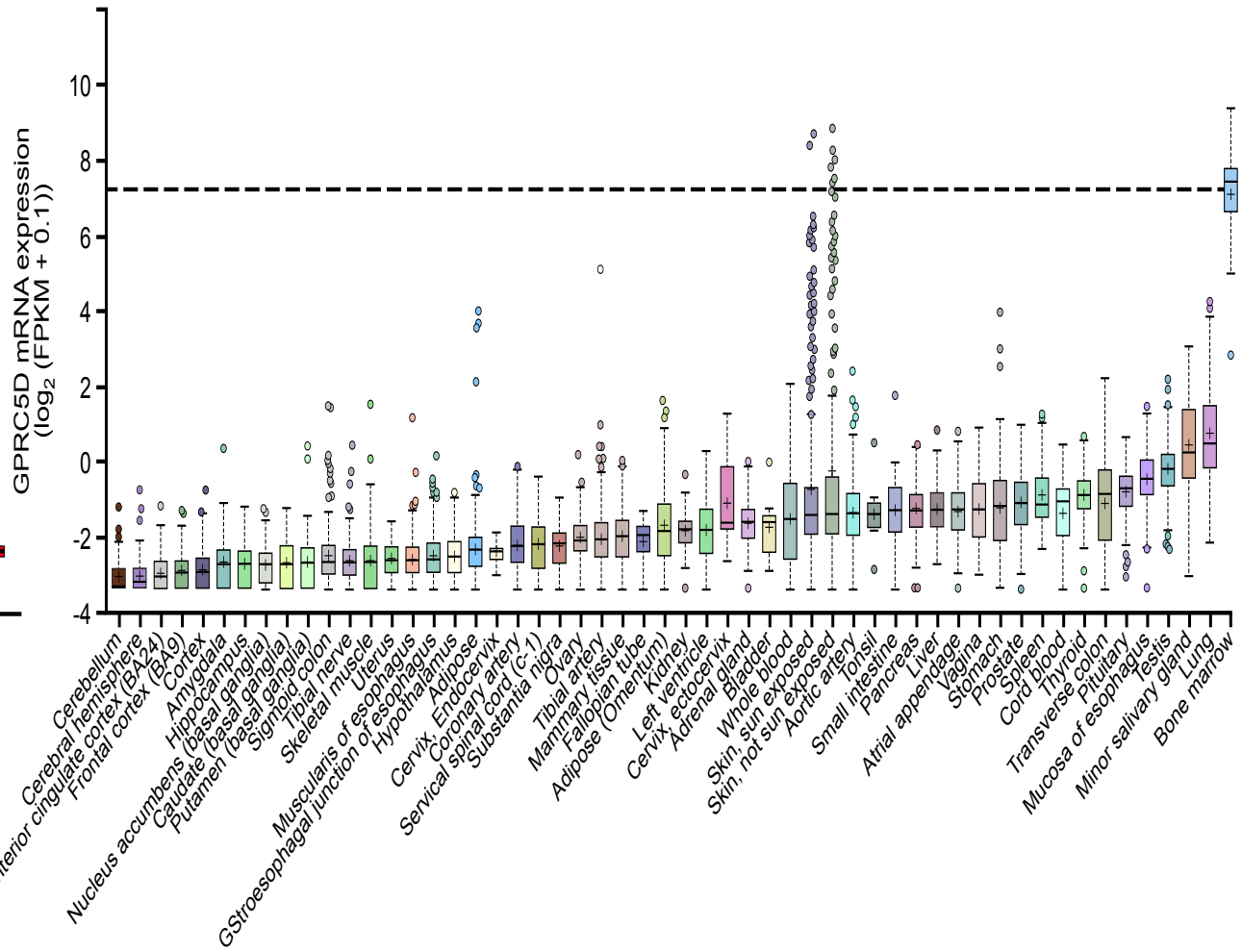
Dual-targeting

Carlos Fernandez de Larrea

- Next-gen CARs
- Intracellular targets • non-T cell types
- mRNA as a target and a therapeutic
- Advances in manufacturing

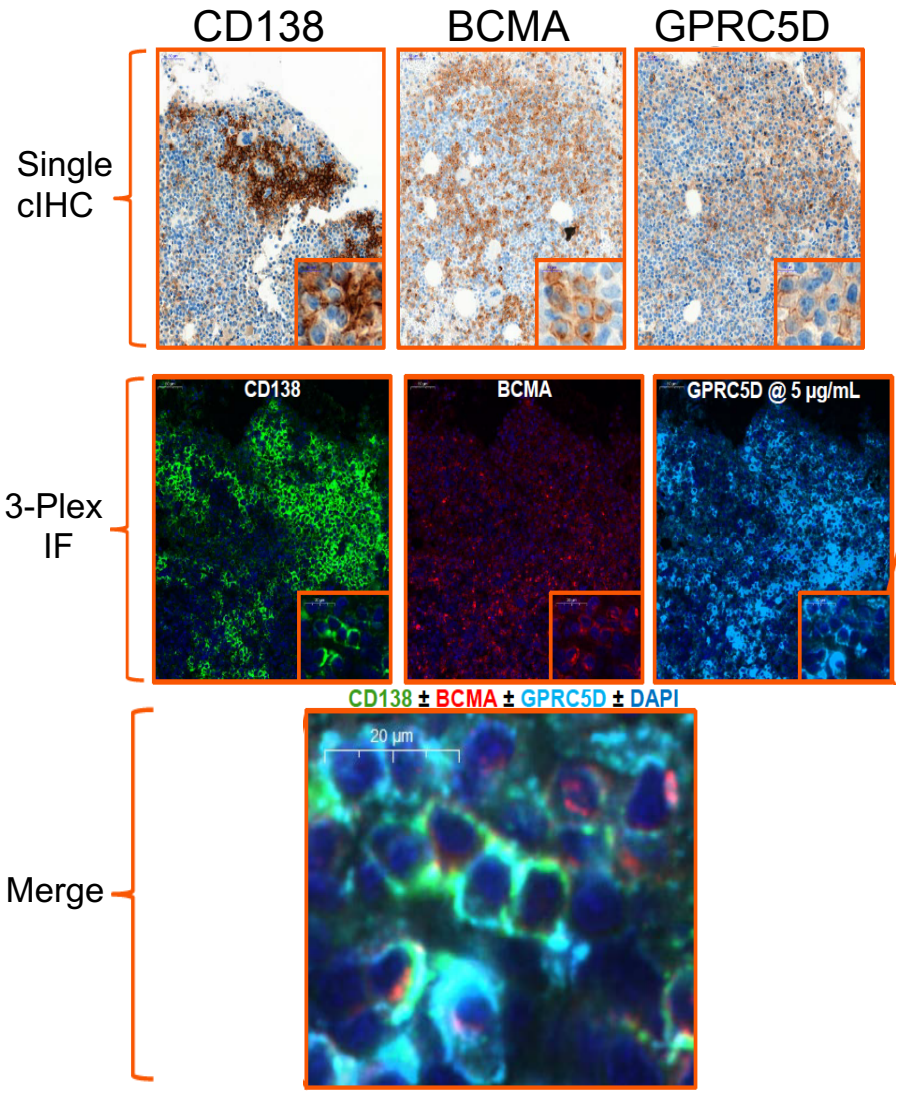
G Protein-Coupled Receptor Class C Group 5 Member D (**GPRC5D**)

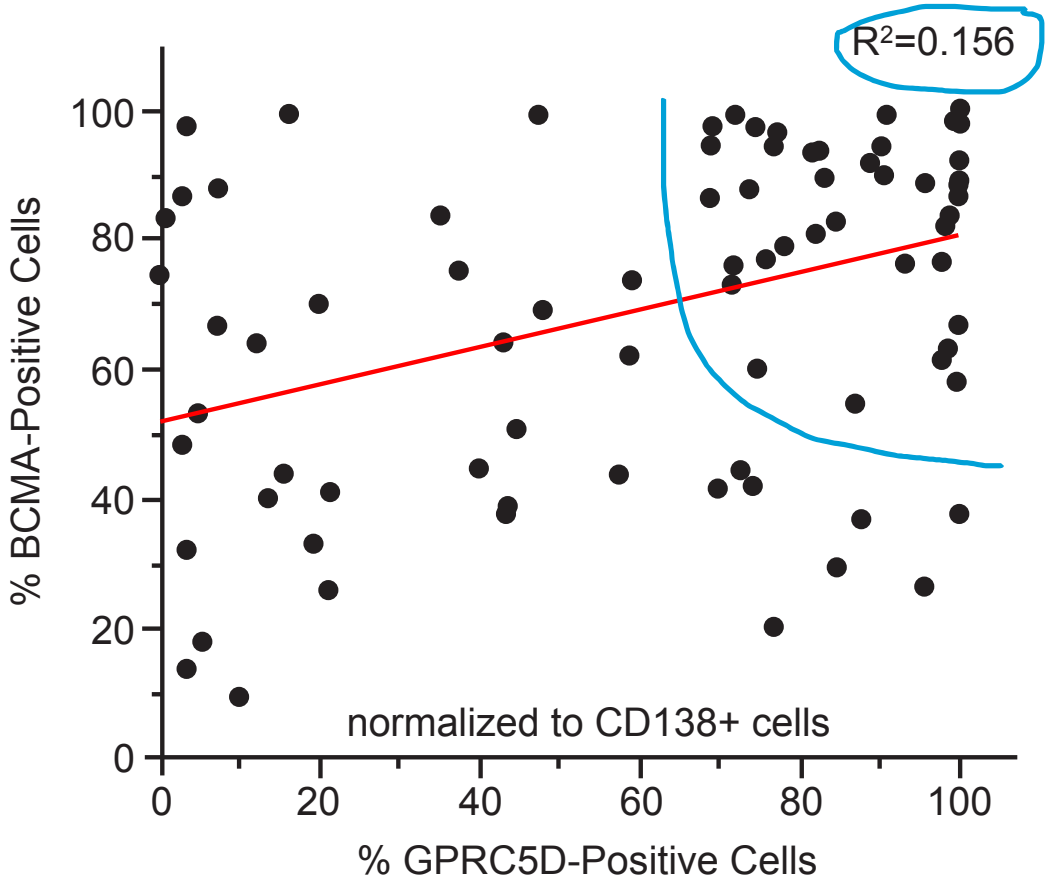




- Orphan 7 trans-membrane receptor
- Expressed in subset of cells in hair follicle, hard keratinizing tissue

GPRC5D protein expression is identified on MM cells and is expressed independently of BCMA

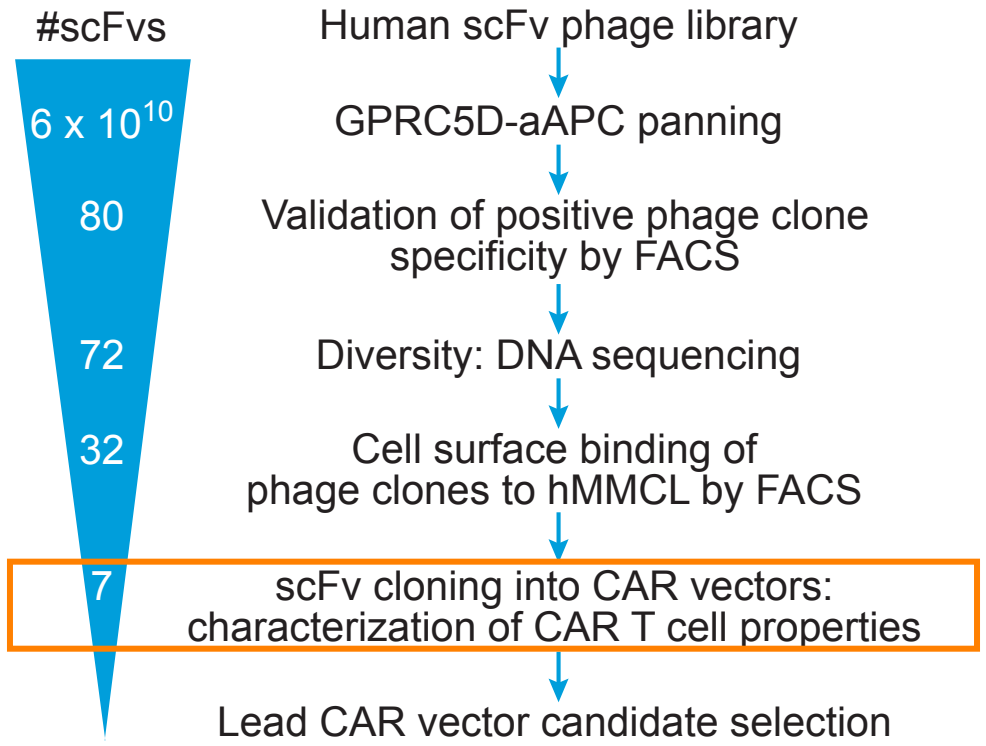


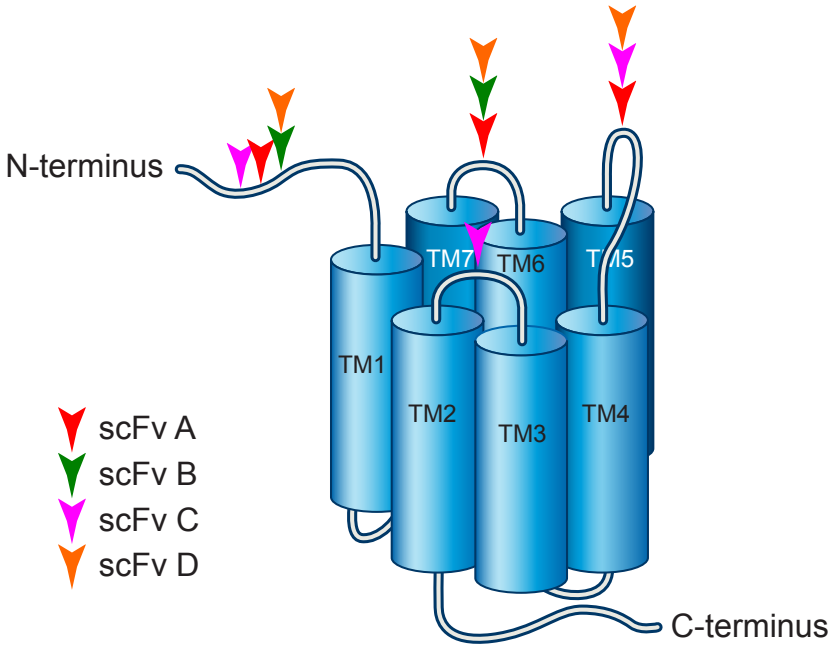


Dana-Farber Cancer Institute

Smith EL et al. *Science Translational Medicine* 2019

Identification of candidate GPRC5D-specific scFvs by screening a human B cell-derived phage display library





