CAR T Cell Therapy for Cancer: What have we learned so far?

Terry J. Fry, M.D.

Outline

- Brief History of Immunotherapy
- Development of CAR Concept
- Clinical CART experience
- Future of CART therapy

Coley's Toxin: The beginnings of Immunotherapy

Figure 1. William B. Coley (1862-1936) from *Trans Am Surg Assoc* 54(1936):415. Courtesy of the Welch Library of the History of Medicine.

1891

CONTRIBUTION TO THE KNOWLEDGE OF SARCOMA.[1]

By WILLIAM B. COLEY, M.D.,

OF NEW YORK.

I. A Case of Periosteal Round-Celled Sarcoma of the Metacarpal Bone; Amputation of the Forearm; General Dissemination in Four Weeks; Death Six Weeks Later.

II. The General Course and Prognosis of Sarcoma, Based Upon an Analysis of Ninety Unpublished Cases.

III. The Treatment of Sarcoma by Inoculation With Erysipelas, With a Report of Three Recent (Original) Cases.

I. THE patient a young lady, æt. 18, had been in perfect health from earliest childhood. The family history was likewise good with the exception of a remote tubercular tendency, and the fact that an ancester, three generations before, had died of "cancer" of the lip, presumably epithelioma.

In the early part of July, 1890, she received a slight blow upon the back of the right hand. The hand became a little swollen and somewhat painful the first night. The next few days the pain became a trifle less and the swelling subsided, but did not entirely disappear. About a week later the swelling again began to increase very slowly, and the pain became more severe. She consulted a physician at the time of the injury, but there being no evidence of anything more than an ordinary bruise the usual local applications were applied.

August 12. The pain and swelling continuing, she again sought

[1]Read before the Surgical Section of the New York Academy of Medicine, April 27, 1891. (With a report of three cases treated since).

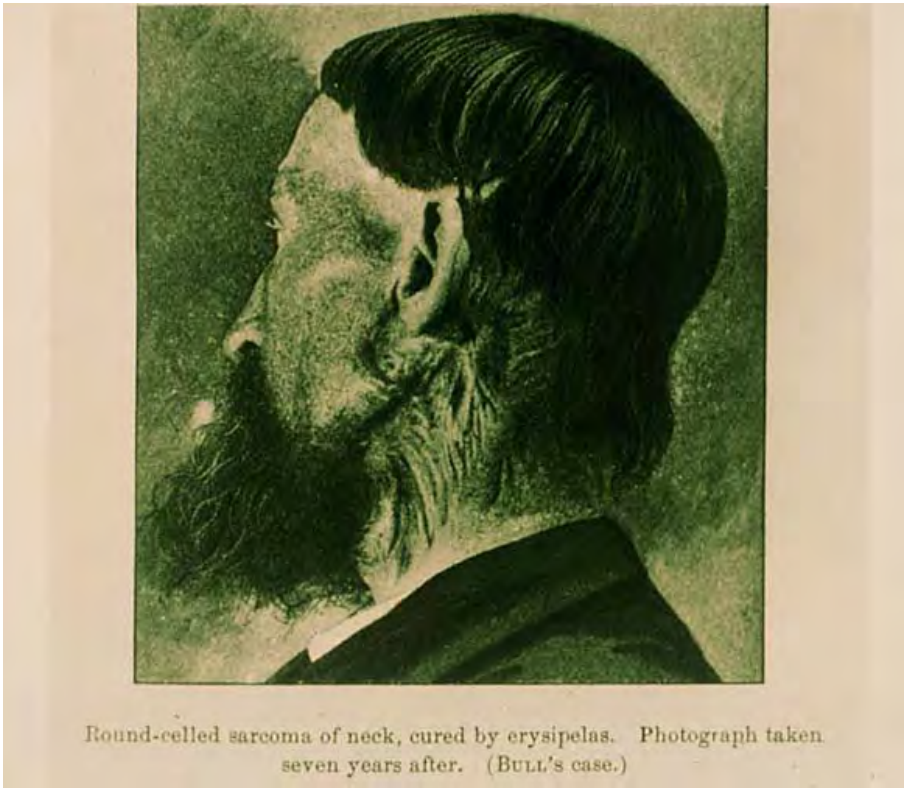
(993)

- William Coley, MD
- New York Cancer Hospital (later to become part of MSKCC)
- Bone Sarcoma Surgeon
- Took care of Elizabeth Dashiell, friend of JD Rockefeller, Jr, who died as a teen of aggressive bone cancer
- 19th century treatments based on theory that post-surgical infections improved chance for survival from cancer.
  - "Coley's Toxins"

Learning from Exceptional Responders

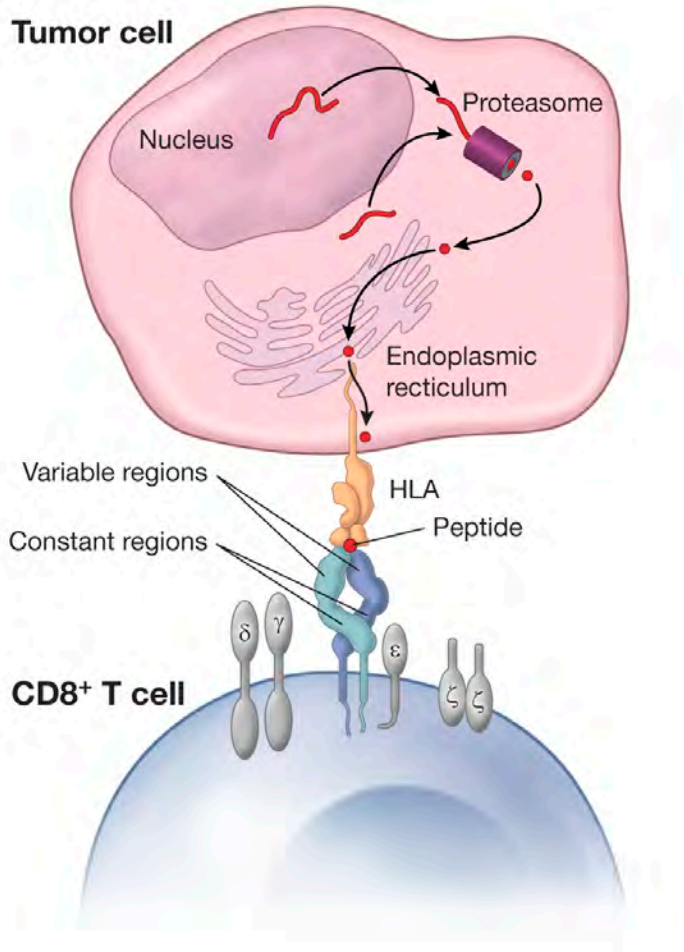
“Nature often gives us hints to her profoundest secrets…”

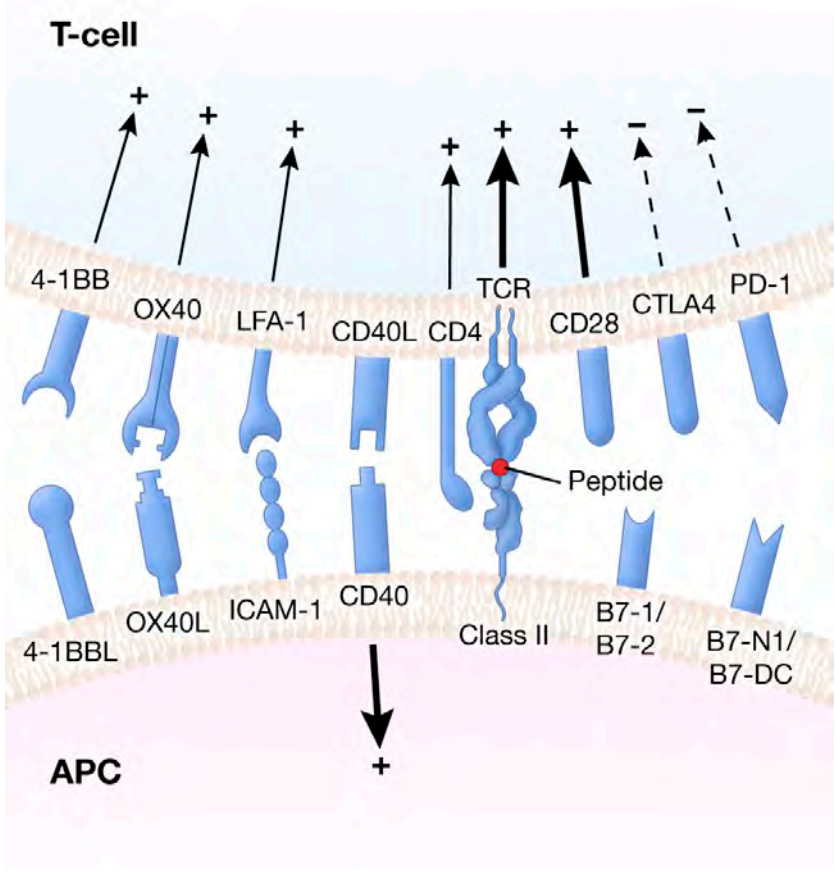
(W. Coley, 1882-1936)



Round-celled sarcoma of neck, cured by erysipelas. Photograph taken seven years after. (Bull's case.)

T cell Activation





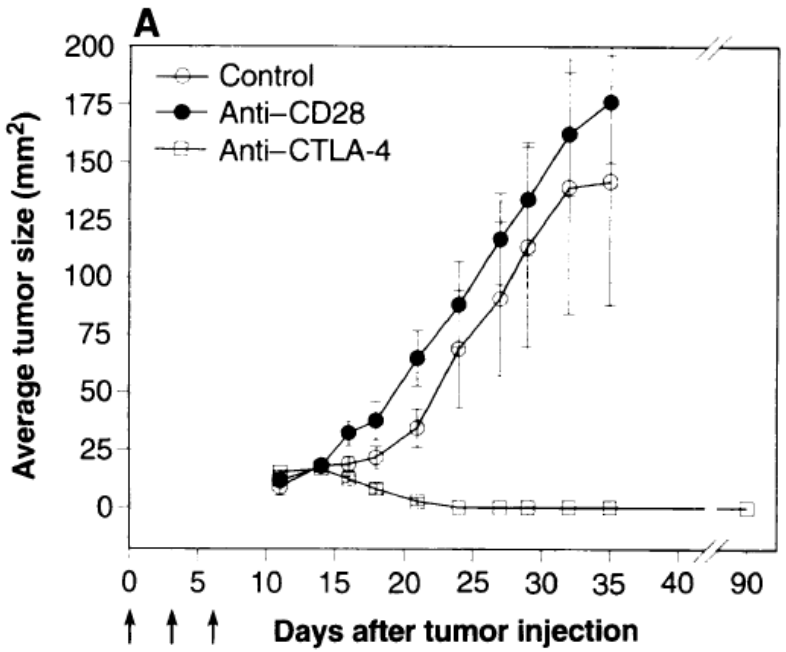
Adapted from Fry et al, in Principles and Practice of Pediatric Oncology, Seventh Edition, 2015.