V_H/V_L
V_L/V_H

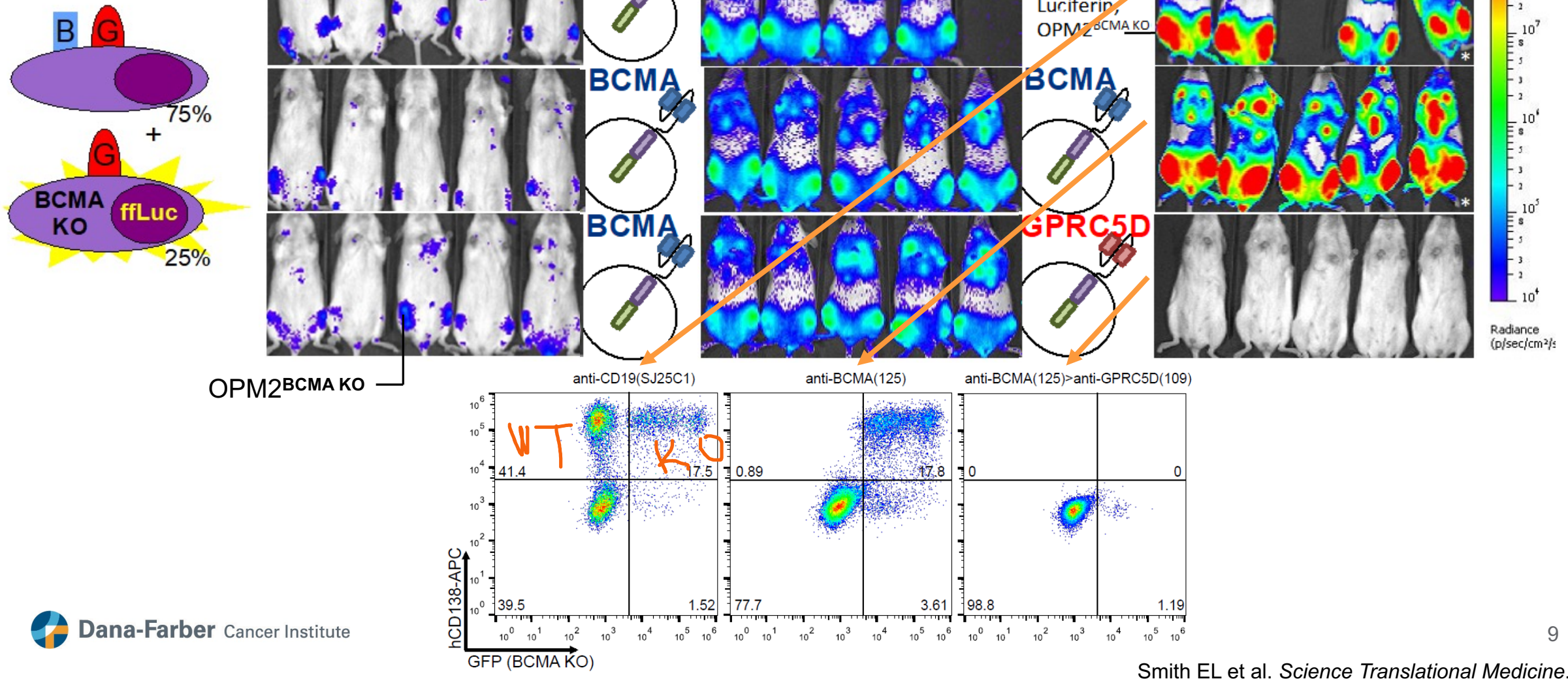
short (hinge only)
medium (hinge-CH3)
long (hinge-CH2-CH3)

7 x 2 x 3 = 42 CARs

Dana-Farber Cancer Institute

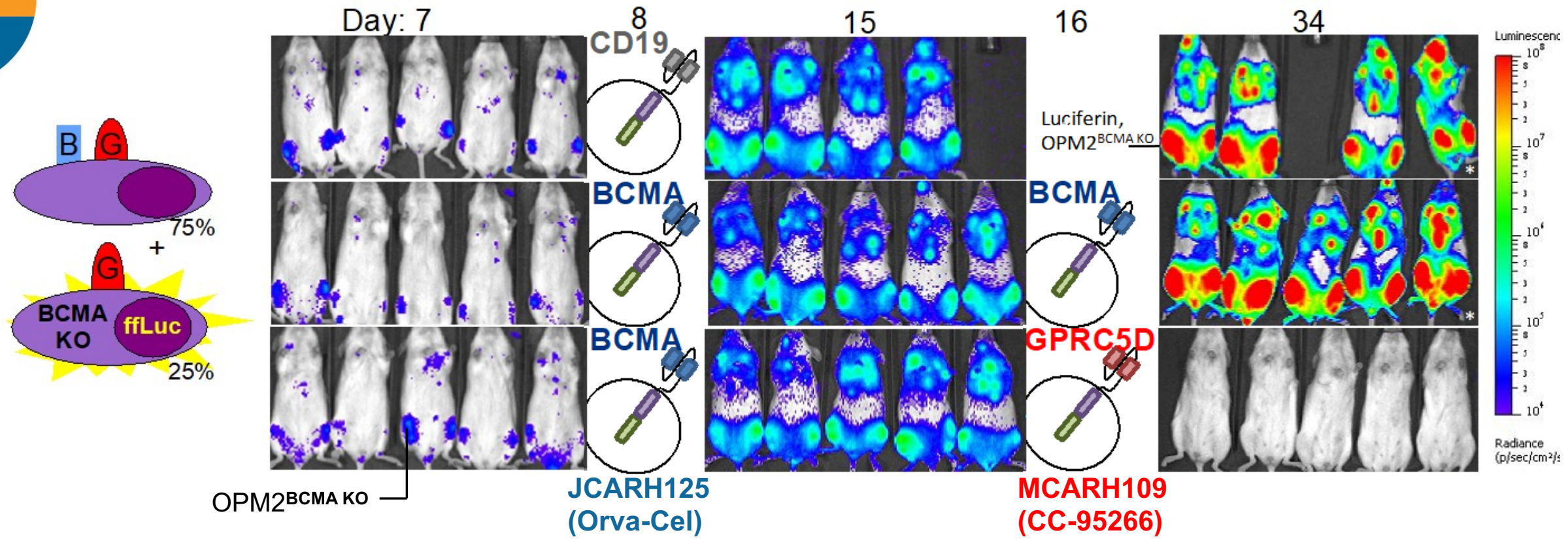
Smith EL et al. *Science Translational Medicine* 2019

GPRC5D-targeted CAR T cells rescued mice from BCMA negative tumor escape model



Smith EL et al. *Science Translational Medicine*. 2019

GPRC5D-targeted CAR T cells rescued mice from BCMA negative tumor escape model



NIH U.S. National Library of Medicine

ClinicalTrials.gov

MCARH109 Chimeric Antigen Receptor (CAR) Modified T Cells for the Treatment of Multiple Myeloma

Sham Mailankody, PI ClinicalTrials.gov Identifier: NCT04555551

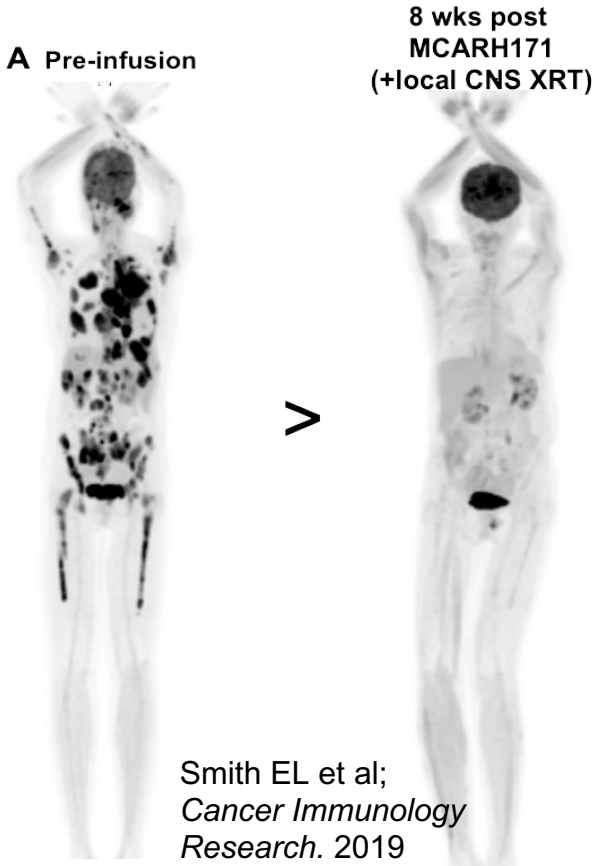
A Study of CC-95266 in Subjects With Relapsed and/or Refractory Multiple Myeloma

Omar Nadeem, PI ClinicalTrials.gov Identifier: NCT04674813

Dana-Farber Cancer Institute

Smith EL et al. *Science Translational Medicine*. 2019

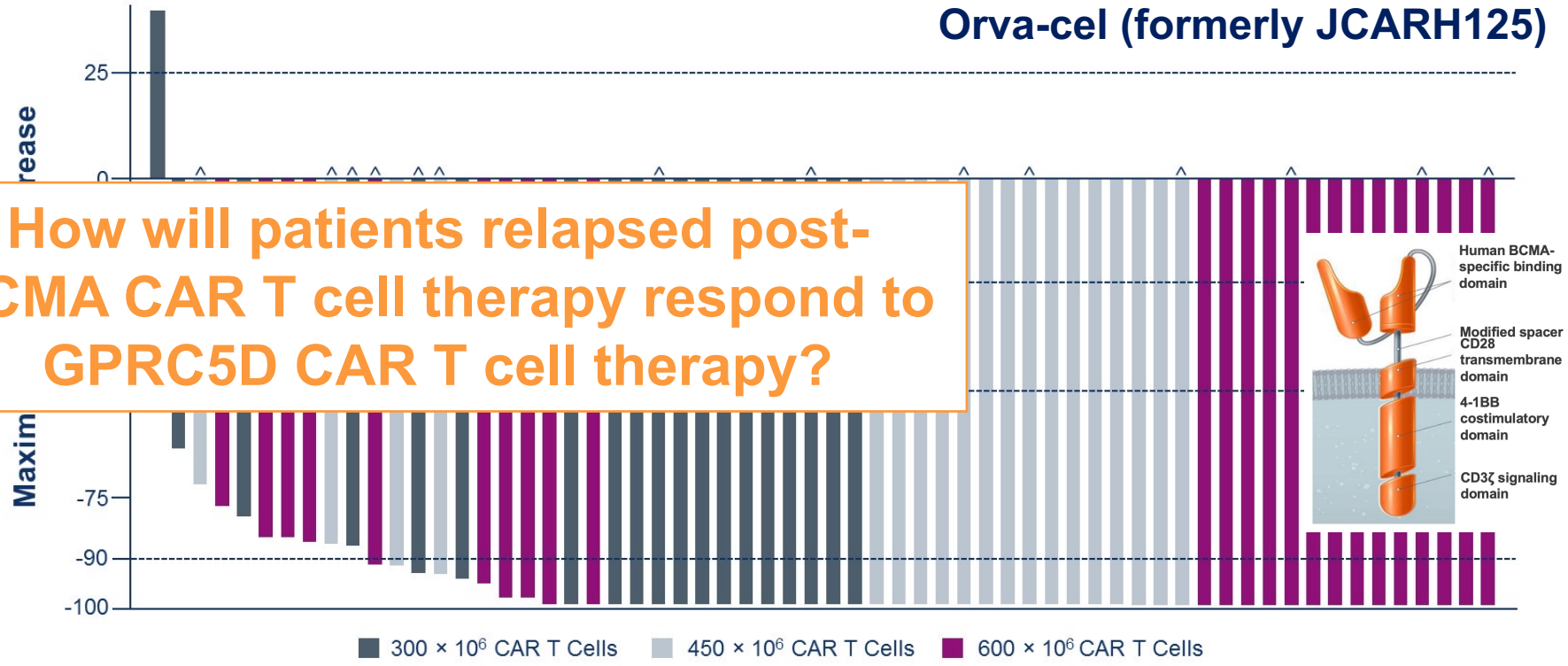
BCMA CAR T cell therapies have dramatic efficacy in RRMM



Smith EL et al;
Cancer Immunology Research. 2019

EVOLVE: Deep Tumor Burden Reduction Across Dose Levels

Orva-cel (formerly JCARH125)



How will patients relapsed post-BCMA CAR T cell therapy respond to GPRC5D CAR T cell therapy?

Serological responses* were observed in all patients treated at 450 × 10^6 and 600 × 10^6 DLs

*Involved serum or urine paraprotein, free light chains. ^Patient with baseline extramedullary plasmacytoma.

Memorial Sloan Kettering Cancer Center

Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Patients with Relapsed or Refractory Multiple Myeloma

Sham Mailankody, Claudia Diamonte, Lisa Fitzgerald, Peter Kane, Xiuyan Wang, Devanjan Sikder, Brigitte Sénéchal, Vladimir Bermudez, Diana Frias, Justina Morgan, Patrick Grant, Terence Purdon, Kinga Hosszu, Sean Devlin, Urvi Shah, Jonathan Landa, Alexander Lesokhin, Neha Korde, Hani Hassoun, Carlyn Tan, Malin Hultcrantz, Gunjan Shah, Heather Landau, David Chung, Michael Scordo, Mikhail Roshal, Ola Landgren, Ahmet Dogan, Sergio Giralt, Jae Park, Isabelle Rivière, Renier Brentjens, **Eric L. Smith**

ASH Annual Meeting 12/2021; Abstract 827

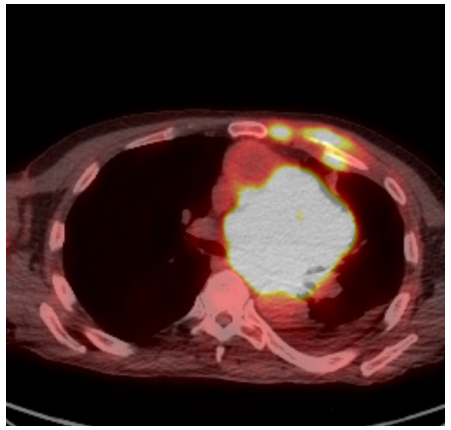
Memorial Sloan Kettering Cancer Center

Key Safety Events (n=16)

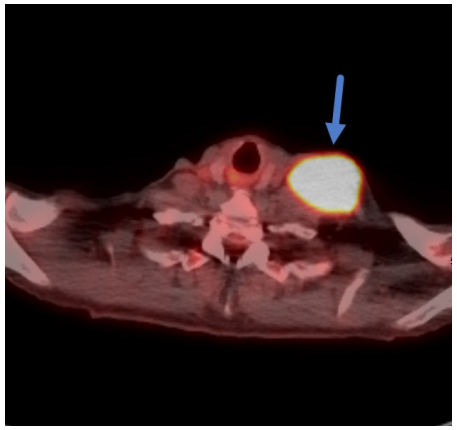
	25 X10⁶ CAR+ T cells (n=3)	50 X10⁶ CAR+ T cells (n=3)	150 X10⁶ CAR+ T cells (n=5)	450 X10⁶ CAR+ T cells (n=5)	Total (N=16)
Cytokine Release Syndrome, Any Grade, n (%)	3 (100)	3 (100)	4 (100)	4 (80)	14 (93)
Cytokine Release Syndrome, Grade 3 or higher, n (%)	0 (0)	0 (0)	0 (0)	1 (20)	1 (7)
Neurologic Toxicity, Any Grade, n (%)	0 (0)	0 (0)	0 (0)	1 (20)	1 (7)
Neurologic Toxicity, Grade 3 or higher, n (%)	0 (0)	0 (0)	0 (0)	1 (20)	1 (7)
Macrophage Activation Syndrome, n (%)	0 (0)	0 (0)	0 (0)	1 (20)	1 (7)
Infections, n (%)	1 (33)	0 (0)	1 (20)	1 (20)	3 (19)
Grade 1 Nail changes, n (%)	1 (33)	2 (67)	2 (40)	4 (80)	9 (56)
Grade 1 Maculo-papular rash, n (%)	0 (0)	0 (0)	2 (40)	1 (20)	3 (19)
Grade 1 Dysgeusia, n (%)	0 (0)	0 (0)	1 (20)	0 (0)	1 (6)
Grade 3 or higher Hematologic Toxicities, n (%)					
Anemia	3 (100)	0 (0)	1 (20)	3 (60)	7 (44)
Thrombocytopenia	3 (100)	1 (33)	1 (20)	5 (100)	10 (63)
Neutropenia	3 (100)	3 (100)	5 (100)	5 (100)	16 (100)

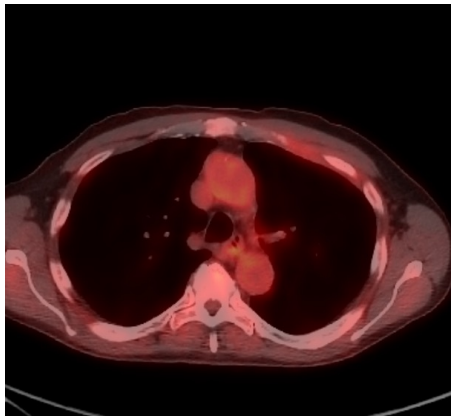
Mailankoday S et al. ASH 2021

Radiologic Response: Patient #1 (25M cells)



Pre-treatment





4 week follow-up

Clinical Responses (n=16)

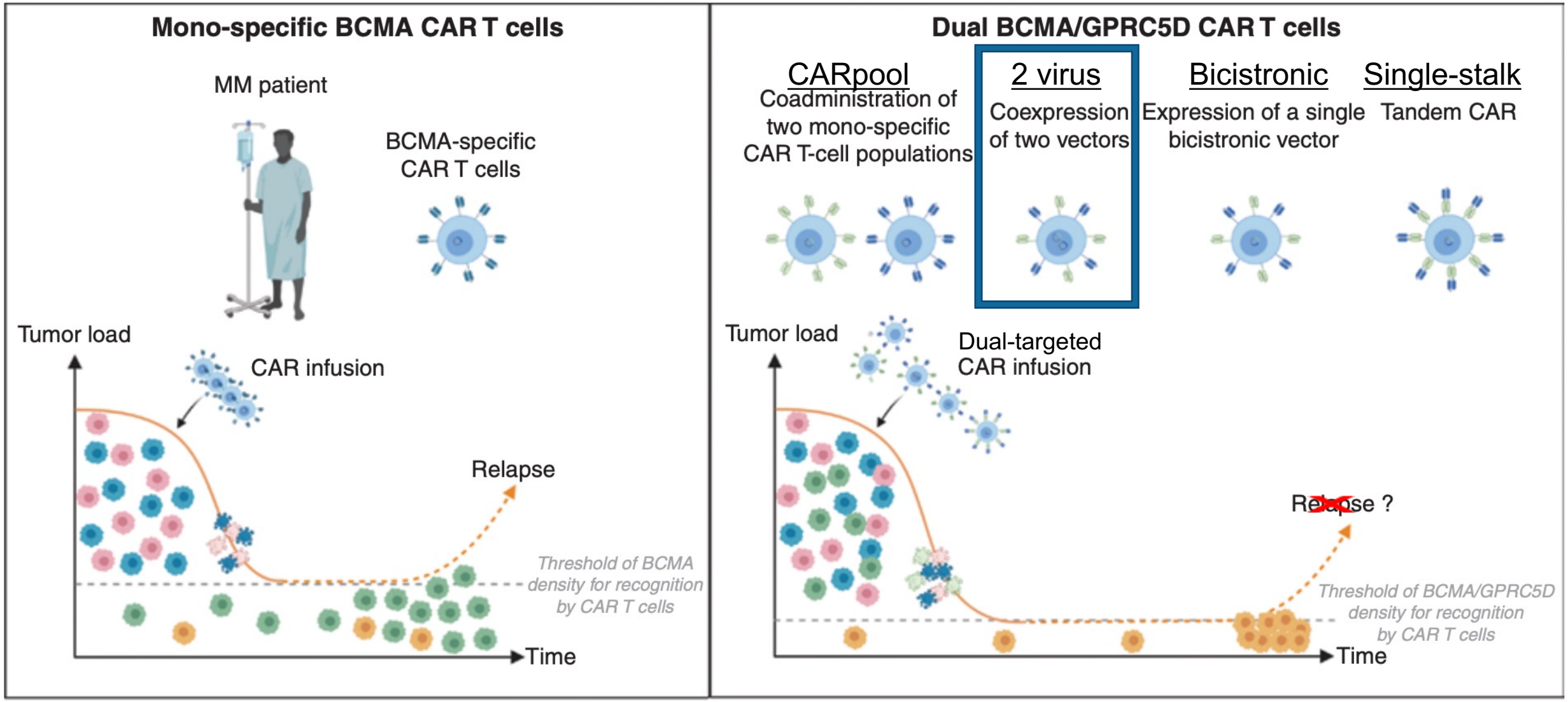
Response	25 X10⁶ CAR+ T cells (n=3)	50 X10⁶ CAR+ T cells (n=3)	150 X10⁶ CAR+ T cells (n=5)	450 X10⁶ CAR+ T cells (n=5)	Total (N=16)
Minimal Response or better, n (%)	2 (67)	3 (100)	3 (60)	5 (100)	13 (81)
Partial Response (%)				(100)	11 (69)
Very Good Partia or better, n (%)				(80)	7 (44)
Complete Respo n (%)				(60)	4 (25)
BM MRD negativi				(50)	8 (50)

CAN WE ENGINEER AROUND BCMA-low RESIVIOR FOR RELAPSE WITH DUAL-TARGETING TO *PREVENT* ANTIGEN ESCAPE RELAPSE AND IMPROVE DURABILITY OF REMISSIONS?

Response	Prior BCMA therapy (n=10)	Prior CAR T therapy (n=8)
Partial Response or better, n (%)	8 (80)	6 (75)
Complete Response or better	3 (30)	3 (38)

*MRD negativity to >10^{-5}

Mailankoday S et al. ASH 2021



Dana-Farber Cancer Institute

Simon S and Riddell S. *Blood Can Discov* 2020

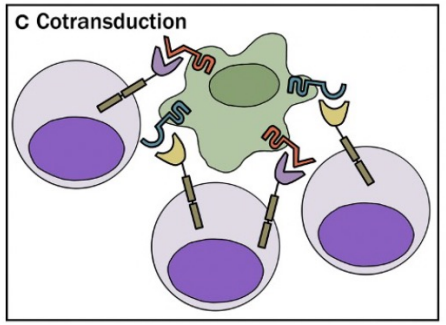
PLAT-05: Phase 1 Trial of Dual Specificity of CD19 and CD22 CAR T cell products in Rel/Ref Pediatric and Young Adult B-ALL

Study Objectives

- Determine feasibility of manufacturing SCRI-CAR19x22 in patients with Rel/Ref B-ALL
- Determine safety of SCRI-CAR19x22 cell product infusion
- Determine toxicity profile in Rel/Ref pediatric and young adult CD19+ B-ALL

Eligibility Criteria

- Age: < 27 years
- Relapsed or refractory CD19+ CD22+ acute leukemia
- No active GVHD
- Absolute lymphocyte count of ≥ 100/µl

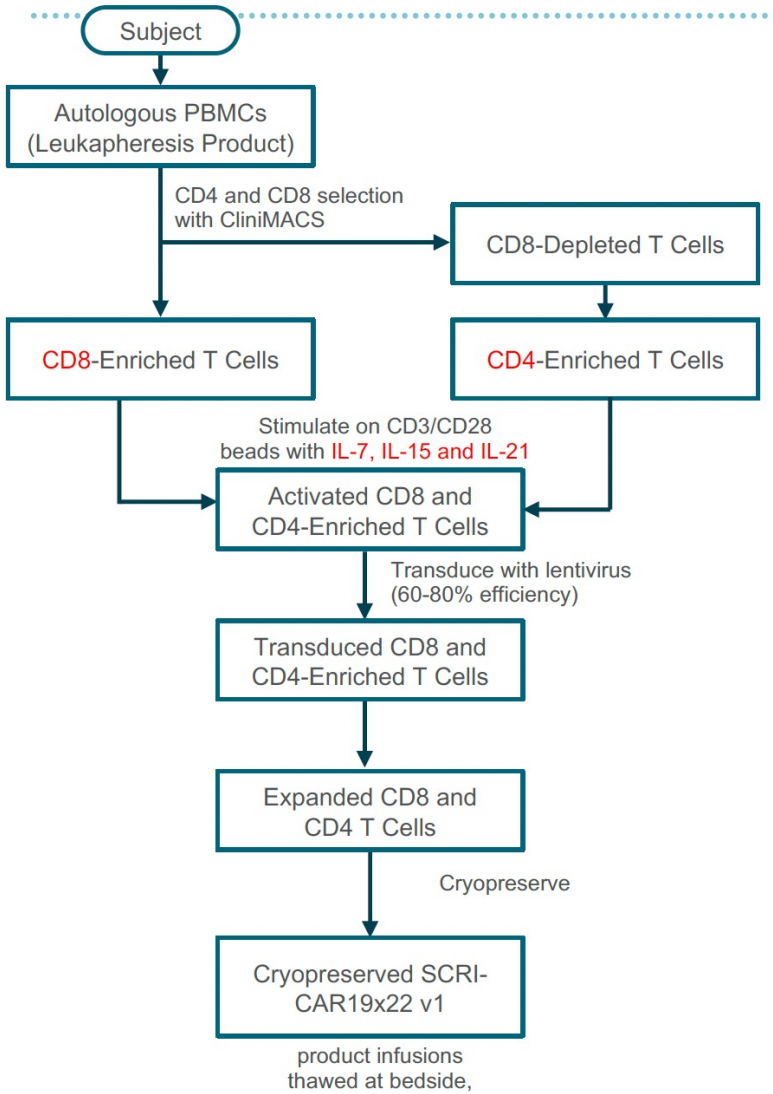


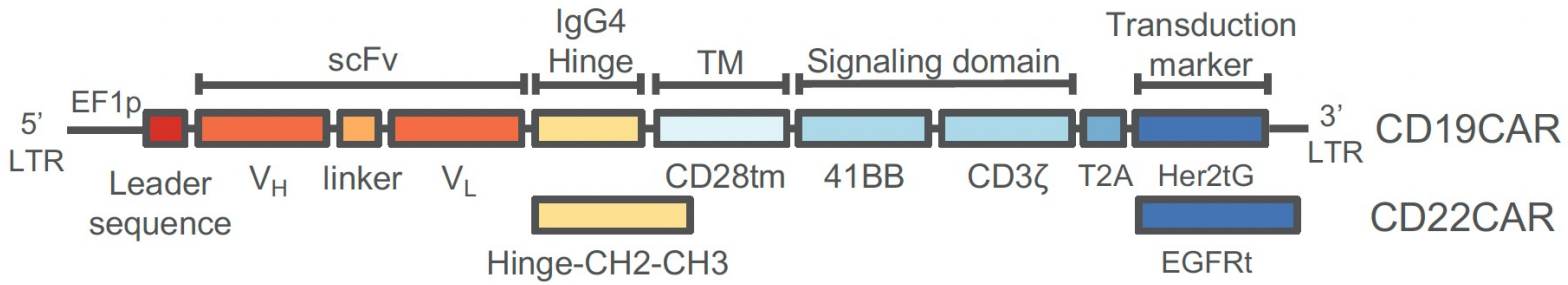
Seattle Children's HOSPITAL • RESEARCH • FOUNDATION