Basic Science and Translation:
Report of Tumor Rejection following anti-CTLA4 Treatment

Enhancement of Antitumor Immunity by CTLA-4 Blockade

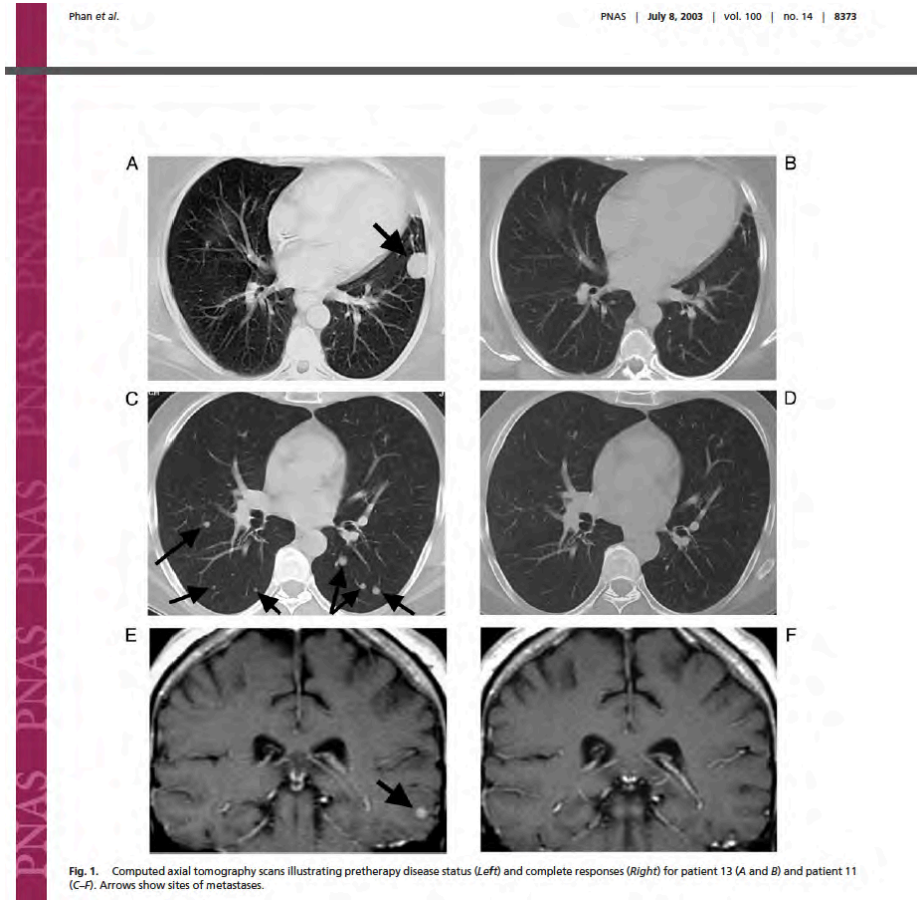
Dana R. Leach, Matthew F. Krummel, James P. Allison*

One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.



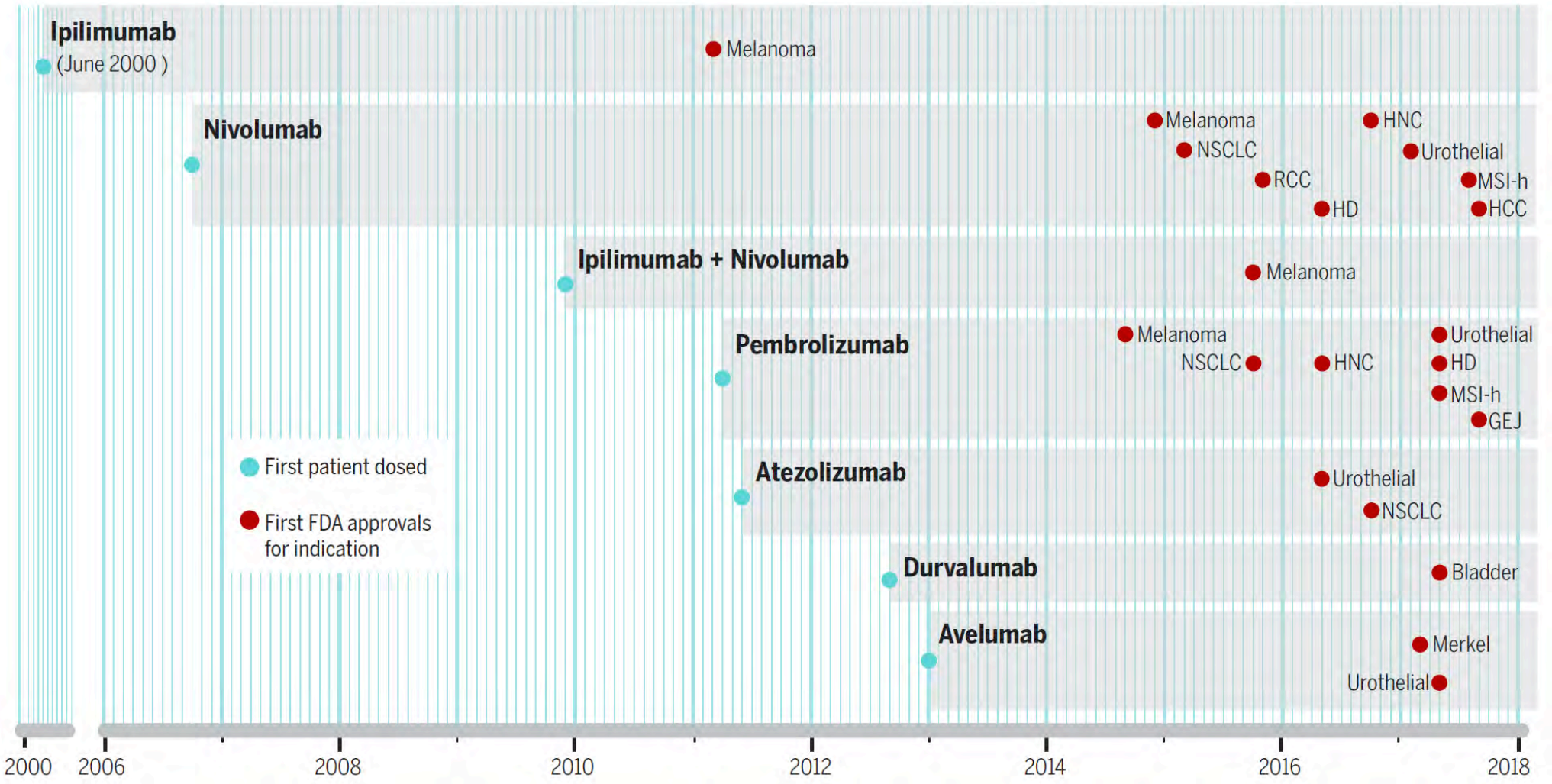
SCIENCE • VOL. 271 • 22 MARCH 1996

Clinical Response in Melanoma: NCI Surgery Branch anti-CTLA4 Trial



July, 2003

Complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.