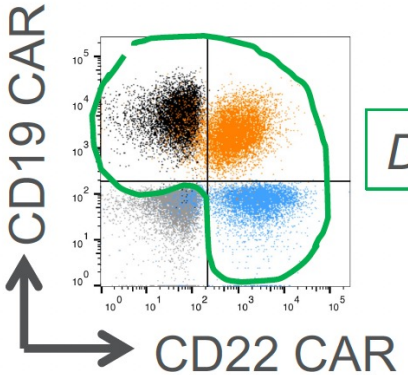
Annesley C et al. ASH 2021

ClinicalTrials.gov Identifier: NCT03330691

SCRI-CAR19x22v1







Dosing is based off the three CAR+ populations in total

1 subject died prior to CAR T cells

27 subjects infused

1 X 10^6 CAR T cells/kg [N=4]

3 X 10^6 CAR T cells/kg [N=23]

Toxicity: No Dose Limiting Toxicities Observed

RP2D established at 3 x 10^6 CAR+ T cells/kg

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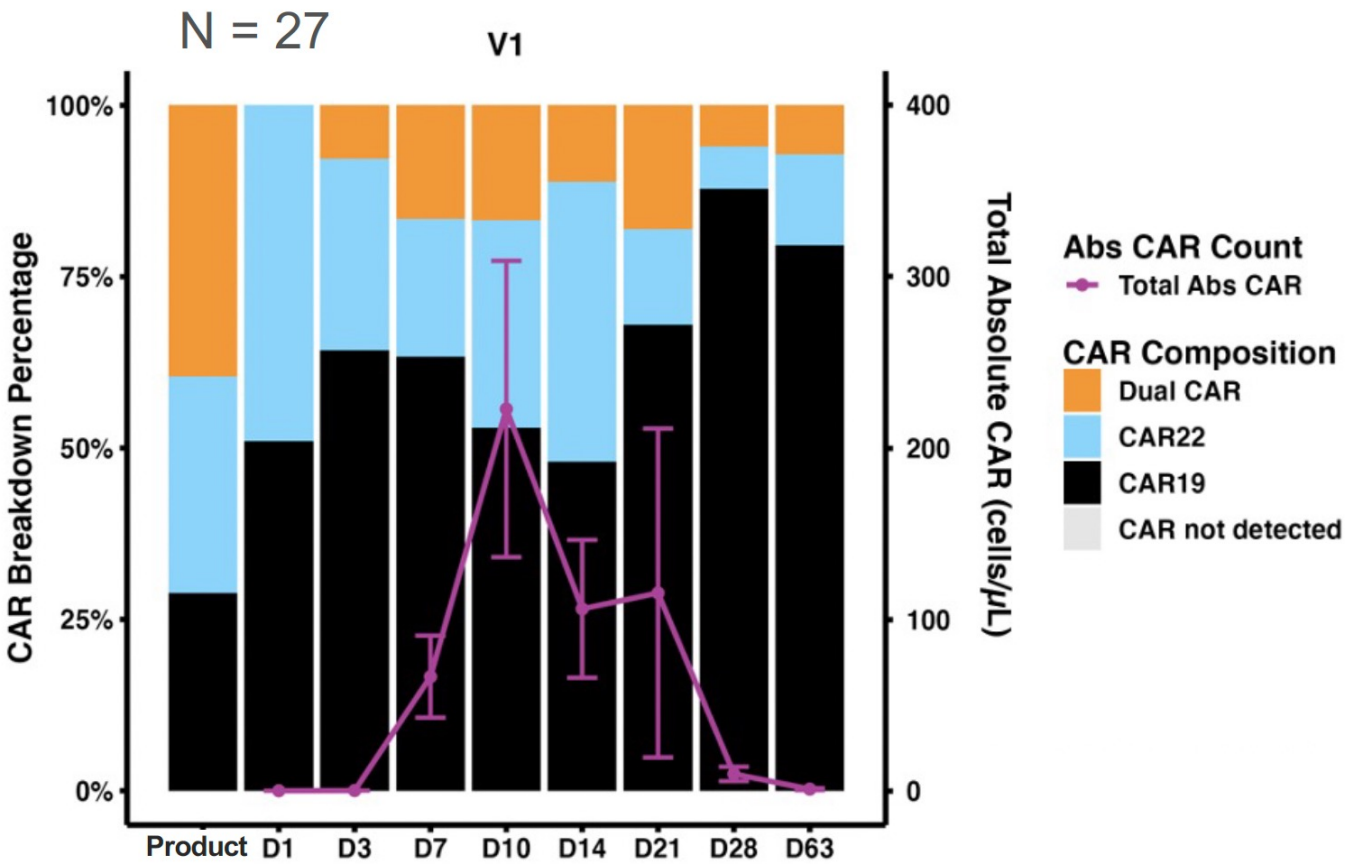
Annesley C et al. ASH 2021

SCRI-CAR19x22v1 on PLAT-05: 85% MRD-neg CR

- Product split nicely between three CAR+ populations
- Engraftment predominated by the CD19 CAR
  - Especially at later timepoints
- Inferior CD22 activity:
  - 2/4 non-responders were related to CD19 negative/CD22+ disease
  - 5/7 relapses were CD19 negative
    - Only 2 had concurrent CD22 dim/negative findings



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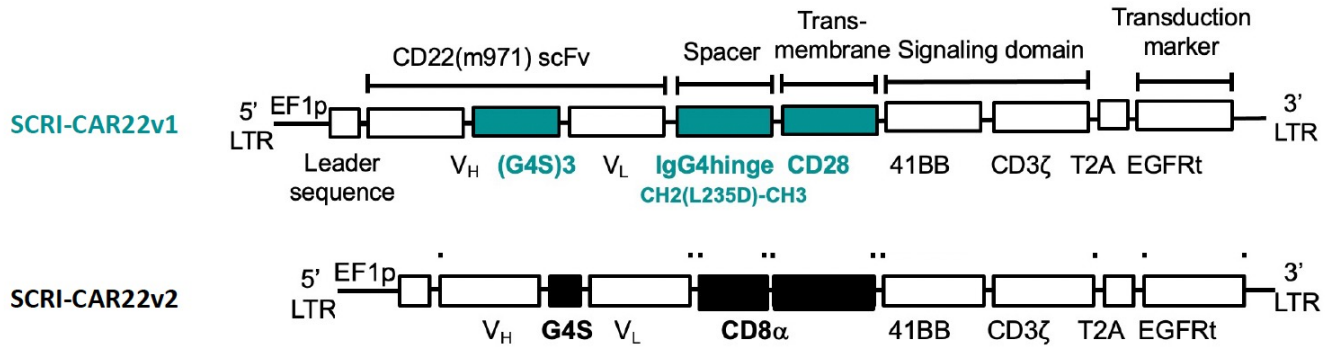
Annesley C et al. ASH 2021

SCRI-CAR19x22v2: A re-engineered CD22 CAR construct

- Although SCRI-CAR19x22v1 is safe and tolerable with strong initial efficacy, the CD22 CAR lacked activity
  - Re-engineered the CD22 CAR (C Summers et al, ASH 2021 abstract #403) to create SCRI-CAR19x22v2



  - Modified the PLAT-05 protocol to investigate SCRI-CAR19x22v2 with dose finding and expansion cohort

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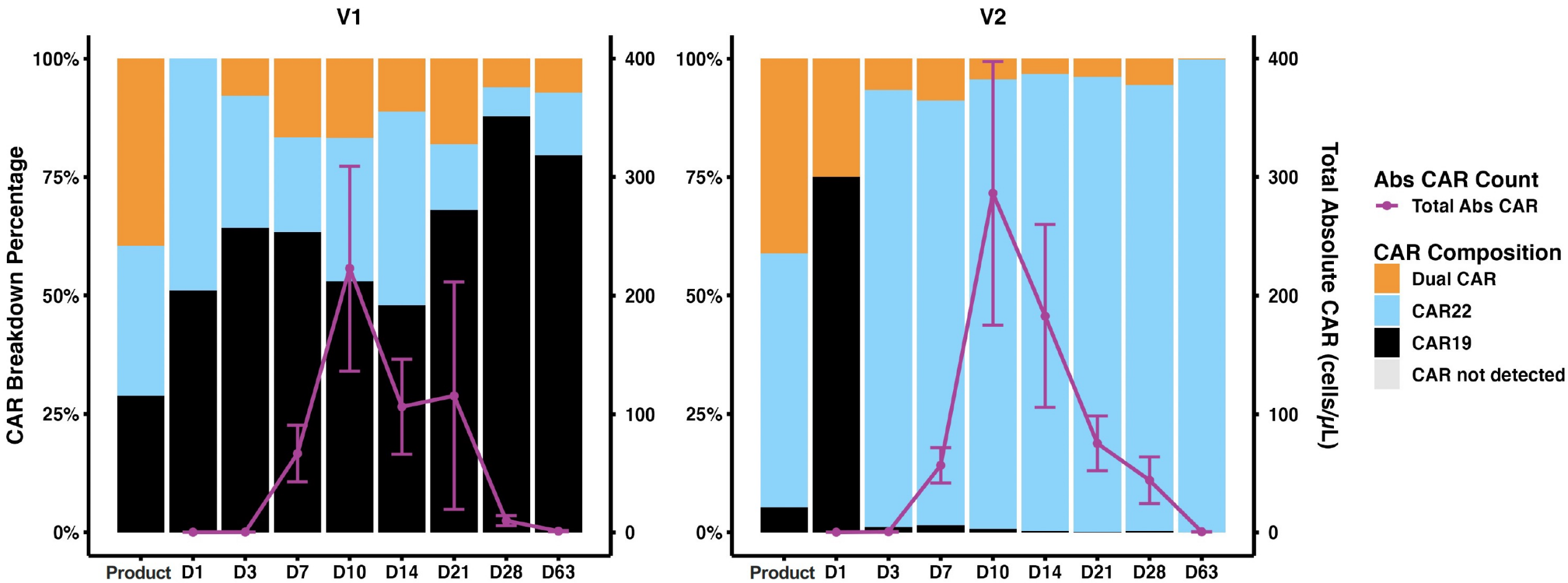
Annesley C et al. ASH 2021

SCRI-CAR19x22v2 engraftment favors CD22 CAR



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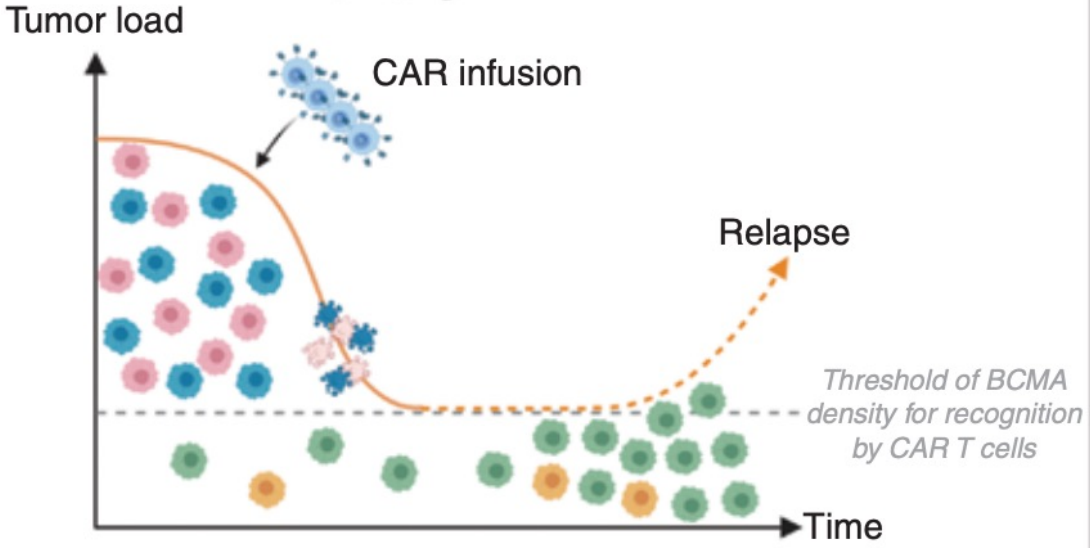
Mono-specific BCMA CAR T cells

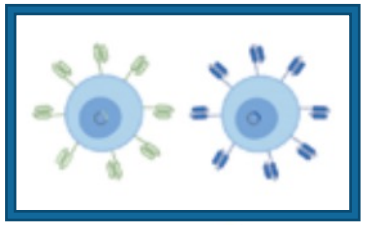
MM patient

BCMA-specific CAR T cells



Dual BCMA/GPRC5D CAR T cells

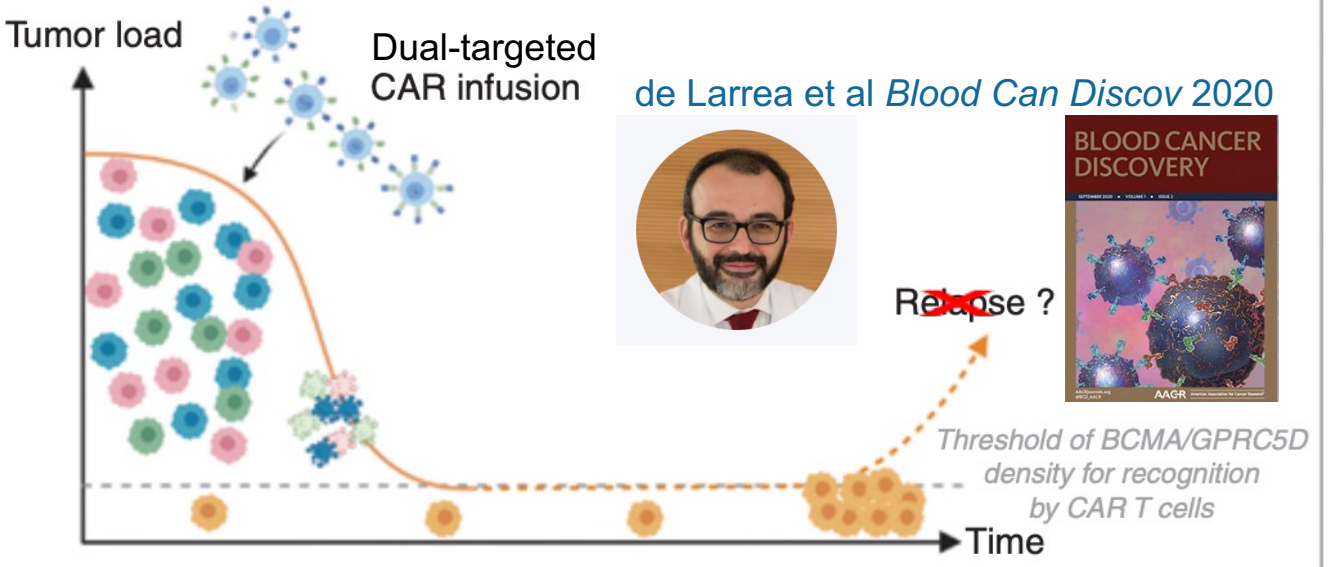
CARpool
Coadministration of two mono-specific CAR T-cell populations