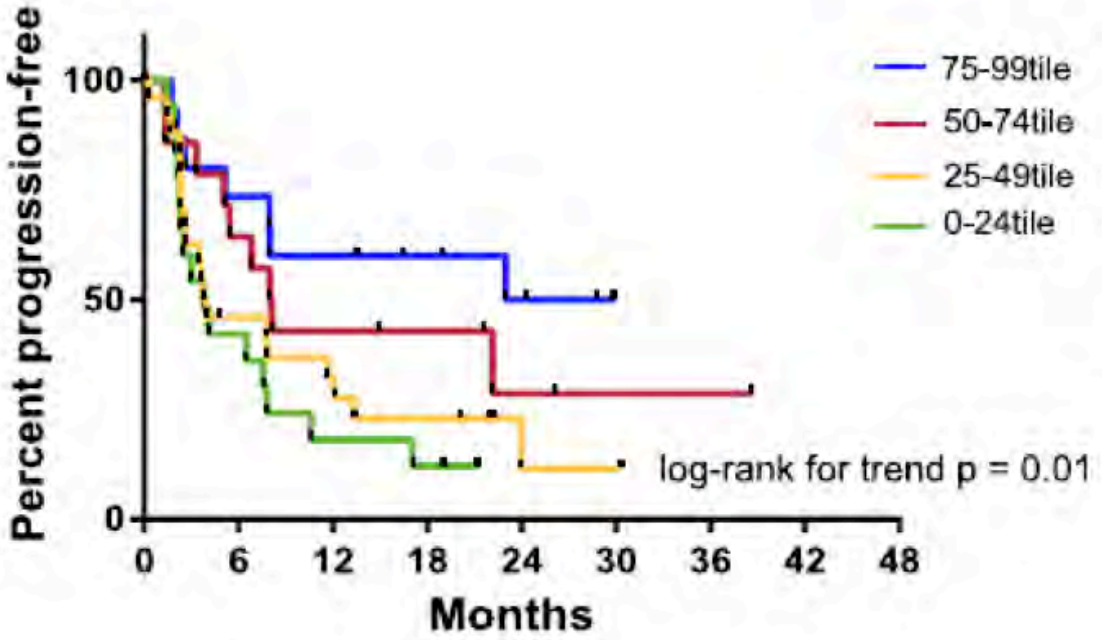


Ribas and Wolchock, Science 2018

Cancer Cell
Article

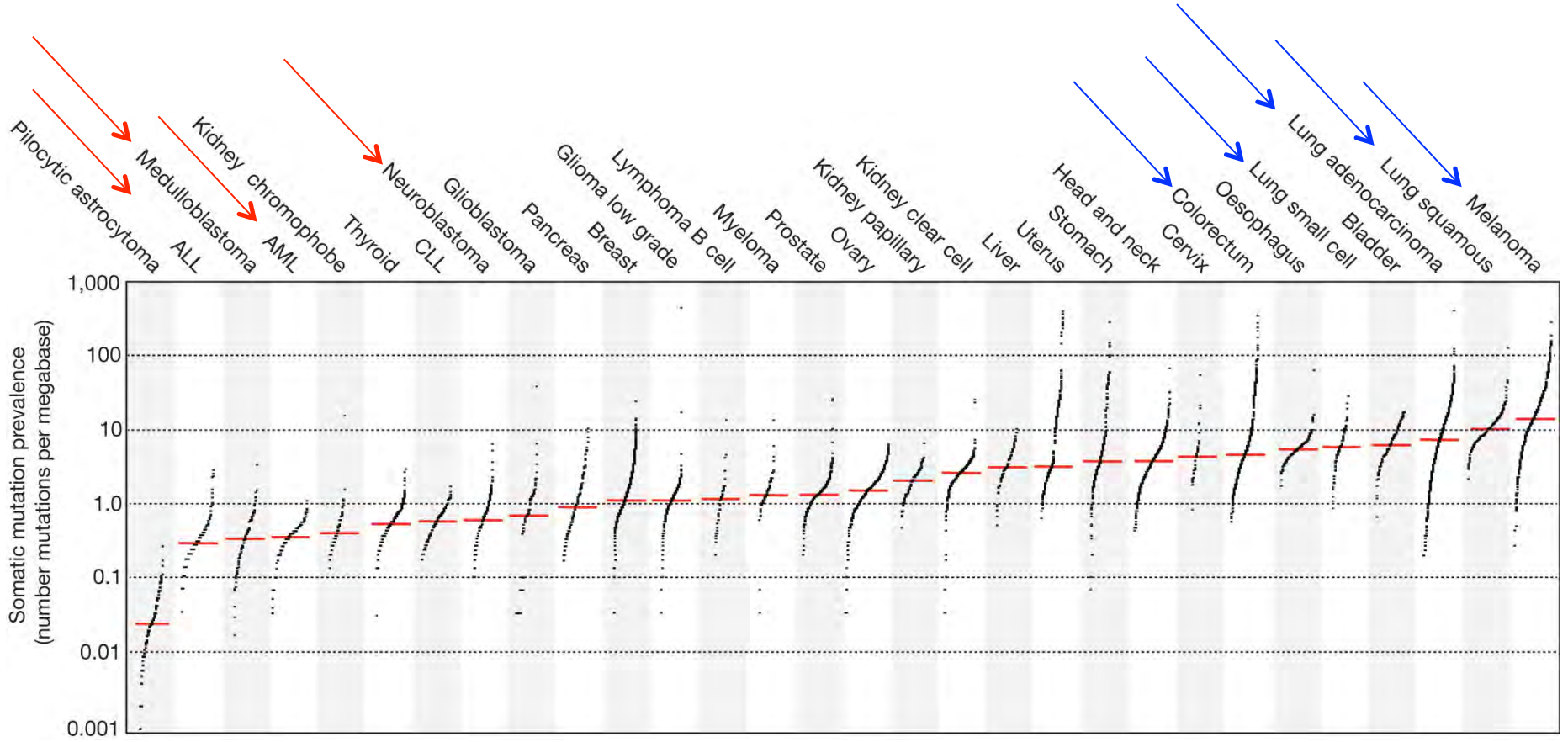
Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer

Matthew D. Hellmann,[1,2,3,4,17,*] Tavi Nathanson,[5] Hira Rizvi,[3] Benjamin C. Creelan,[6] Francisco Sanchez-Vega,[7,8] Arun Ahuja,[5] Ai Ni,[9] Jacki B. Novik,[5] Levi M.B. Mangarin,[10] Mohsen Abu-Akeel,[10] Cailian Liu,[10] Jennifer L. Sauter,[11] Natasha Rekhtman,[11] Eliza Chang,[5] Margaret K. Callahan,[1,2,4] Jamie E. Chaft,[1,2,3] Martin H. Voss,[1,2] Megan Tenet,[3] Xue-Mei Li,[12] Kelly Covello,[12] Andrea Renninger,[12] Patrik Vitazka,[12] William J. Geese,[12] Hossein Borghaei,[13] Charles M. Rudin,[1,2,3] Scott J. Antonia,[6] Charles Swanton,[14,15] Jeff Hammerbacher,[5,16] Taha Merghoub,[1,2,4,10] Nicholas McGranahan,[14] Alexandra Snyder,[1] and Jedd D. Wolchok[1,2,4,10]



2018

The prevalence of somatic mutations is low in many cancers



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

nature

Outline

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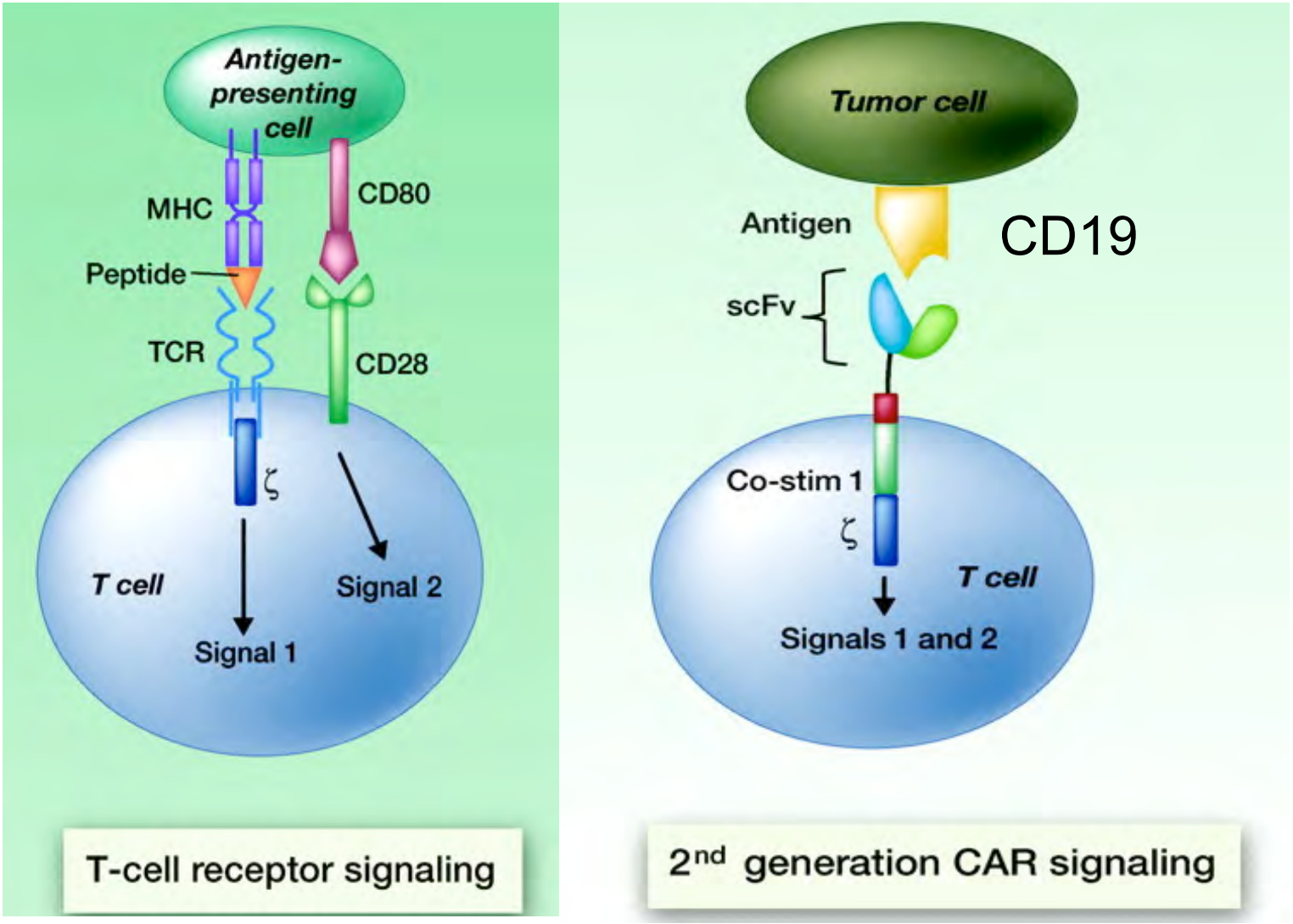
Redirecting Specificity for Adoptive Cell Therapies: Synthetic Immunology



Advantages of CAR

- Specific for a surface antigen
- Free of MHC restriction
- Signals for full activation are self-contained

Adapted from Lee et al, Clin Can Res, 2012

Vol. 149, No. 3, 1987 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
December 31, 1987 Pages 960-968

EXPRESSION OF CHIMERIC RECEPTOR COMPOSED OF IMMUNOGLOBULIN-DERIVED V RESIONS AND T-CELL RECEPTOR-DERIVED C REGIONS

Yoshihisa Kuwana[1], Yoshihiro Asakura[1], Naoko Utsunomiya[2], Mamoru Nakanishi[2], Yohji Arata[2], Seiga Itoh[3], Fumihiko Nagase[4] and Yoshikazu Kurosawa[1]*

[1]Institute for Comprehensive Medical Science, Fujita-Gakuen Health University, Toyoake, Aichi, 470-11

[2]Faculty of Pharmaceutical Science, University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113

[3]Tokyo Research Laboratories, Kyowa Hakko Co., Asahimachi, Machida, Tokyo, 194

[4]Department of Immunology, Nagoya University School of Medicine, Tsurumai, Showa-ku, Nagoya, 466, Japan

Received November 12, 1987

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

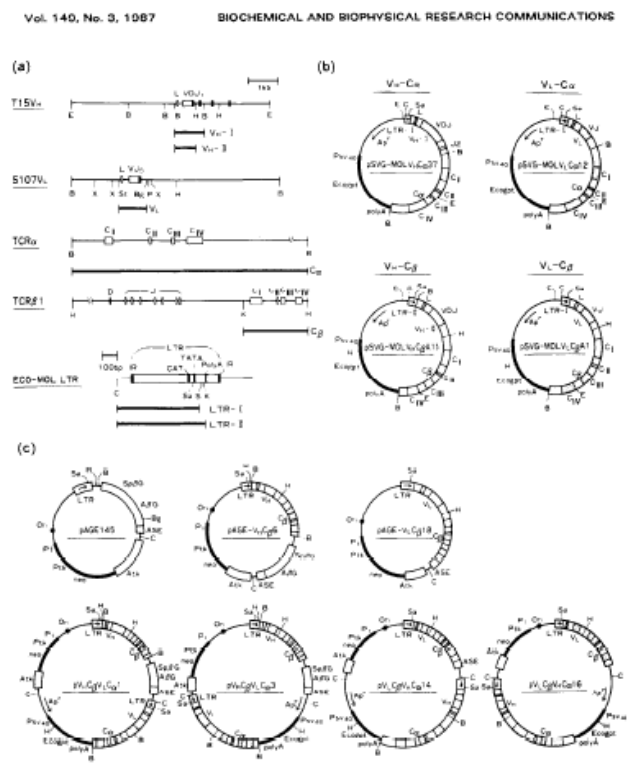
Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)