2 virus
Coexpression of two vectors

Bicistronic
Expression of a single bicistronic vector

Single-stalk
Tandem CAR



de Larrea et al *Blood Can Discov* 2020

Tumor cells BCMA^{+} GPRC5D^{+}
Tumor cells BCMA$^{low/neg}$ GPRC5D^{+}
Tumor cells BCMA^{+} GPRC5D$^{low/neg}$
Tumor cells BCMA$^{low/neg}$ GPRC5D$^{low/neg}$

Tumor antigen expression

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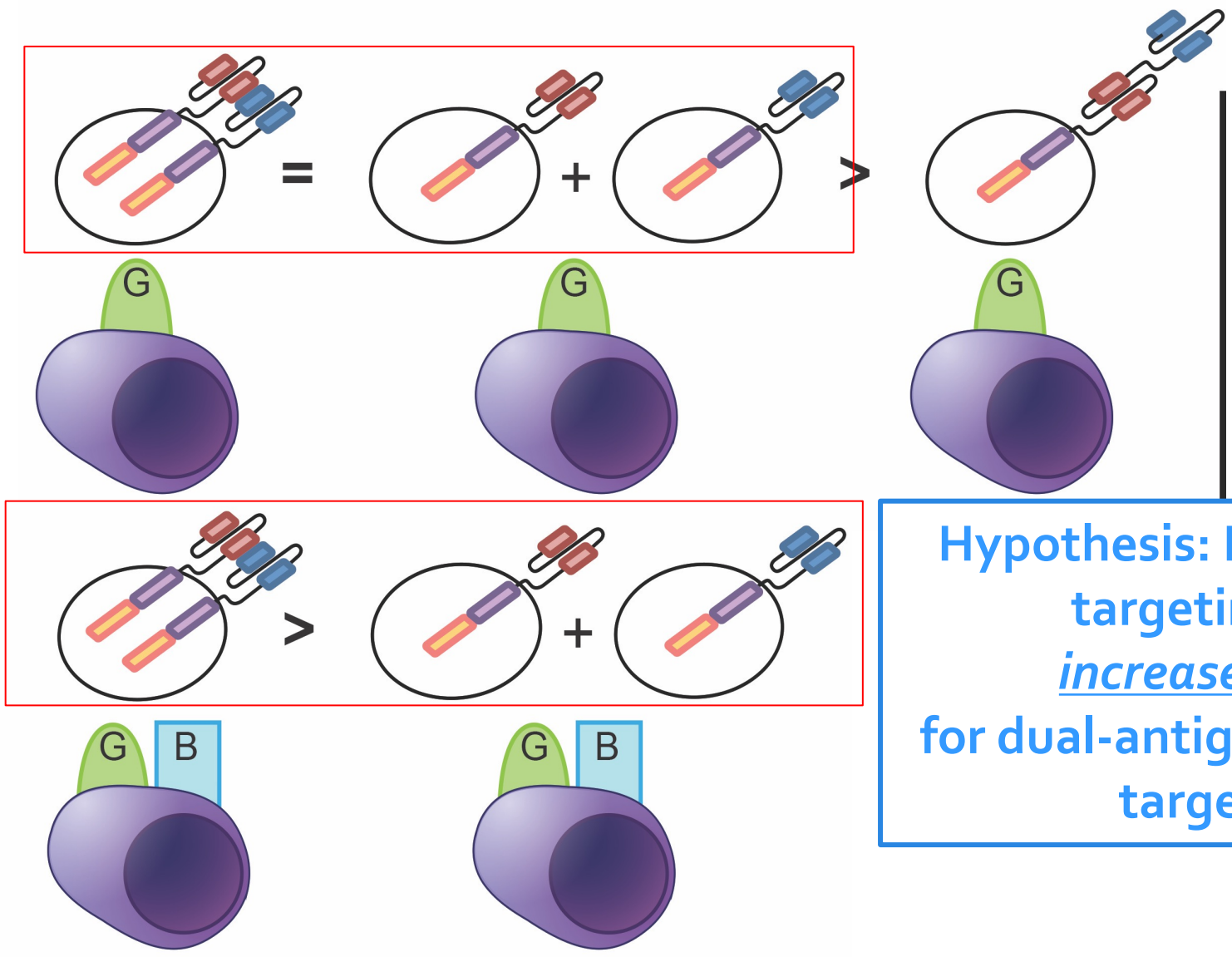
Simon S and Riddell S. *Blood Can Discov* 2020

Dual-targeting model

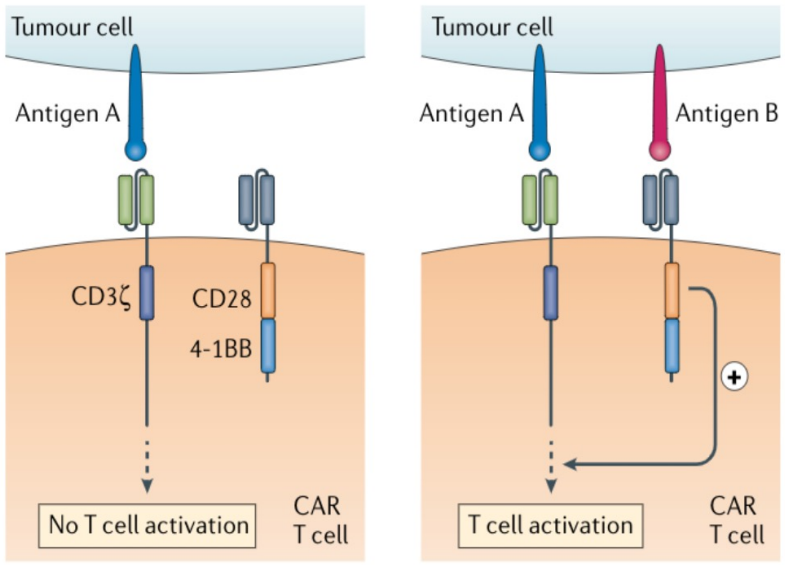


Hypothesis: Dual-Antigen targeting may *increase avidity* for dual-antigen expressing target cell

de Larrea et al *Blood Can Discov* 2020

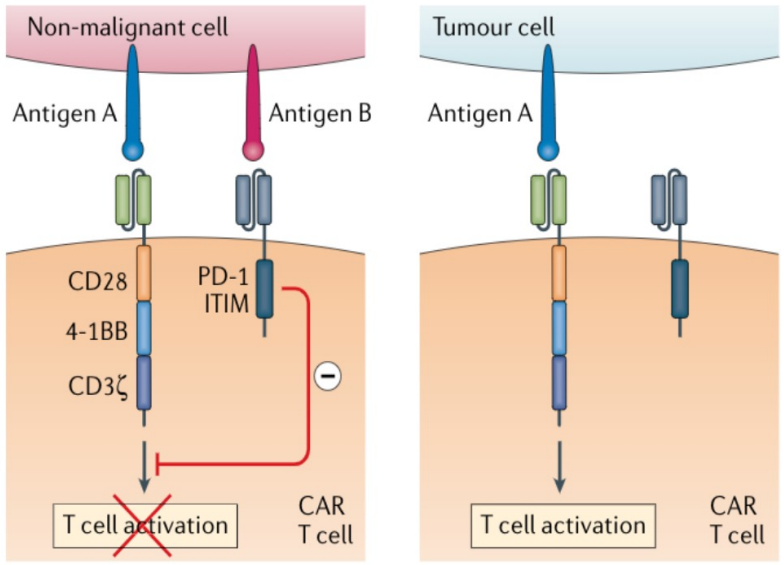
Logic Gated/Conditional CARs to increase specificity

AND



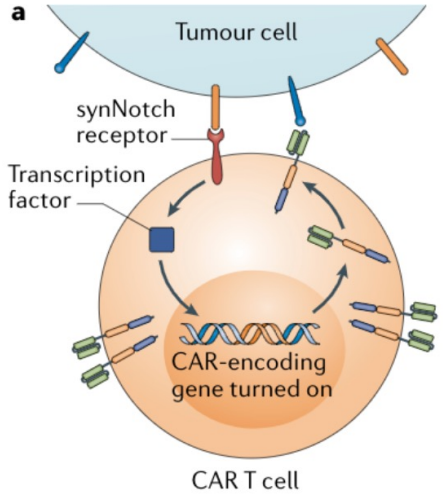
Split CARs: one receptor with a CD3ζ activation domain and a second with a co-stimulatory domain, requiring binding to multiple TAAs for CAR T cell activation

NOT

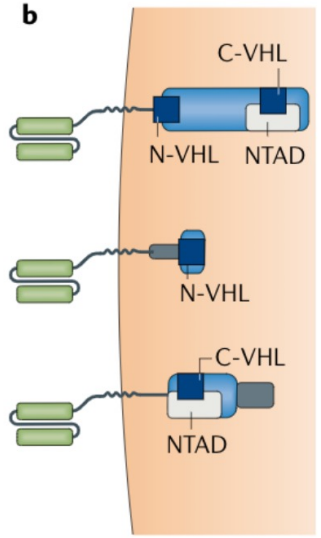


iCARs: inclusion of inhibitory CAR against a specific non-tumour antigen, requiring the absence of this antigen on tumour cells for CAR T cell activation

IF->THEN



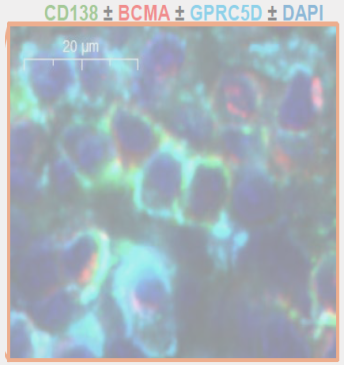
SynNotch CARs: in which a receptor for one TAA drives expression of a second receptor for a different TAA, requiring binding to multiple TAAs for CAR T cell activation



HIF-CARs designed to be expressed selectively in the hypoxic TME

Rafiq S, Hackett C, Brentjens R. *Nature Rev Clin Onc*. 2020

- New targets and logic gating



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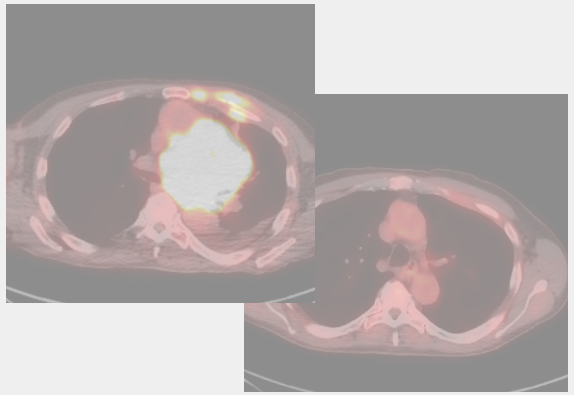

>>

GPRC5D as target for MM
Mette Staehr

GPRC5D CAR T clinical trial
Sham Mailankody

Dual-targeting
Carlos Fernandez de Larrea

- Next-gen CARs
- Intracellular targets • non-T cell types
- mRNA as a target and a therapeutic
- Advances in manufacturing

CARPOOL: A library-based platform to rapidly identify next generation chimeric antigen receptors

Taeyoon Kyung, Khloe S. Gordon, Caleb R. Perez, Patrick V. Holec, Azucena Ramos, Angela Q. Zhang, Yunpeng Liu, Catherine Koch, Alina Starchenko, Brian Joughin, Douglas A. Lauffenburger, Darrell J. Irvine, Michael T. Hemann, Michael E. Birnbaum

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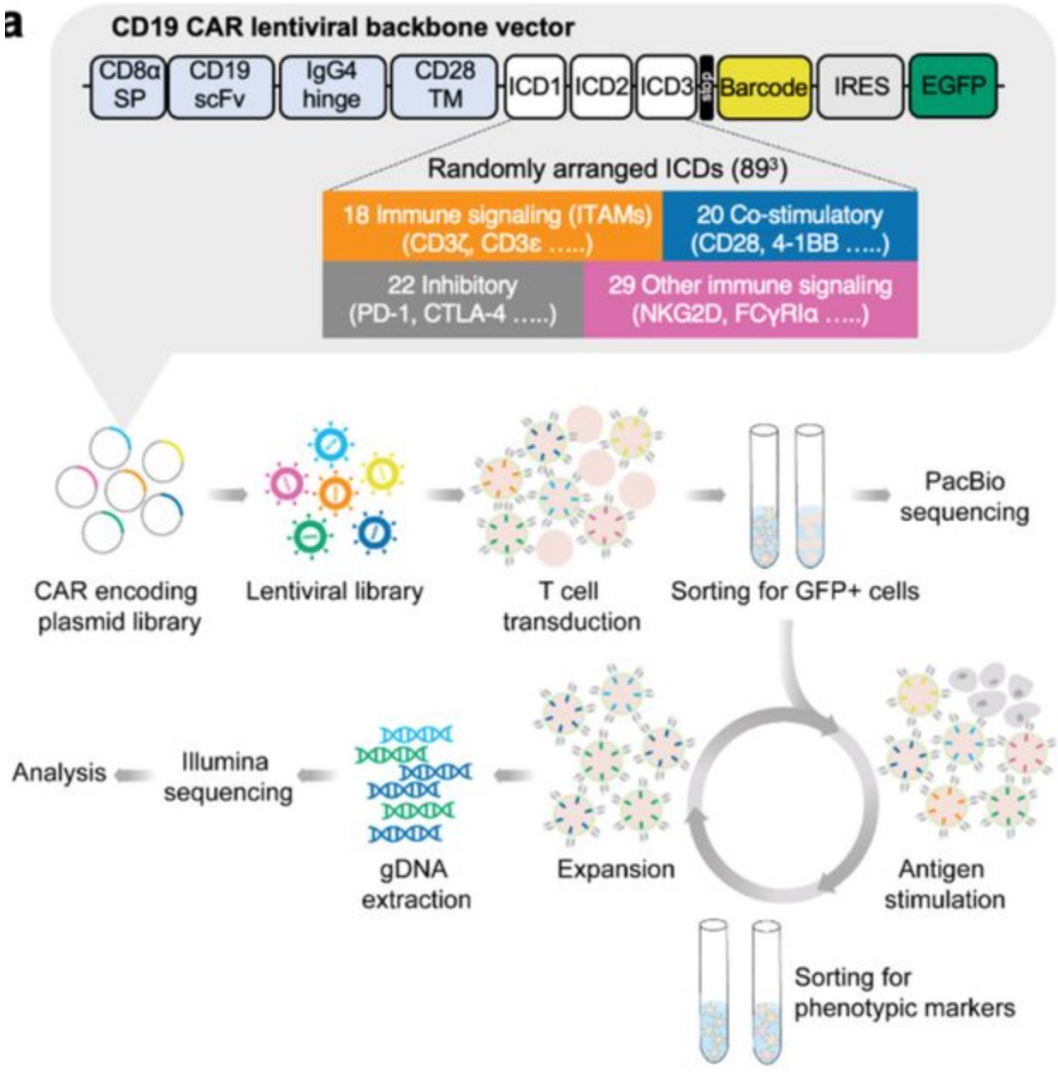

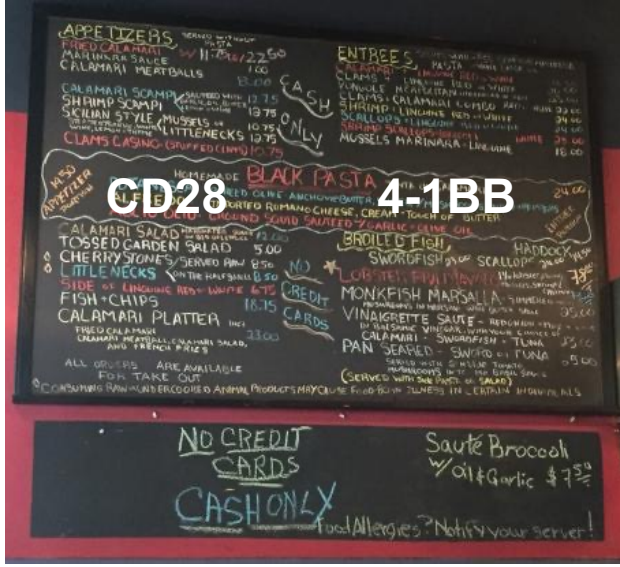

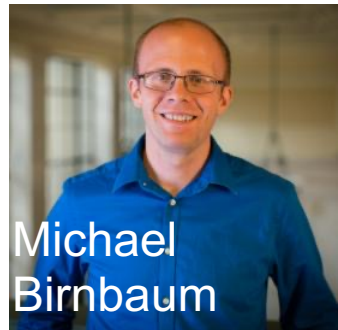

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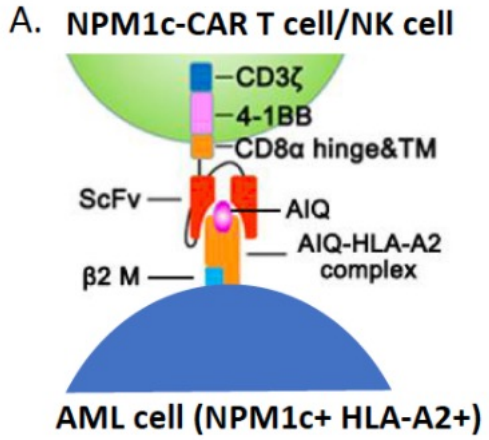
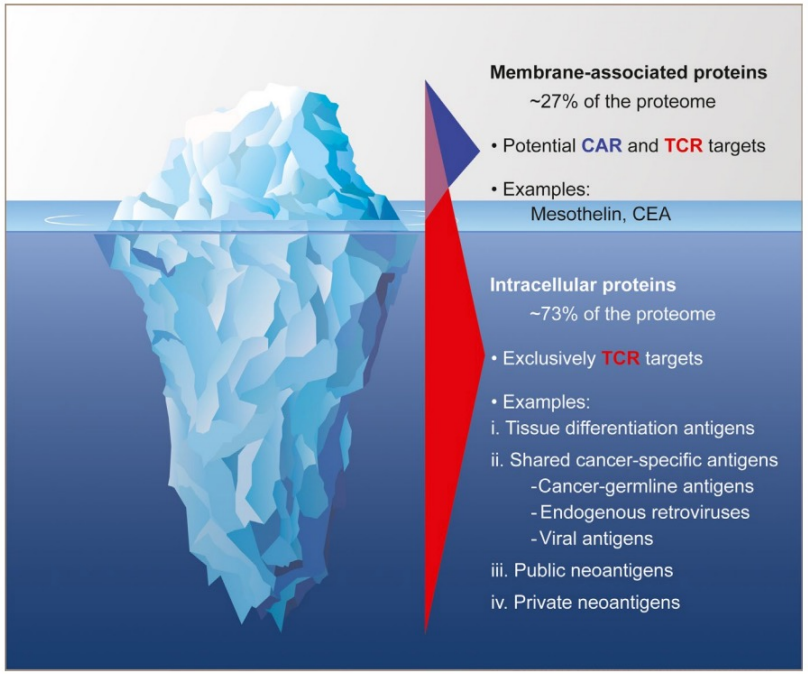
Intracellular targets CAR NK cells

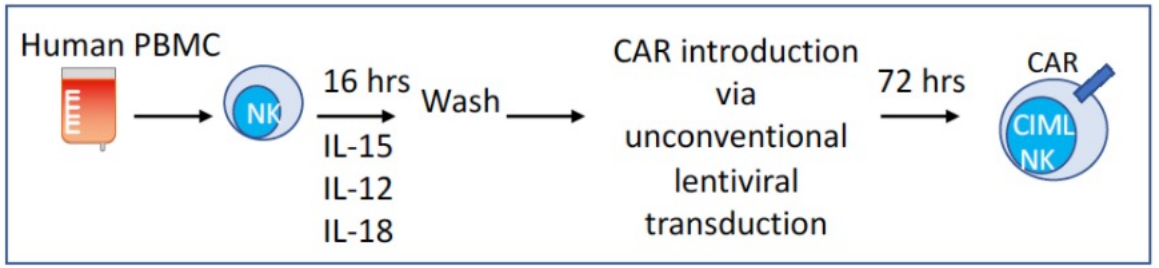
nature biomedical engineering
ARTICLES
https://doi.org/10.1038/s41551-020-00625-5
Check for updates

CAR-T cells targeting a nucleophosmin neoepitope exhibit potent specific activity in mouse models of acute myeloid leukaemia

Guozhu Xie[1,2], Nikola A. Ivica[1,2], Bin Jia[1,2], Yingzhong Li[1,2], Han Dong[3,4], Yong Liang[5], Douglas Brown[1,2], Rizwan Romee[5] and Jianzhu Chen[1,2] ✉

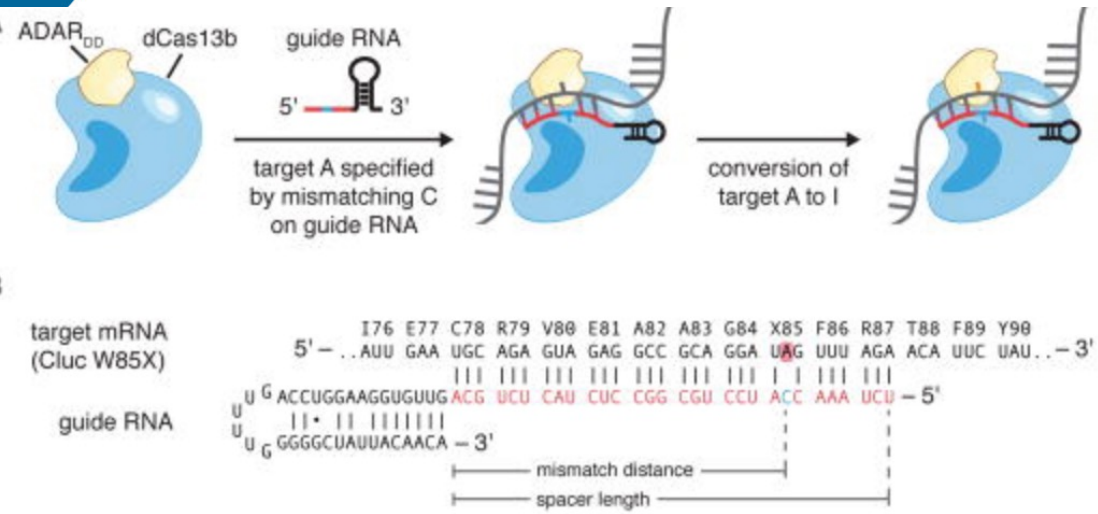






Dong H et al (Chen, Ritz, and Romee). *ASH*. 2020

Therapeutics to edit mRNA

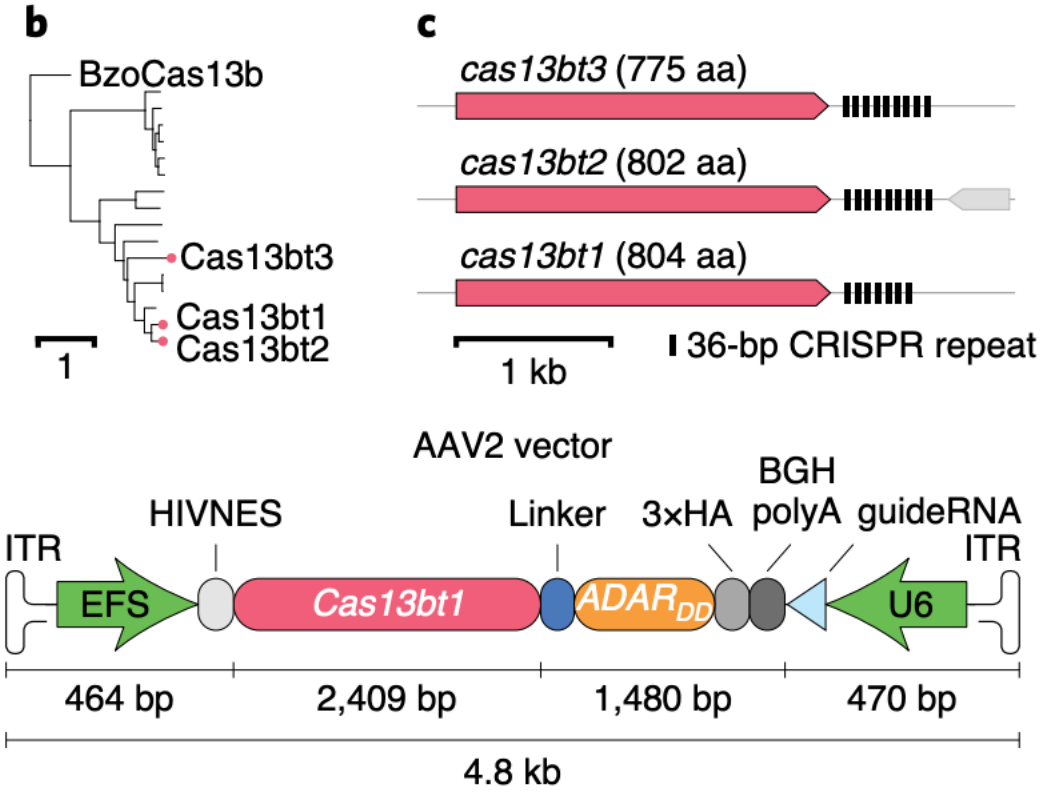


Science **358**, 1019–1027 (2017)

RNA editing with CRISPR-Cas13

David B. T. Cox,[1,2,3,4,5,6]* Jonathan S. Gootenberg,[1,2,3,4,7]* Omar O. Abudayyeh,[1,2,3,4,6]* Brian Franklin,[1,2,3,4] Max J. Kellner,[1,2,3,4] Julia Joung,[1,2,3,4] Feng Zhang[1,2,3,4]†