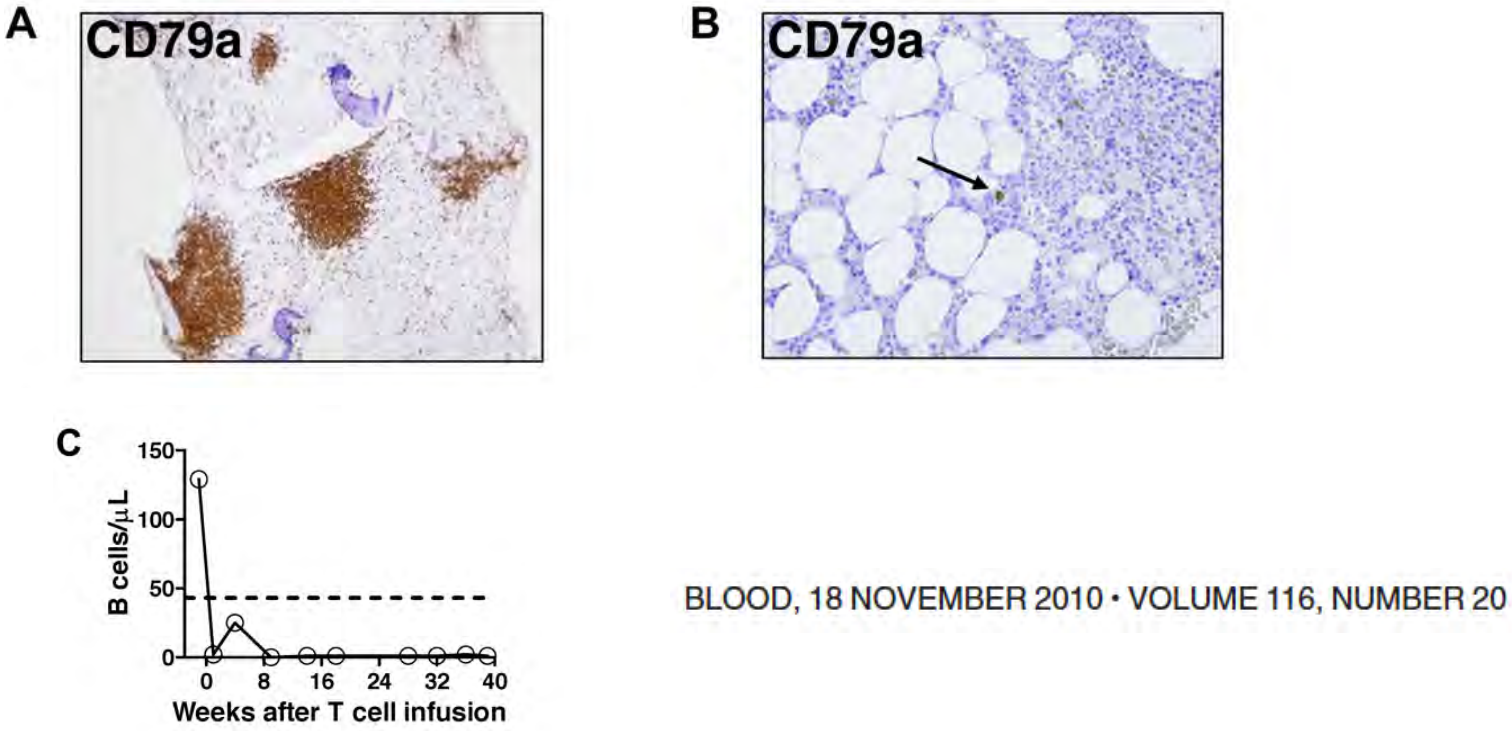
CD19 CAR: First report

Brief report

Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19

James N. Kochenderfer,[1] Wyndham H. Wilson,[2] John E. Janik,[2] Mark E. Dudley,[1] Maryalice Stetler-Stevenson,[3] Steven A. Feldman,[1] Irina Maric,[4] Mark Raffeld,[3] Debbie-Ann N. Nathan,[1] Brock J. Lanier,[1] Richard A. Morgan,[1] and Steven A. Rosenberg[1]

[1]Surgery Branch, [2]Metabolism Branch, and [3]Laboratory of Pathology, National Cancer Institute, Bethesda, MD; and [4]Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, MD



BLOOD, 18 NOVEMBER 2010 • VOLUME 116, NUMBER 20

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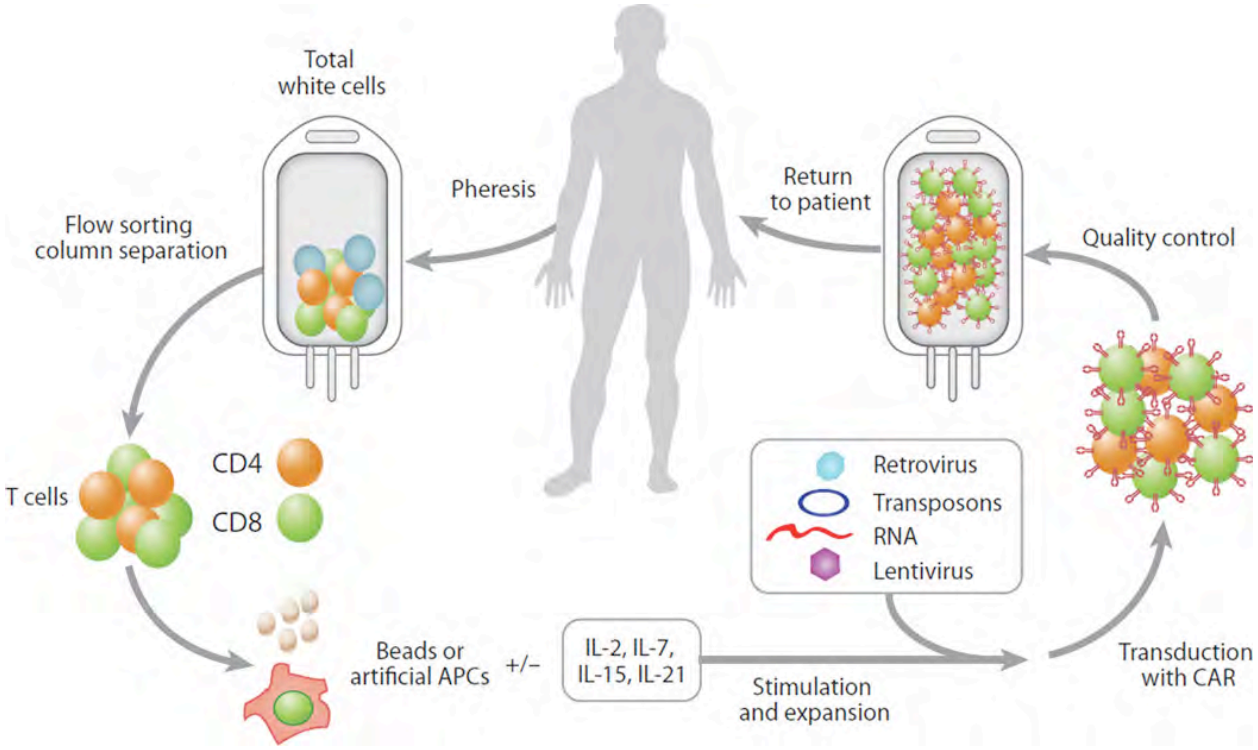
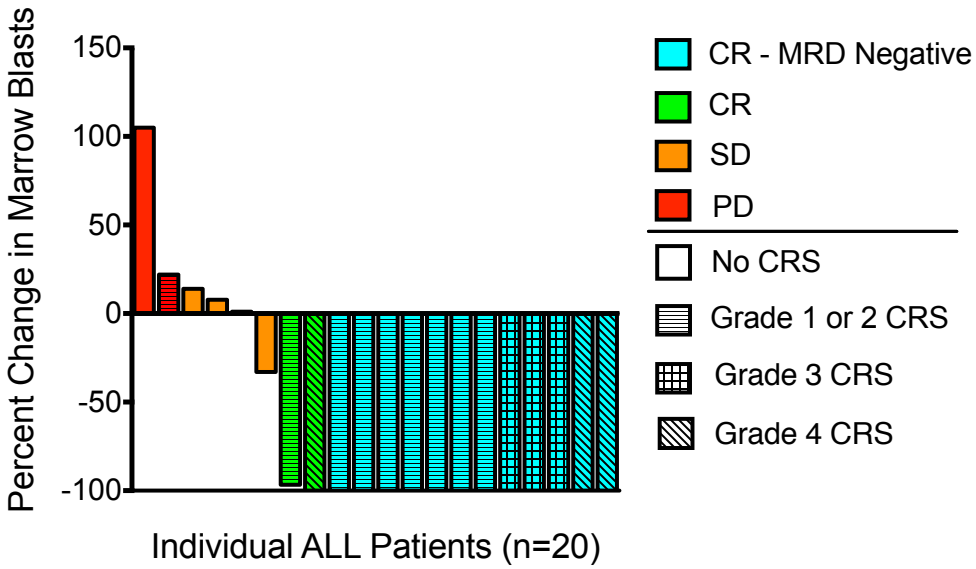
Initial Experiences with CD19 CAR T cells

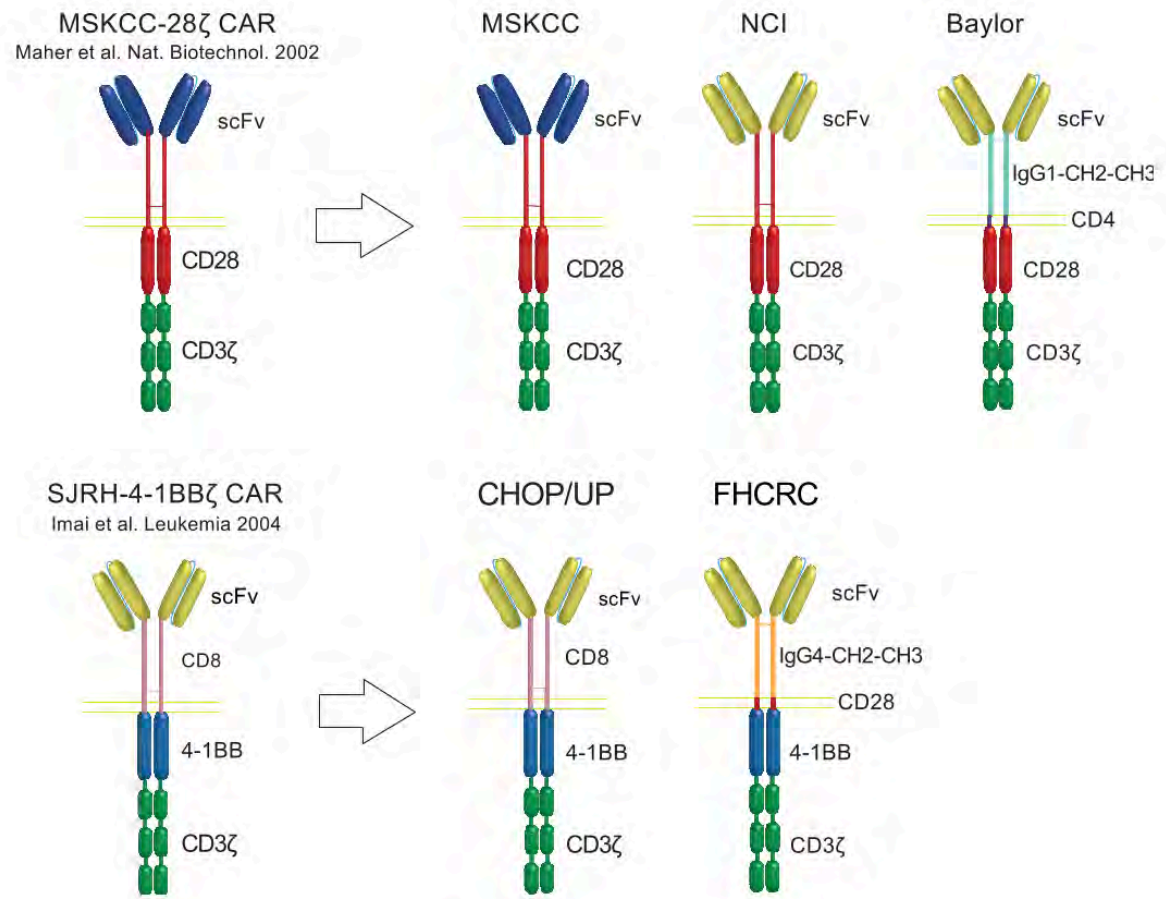


70-90% of patients achieve remission



Lee, D et al. Lancet, 2014

CD19 CARs: original CARs: multiple variants, comparable efficacy in early phase trials