Dana-Farber

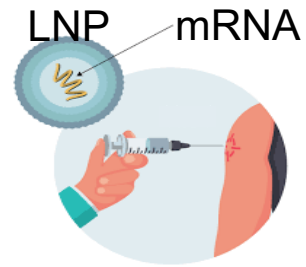


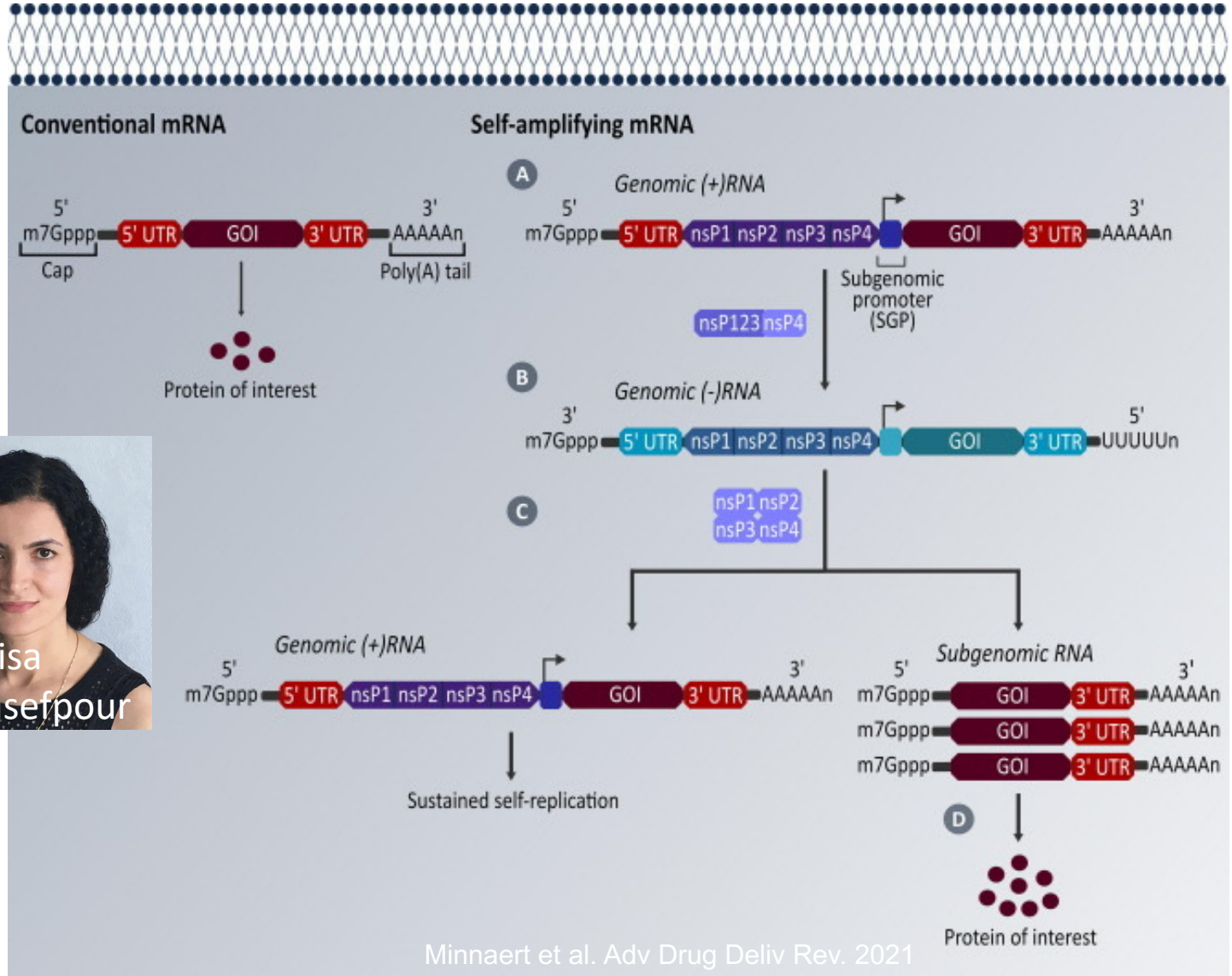
NATURE BIOTECHNOLOGY | VOL 40 | FEBRUARY 2022 | 194–197

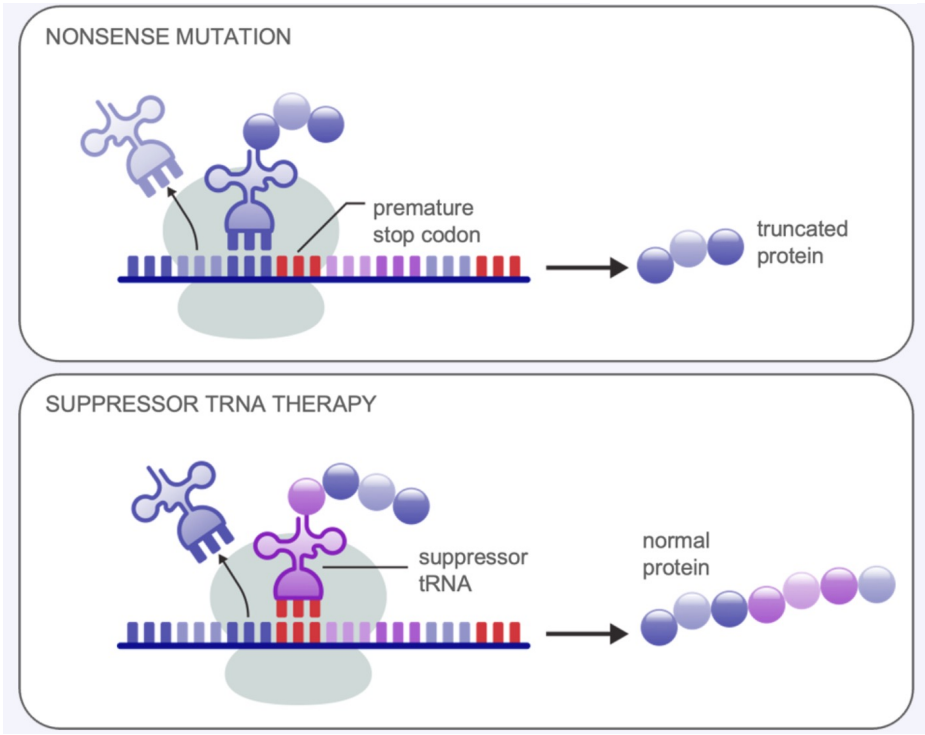
Compact RNA editors with small Cas13 proteins

Soumya Kannan[1,2,3,4,5,9], Han Altae-Tran[1,2,3,4,5,9], Xin Jin[1,2,3,4,5,6,7], Victoria J. Madigan[1,2,3,4,5], Rachel Oshiro[1,2,3,4,5], Kira S. Makarova[8], Eugene V. Koonin[8] and Feng Zhang[1,2,3,4,5]✉

Advances in mRNA therapies







Pioneering tRNA/mRNA-based gene therapy platforms

Gopi Shanker

Chief Scientific Officer, Tevard Biosciences

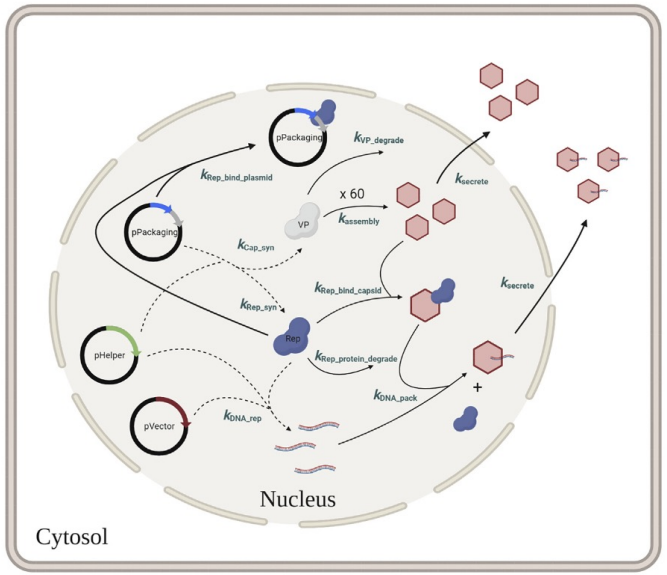
Minnaert et al. Adv Drug Deliv Rev. 2021

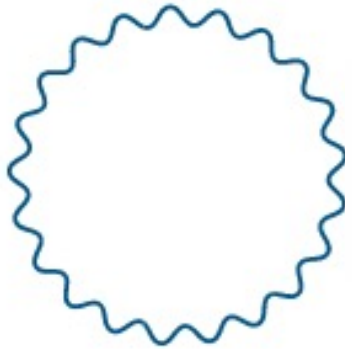
Next-gen cell therapy manufacturing

Rational Design of rAAV Production via Mechanistic Modeling

Richard Braatz
Gilliland Professor, Chemical Engineering
Faculty Research Officer

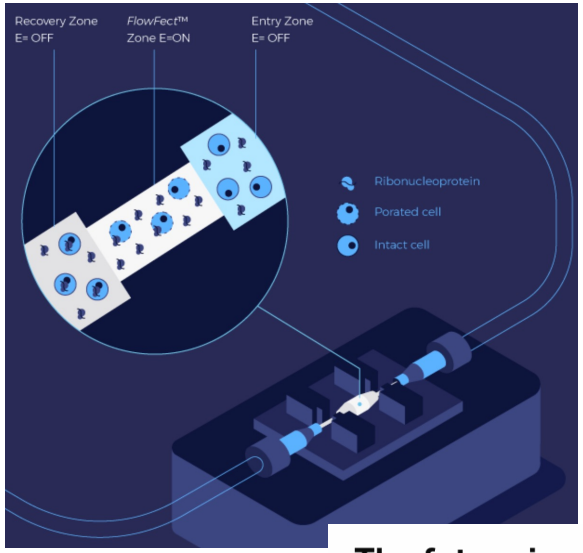
Tam Nguyen
Ph.D. student in chemical engineering at M





Single-stranded DNA vectors for gene insertions and replacement

Floris Engelhardt
CEO, Kano Therapeutics



Label-Free Biophysical Critical Quality Attributes (CQAs) for Cell Therapy Products

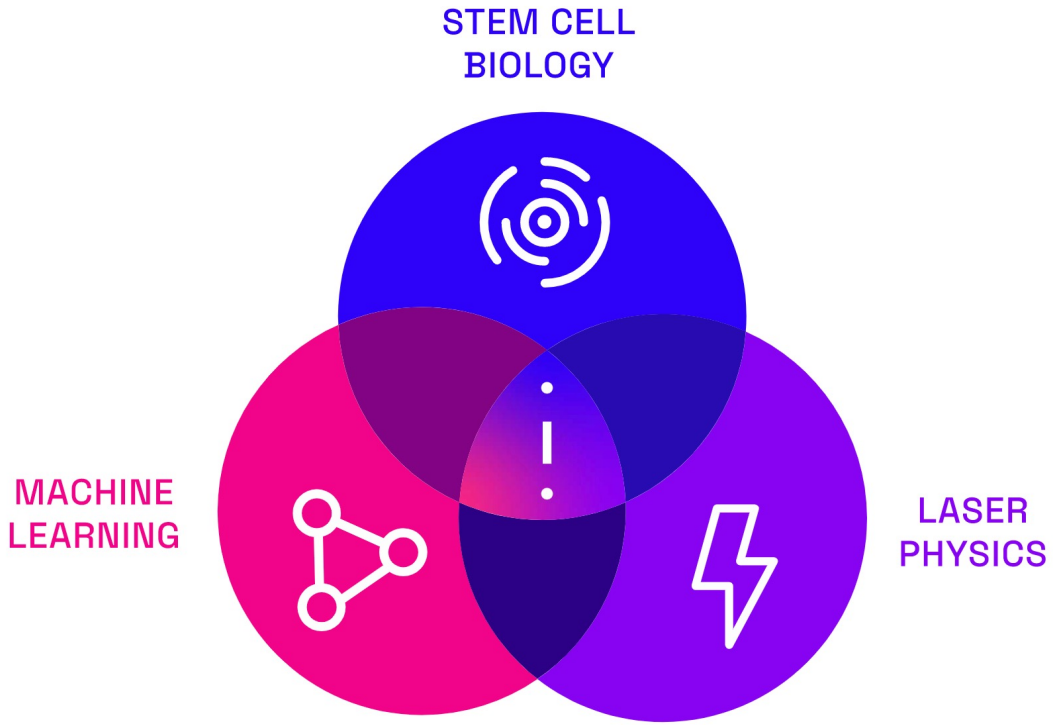
Jongyoon Han
Professor of Electrical Engineering and Professor of Biological Engineering

The future in cell therapy discovery and manufacturing

Paulo Garcia
CEO & Co-founder, Kytopen

Dana-Farber Cancer Institute

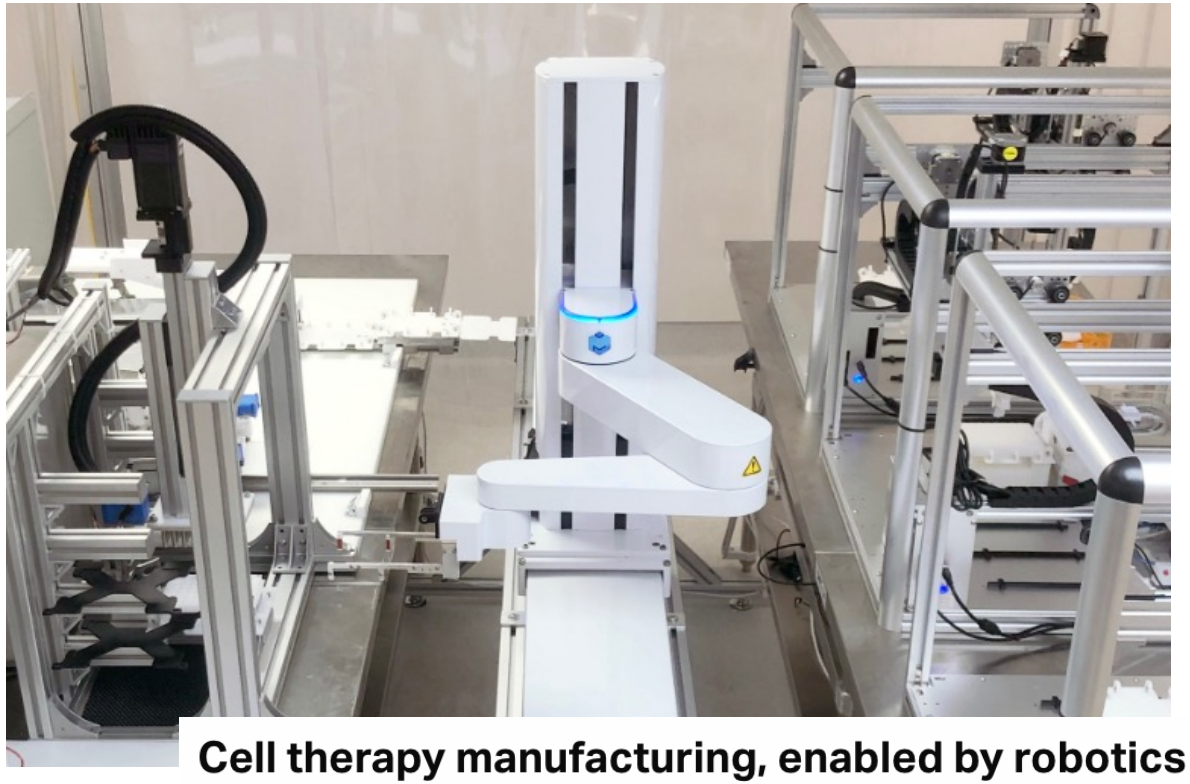
Next-gen manufacturing: automation to increase scale



Making personalized cell therapies scalable

Marinna Madrid

Co-founder, Cellino



Cell therapy manufacturing, enabled by robotics

Fred Parietti

Founder & CEO, Multiply Labs

New cell/gene/mRNA GMP capabilities:

Landmark Bio is building a multi-modality, state-of-the art innovation and development laboratory and GMP manufacturing facility in Watertown, MA to help turn today's cutting-edge research into tomorrow's breakthrough therapies.