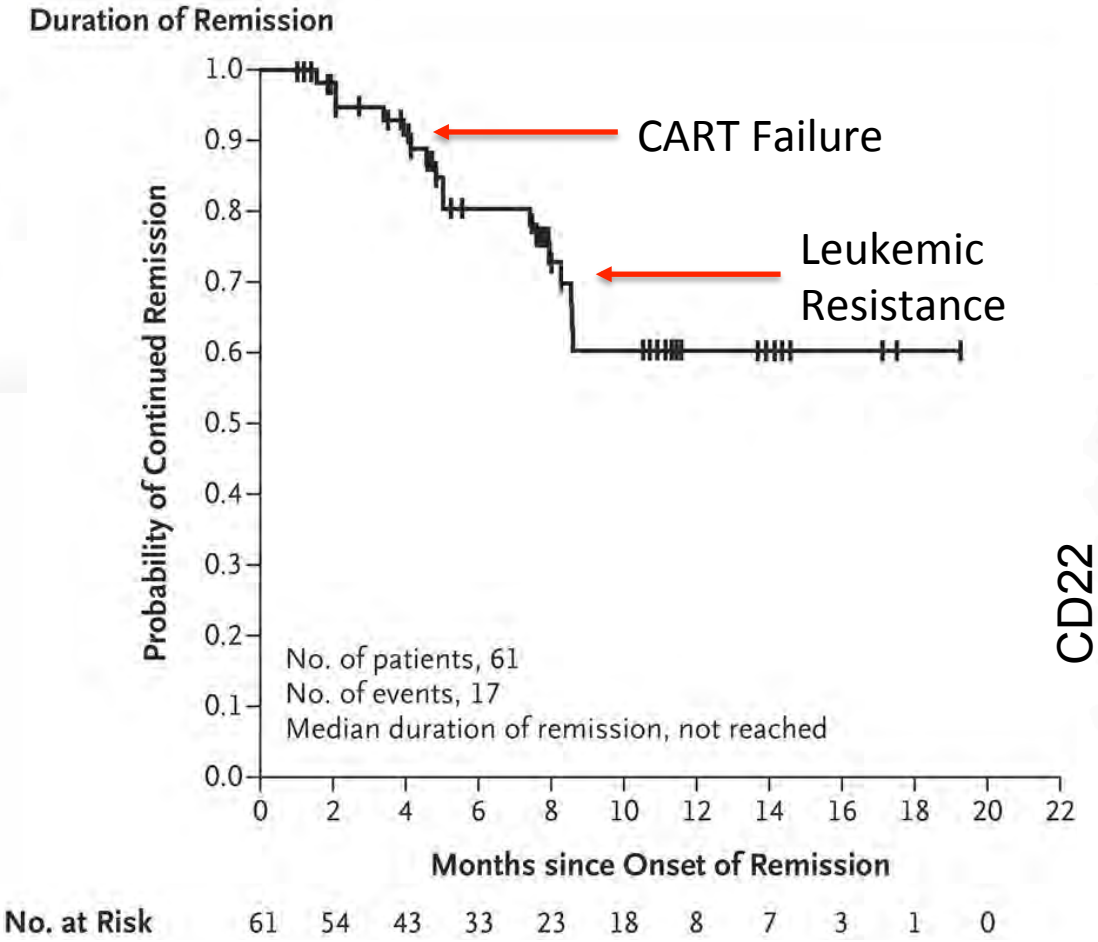
Sadelain, *JCI*, 2015

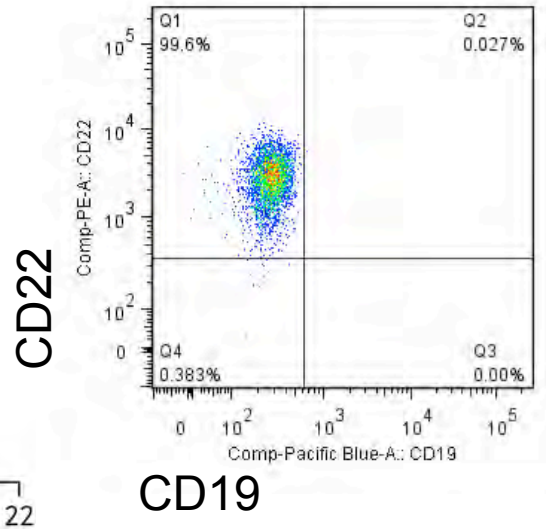
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