Ran Zheng
CEO, LANDMARK BIO

The Massachusetts Center for Advanced Biological Innovation and Manufacturing has closed a $76 million funding round will open its headquarters and a biomanufacturing facility in Watertown's Arsenal on the Charles.

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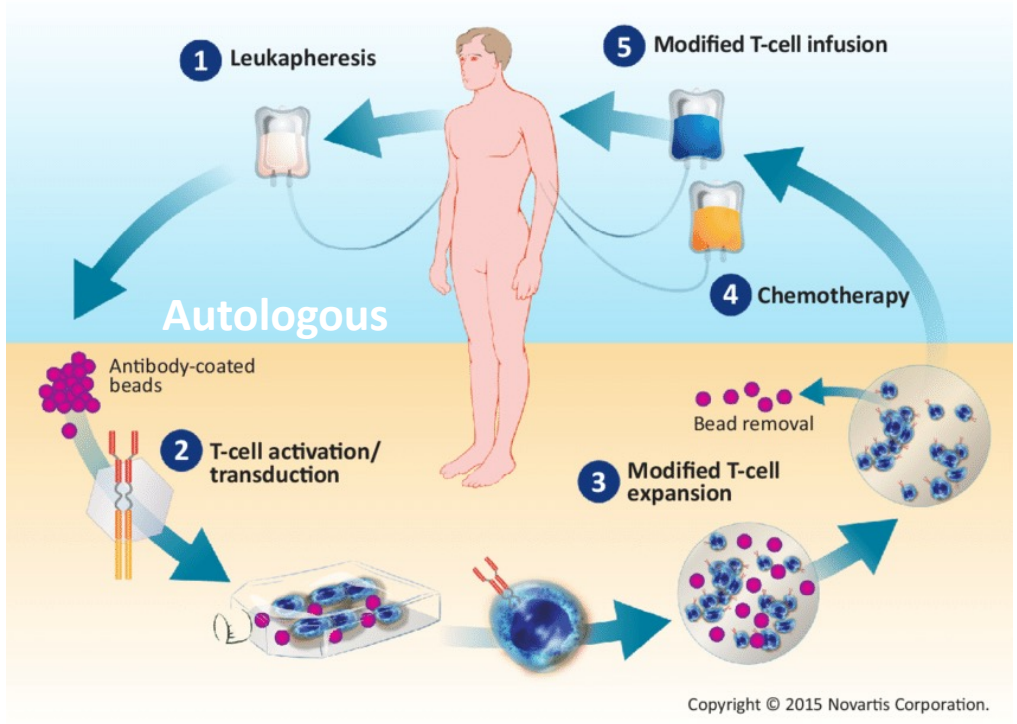
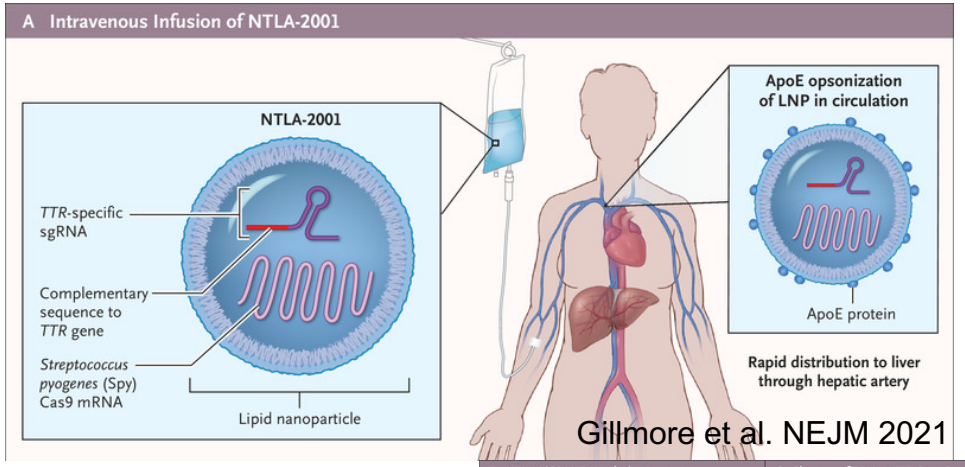
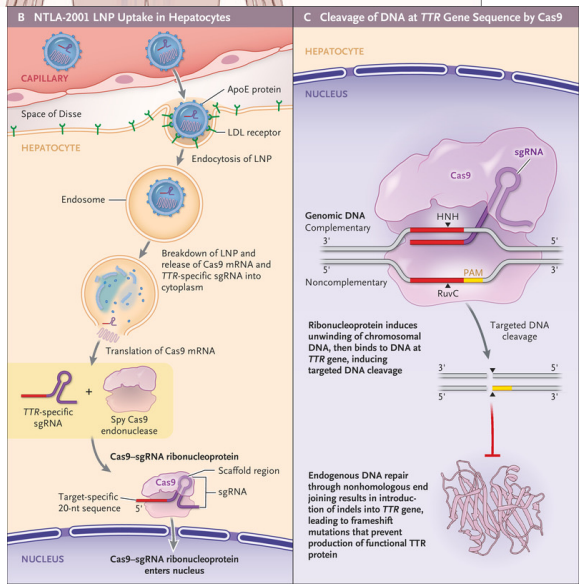
Manufacturing platforms – big picture



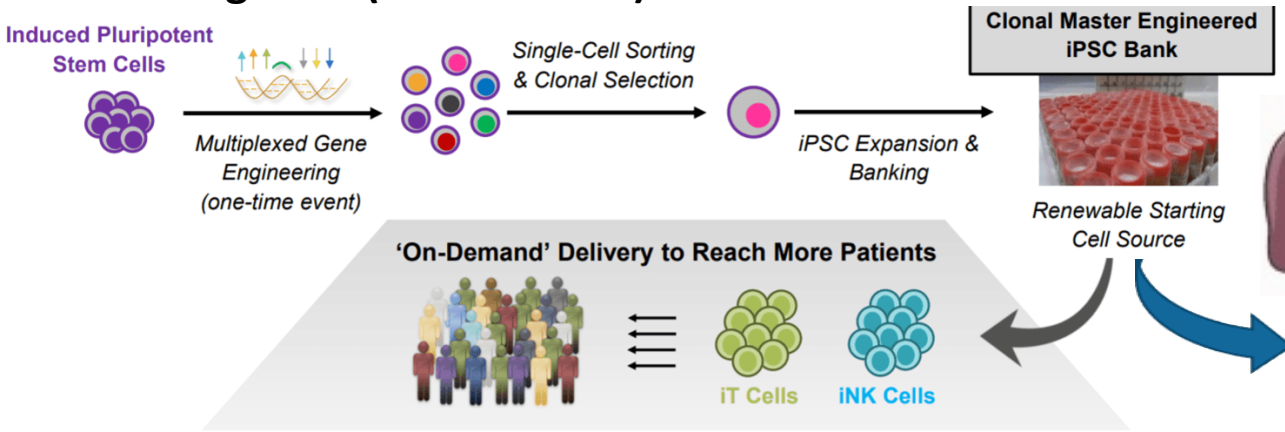
In situ

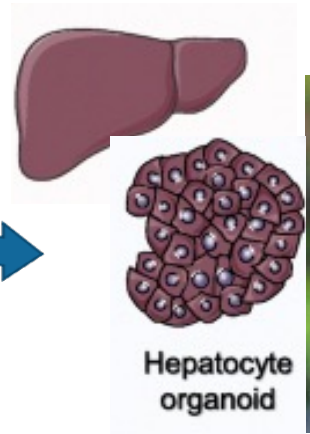


Gillmore et al. NEJM 2021



Allogeneic (Off-the-shelf)

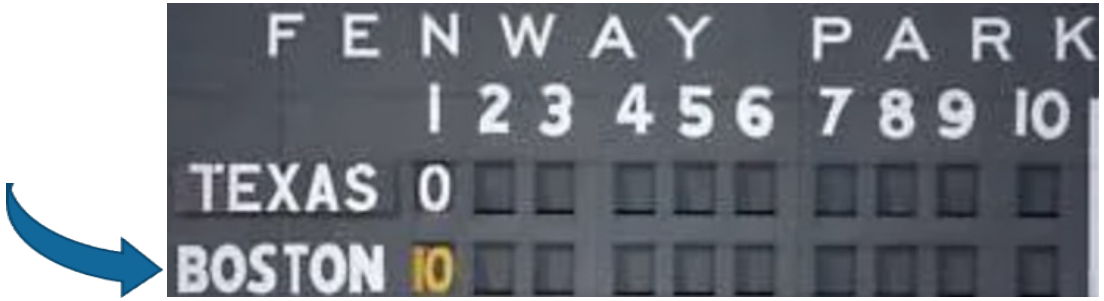




Clonal master iPSC lines are a renewable cell source that can be repeatedly used to mass produce homogeneous, cryopreserved cell product in a cost-effective manner

Summary

- Cellular and genetic based immunotherapies are rapidly translational with the potential for substantial efficacy even in the most heavily pre-treated patients (example: GPRC5D CAR T cells)
- Advances in design/bioengineering and manufacturing will drive improvements in patient outcomes
- Given the rapid advances in technology and practical advantages of cell/gene/mRNA clinical translation, these platforms are likely to supplant traditional biologics over the next several years



ACKNOWLEDGEMENTS

Smith Lab for Gene & Cell Engineering @ DFCI

Katherine Antel
Elliott Brea
Liz Carstens
Tim Haggerty
David Kennedy-Yoon
Cedric Louvet
Abhishek Mangipudi
Alexis Mottram
Erin Rosenberg
Melody Tan
Kartika Venugopal

Former MSKCC Trainees

Mette Staehr (GPRC5D)
Carlos Fernandez de Larrea (DUAL)
Urvi Shah
Yunxin Chen

DFCI/Harvard/MIT/BCH/Broad

Cathy Wu
Jerry Ritz
Bill Hahn
Kevin Hahn
Laurie Glimcher
Ken Anderson
Steve Carr (Broad)
David Mooney (Wyss)
Dan Anderson (MIT)
Omar Nadeem (Clinical PI)
Dave Barbie
Srini Viswanathan
Andy Aguirre
Steve Hodi
Ran Zheng (Landmark Bio)
Kai Wucherpfennig
Gordon Freeman
Xin Zhou

DFCI/Harvard/MIT/BCH/Broad

Rizwan Romee
Ming-Ru Wu
Irene Ghobiral
Nikhil Munshi
Caron Jacobson
Sarah Nikiforow
Myriam Armant
Dan Bauer
Christian Brendel
Susanne Baumeister
Roberto Chiarle
Leslie Kean

MSKCC

Renier Brentjens
Ola Landgren
Sham Mailankody (Clinical PI)
Michel Sadelain

DFCI Accelerator Wong Family

NIH NATIONAL CANCER INSTITUTE
MMRF MULTIPLE MYELOMA Research Foundation
Bristol Myers Squibb
SANOFI
sitc Society for Immunotherapy of Cancer
International Myeloma Society
LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
IOTN Immuno-Oncology Translational Network
AMERICAN SOCIETY OF HEMATOLOGY
Dana-Farber Cancer Institute
leap
DF/HCC Myeloma and GI SPOREs

Thank you

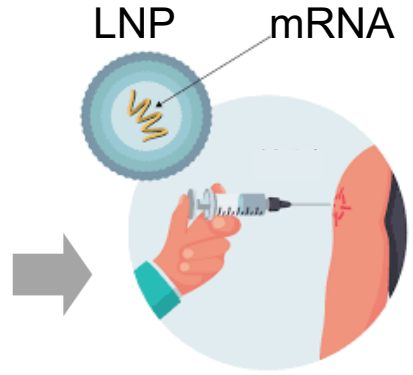
Eric Smith, MD PhD

Director of Translational Research,
Immune Effector Cell Therapies
Dana-Farber Cancer Institute
Email: EricL_Smith@dfci.harvard.edu

Smith Lab for Gene and Cell Engineering

SMITH
CELL THERAPY LAB

ericsmithlab.dana-farber.org/



Expanding Cell/Gene Immunotherapies @ DFCI

Lead Scientist - Immunotherapy Platform for Antibody and CAR Therapeutics discovery (IMPACT)

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Job ID: 23920
Location: 450 Brookline Ave, Boston, MA 02215
Category: Research Technician/Scientist
Employment Type: Full time

mAb engineering
High throughput screening

EricL_Smith@dfci.harvard.edu
ericsmithlab.dana-farber.org

Overview

Dana-Farber Cancer Institute is seeking an experienced PhD scientist to lead IMPACT, a new pre-clinical group with the mission to speed “discovery to translation” of antibody-based therapies for immunotherapy of cancer. The IMPACT team will work closely with DFCI PIs and outside antibody discovery groups to develop and carry out streamlined ‘hit-to-lead’ functional screening and protein engineering approaches for potential therapeutic antibodies/nanobodies/bispecifics and CAR T cell immunotherapies. The candidate should be an exceptionally motivated individual with substantial past lab and management experience in the area of antibody screening and/or protein engineering.