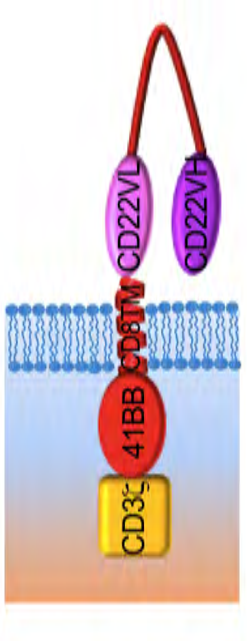


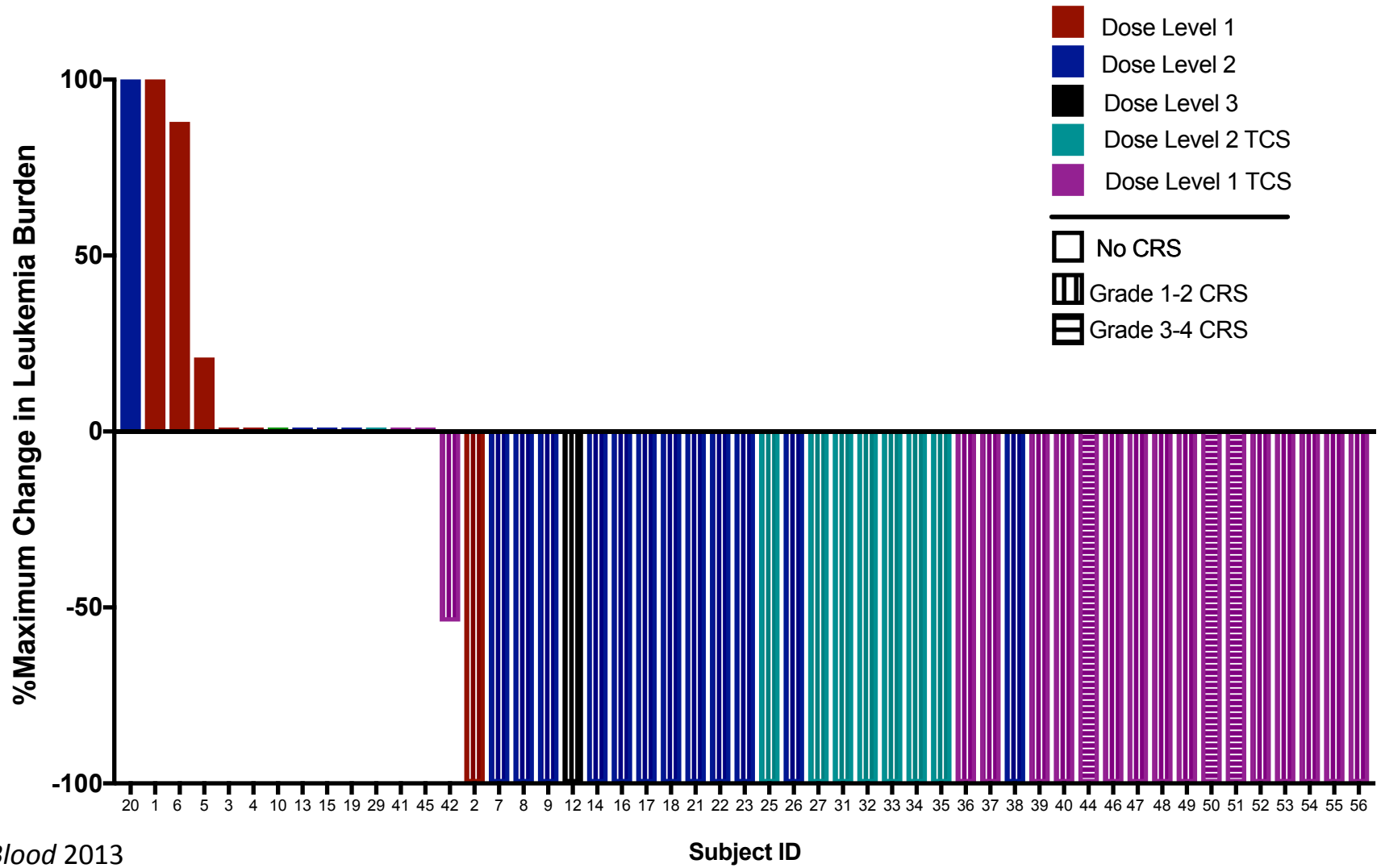


Maude SL et al. N Engl J Med 2018;378:439-448

The NEW ENGLAND JOURNAL of MEDICINE

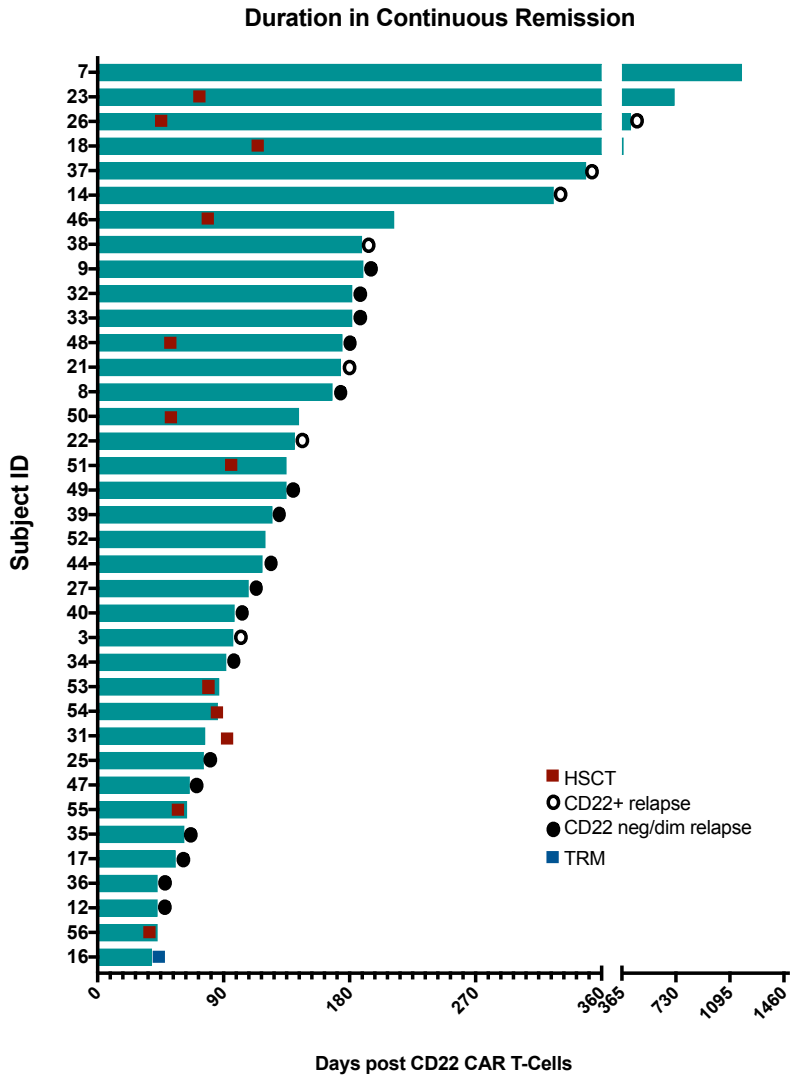
CD22 targeted CART achieves MRD Negative Remission in Relapsed/Refractory ALL

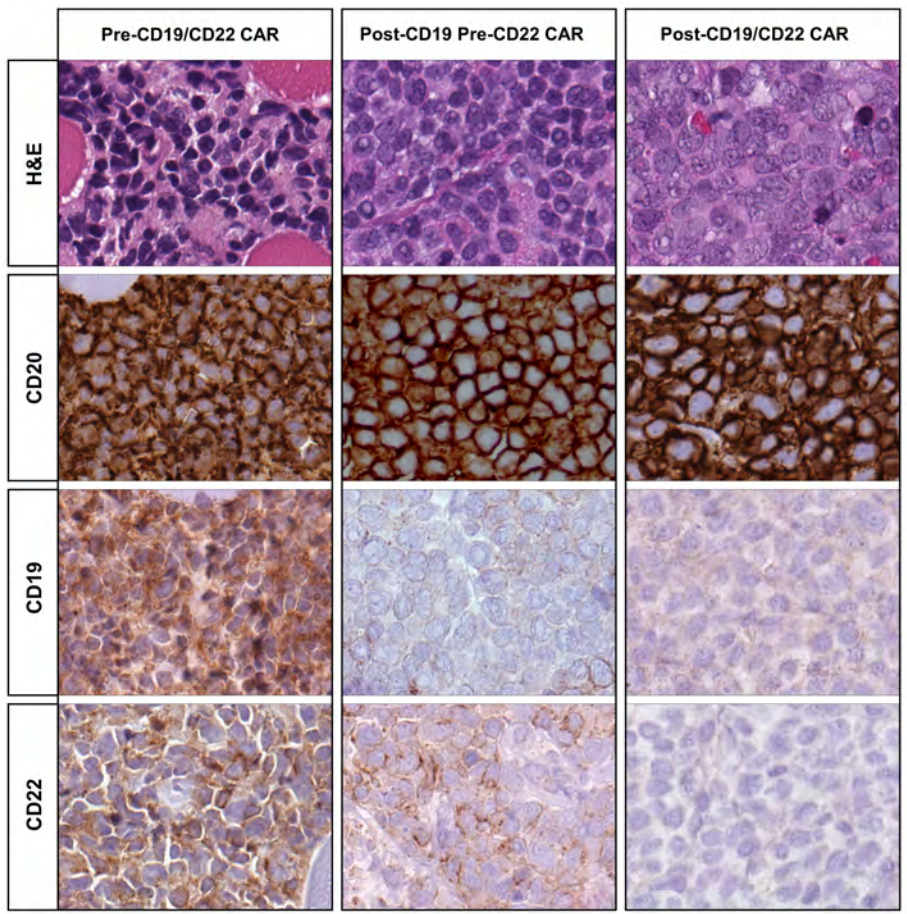




Haso…Orentas, *Blood* 2013
Haso….Fry, *ASH* 2013
Fry/Shah et al., *Nature Medicine 2017*

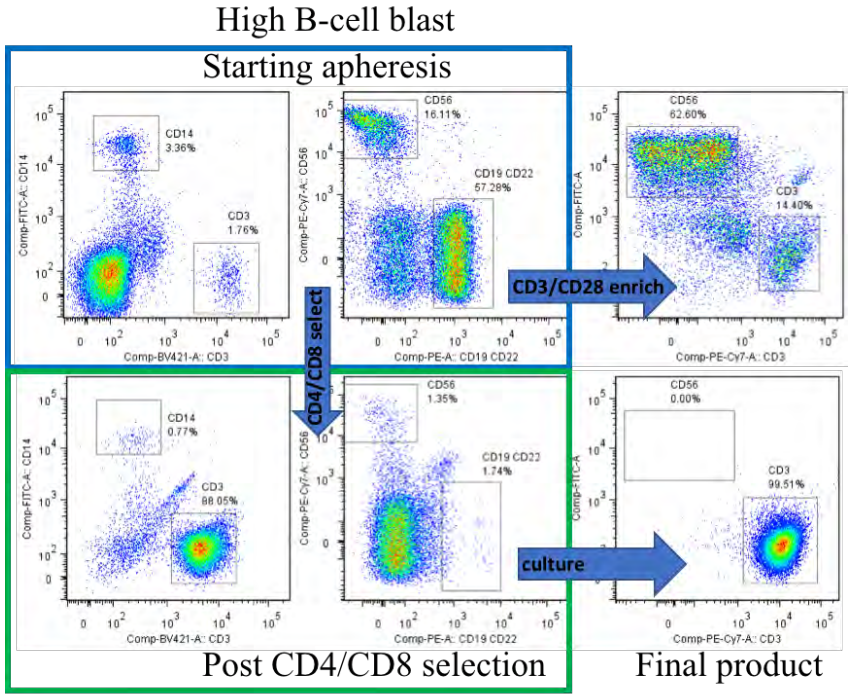
CD22 BBz CAR:
Relapse associated with CD22 modulation





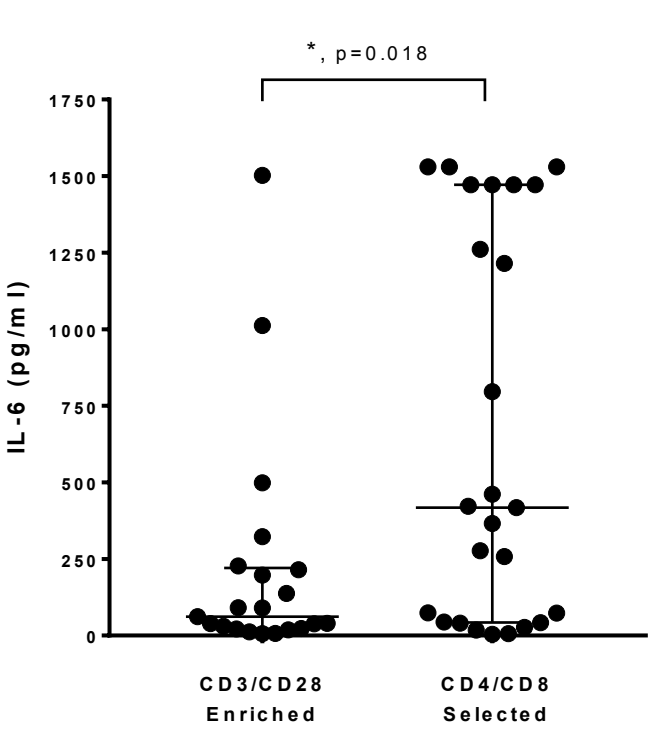
Shalabi…..Fry, Shah, Hematologica, 2017

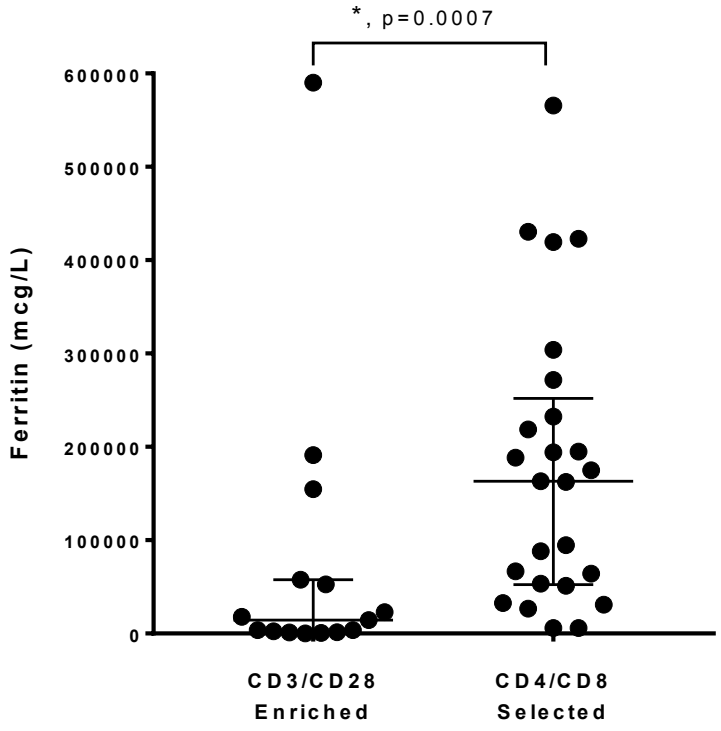
Manufacturing Details Matter



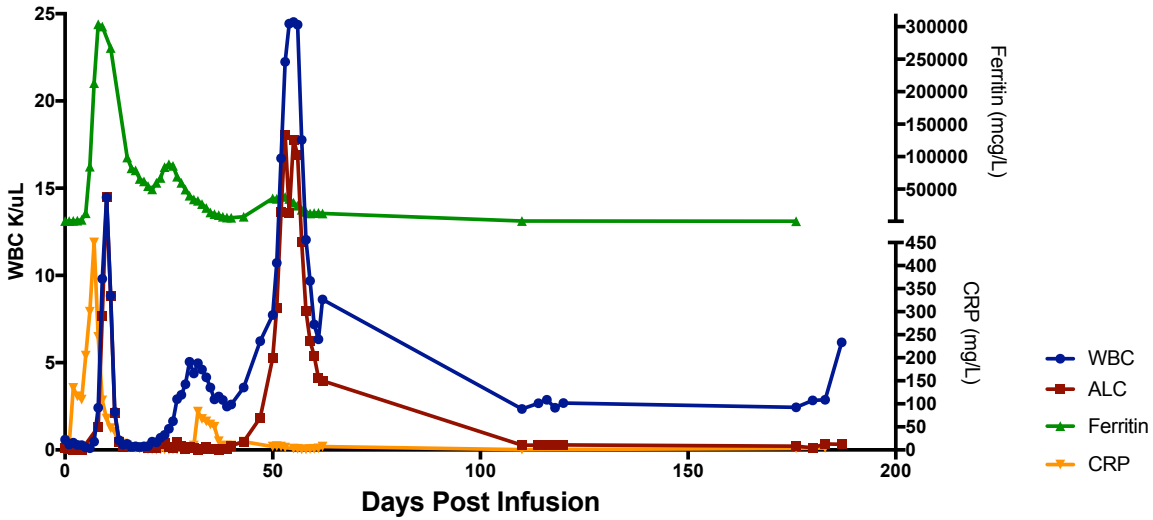
	CD3/CD28 enriched	CD4/CD8 selected
Fold expansion	0	40
Transduction efficiency	0.6	15

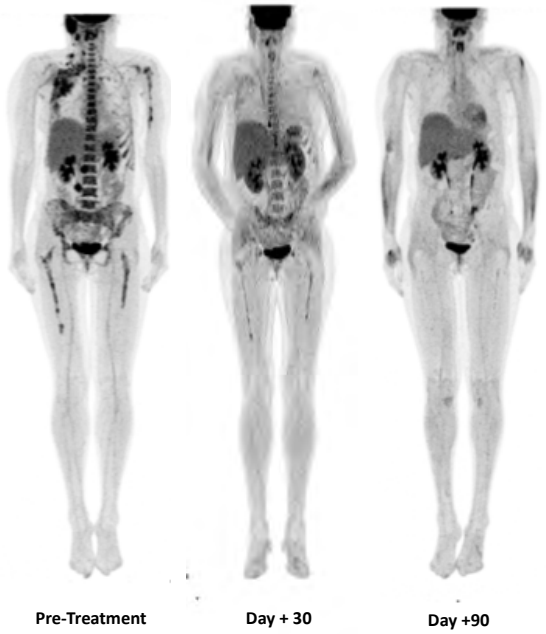
Post-infusion

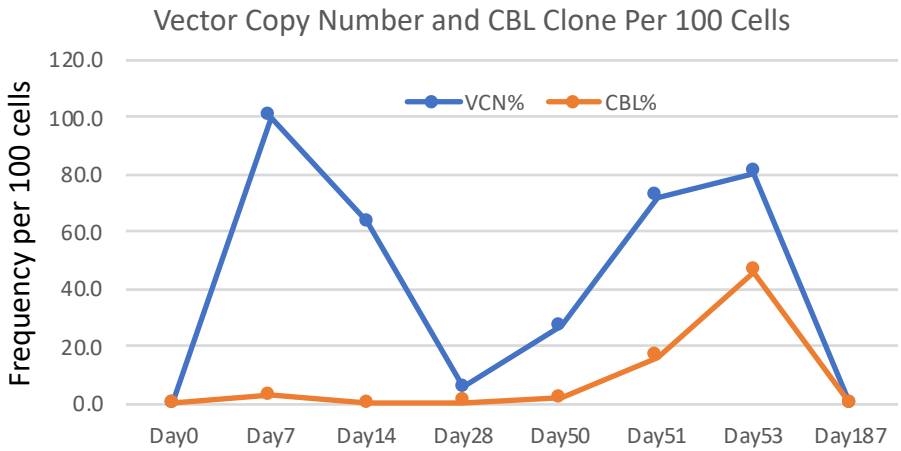


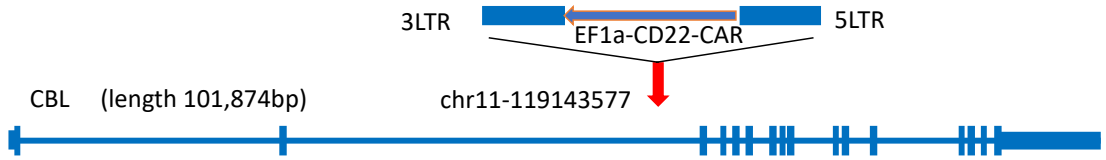


Importance of Correlative Science









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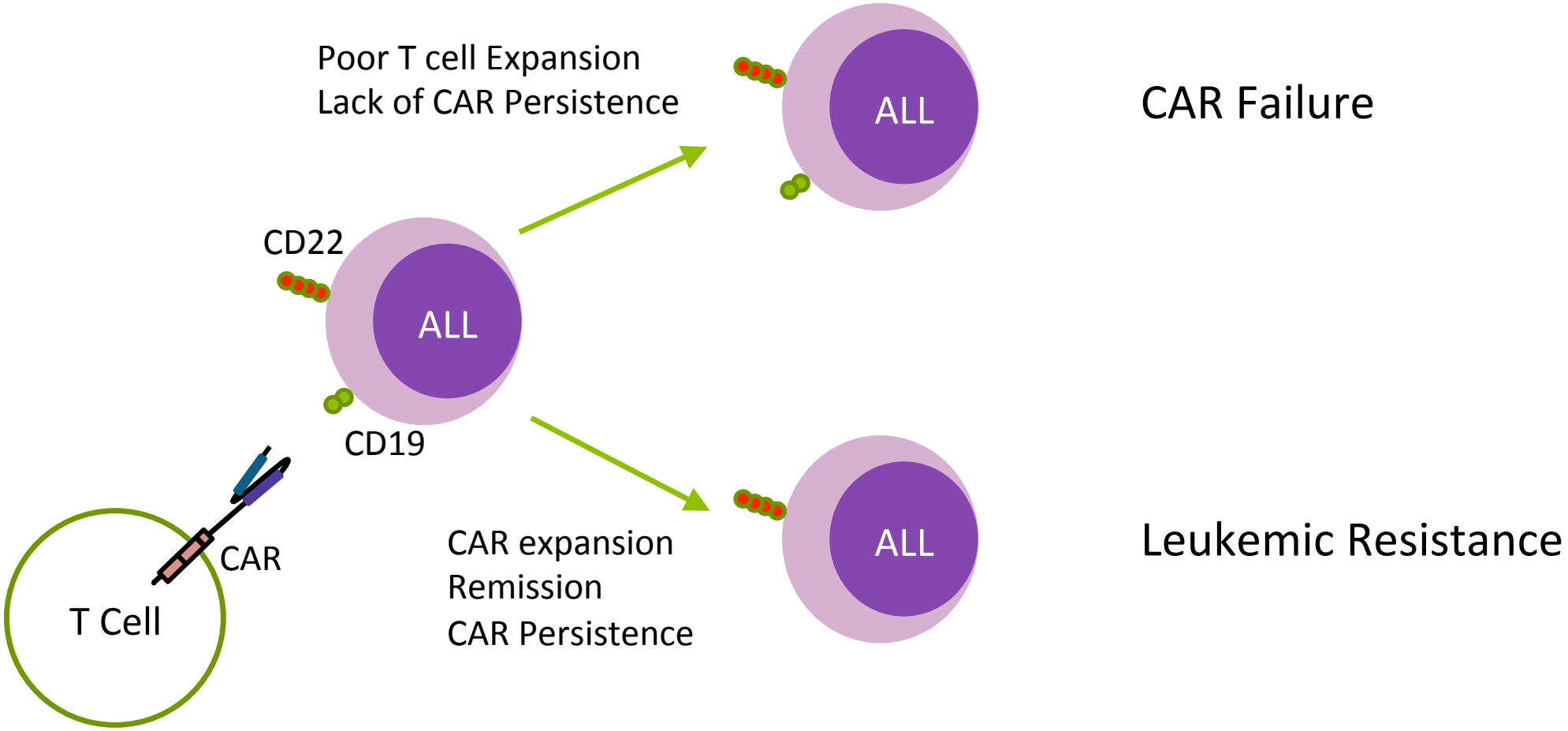
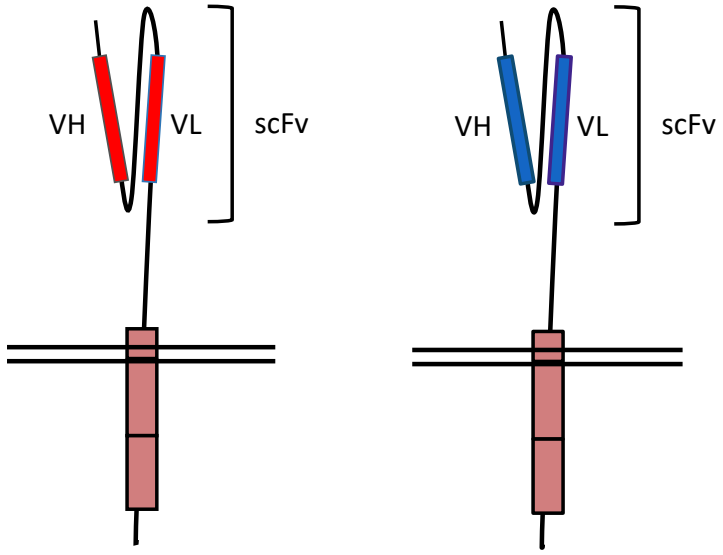
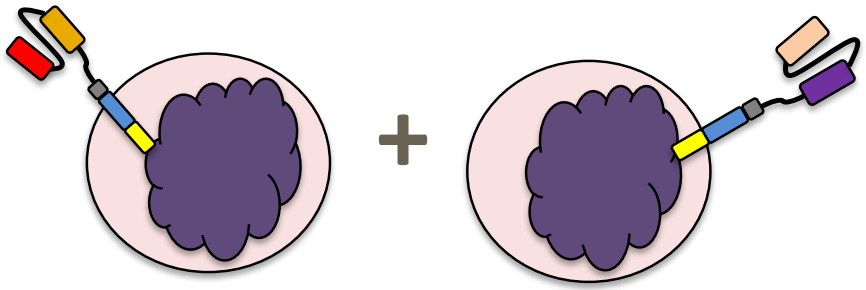
Patterns of Failure after CAR T cell Therapy

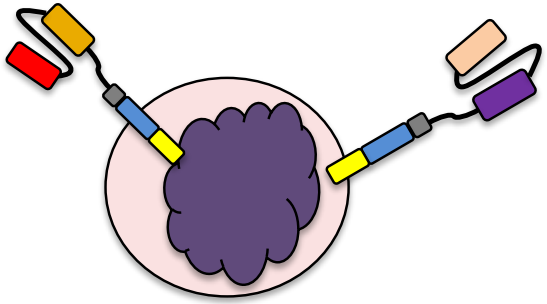


Multispecific CAR Targeting

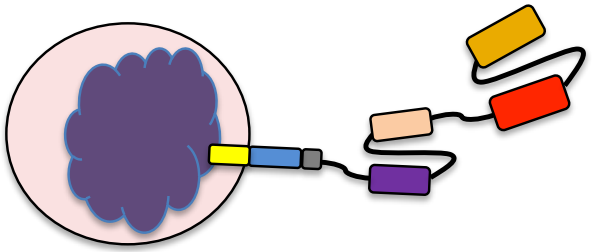




Co-administration



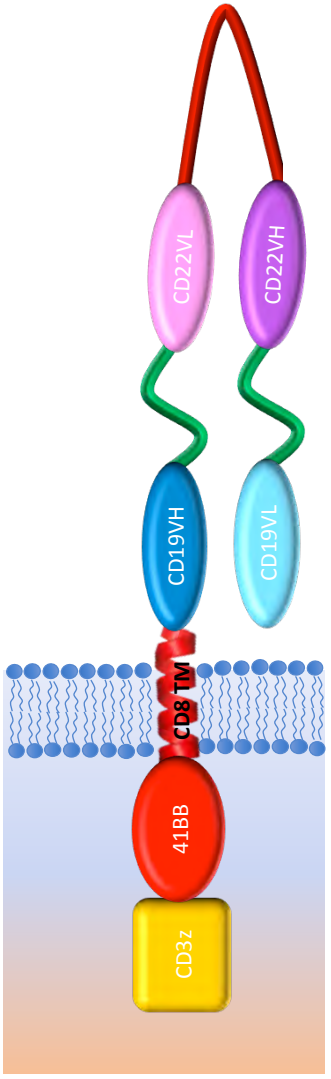
Co-expression

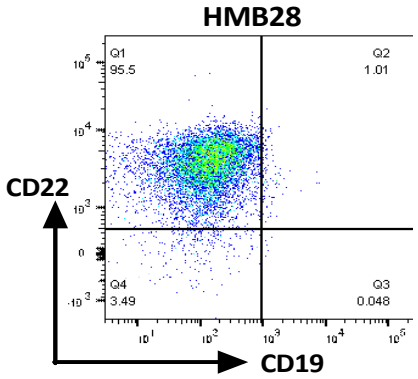


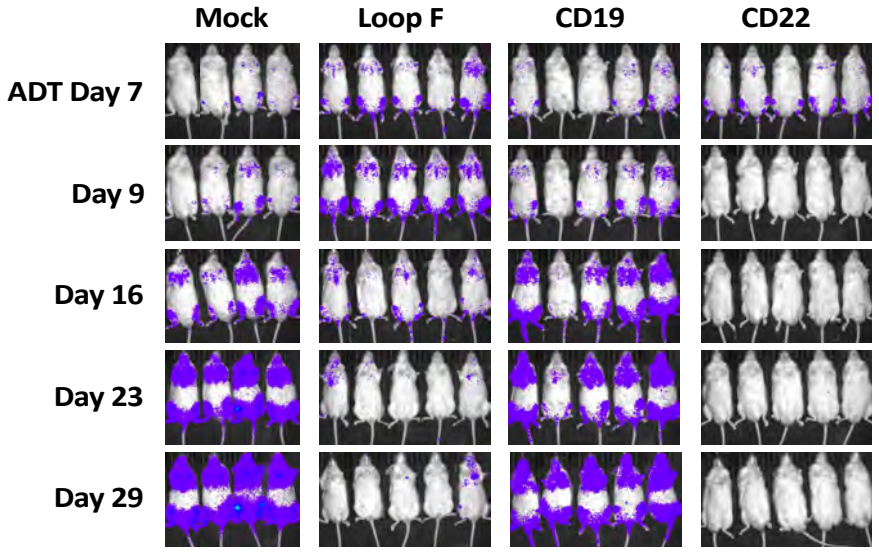
Bispecific Constructs

Development of an Active CD19/CD22 Bivalent CAR

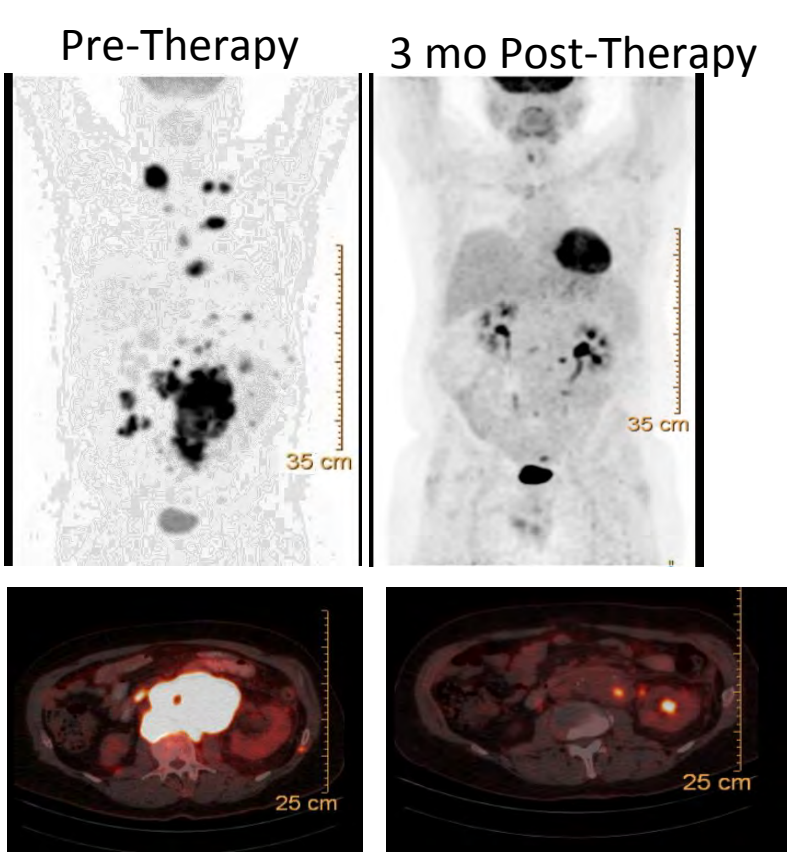
Haiying Qin
Nature Medicine, 2017
Molecular Therapy Oncolytics, 2018

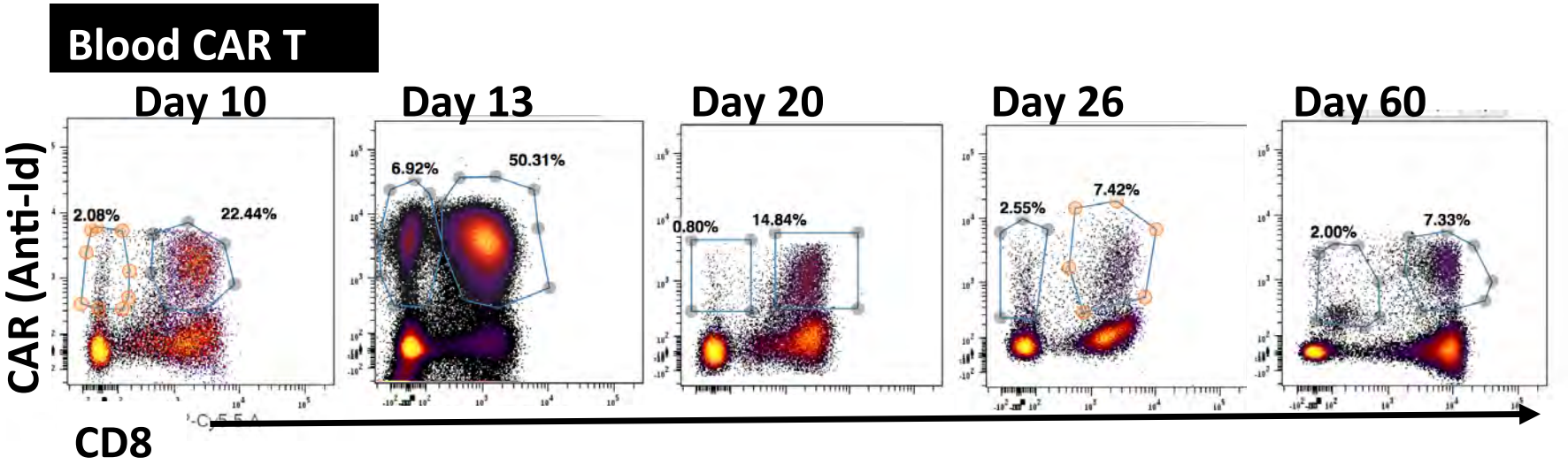




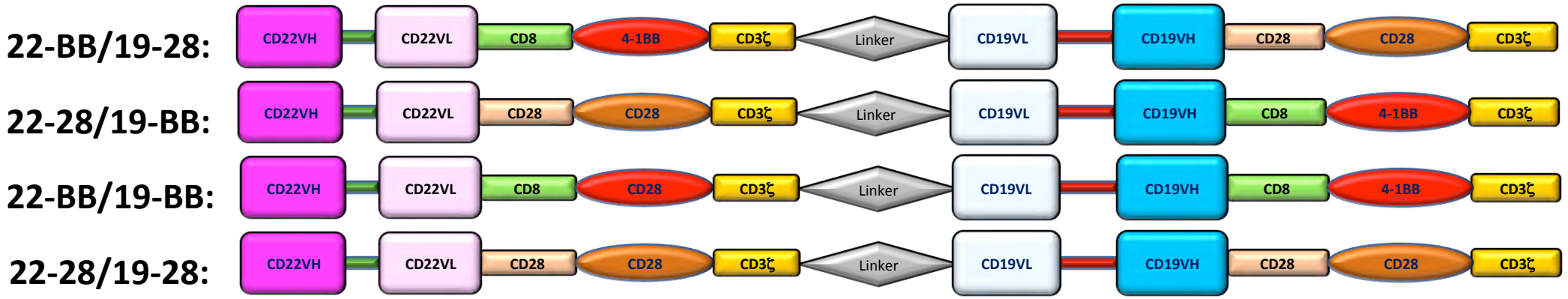


Clinical Activity of TanCAR: Bivalent CD19/22-CAR

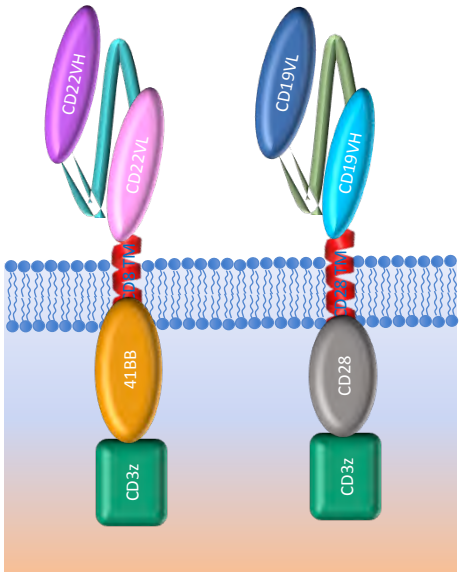




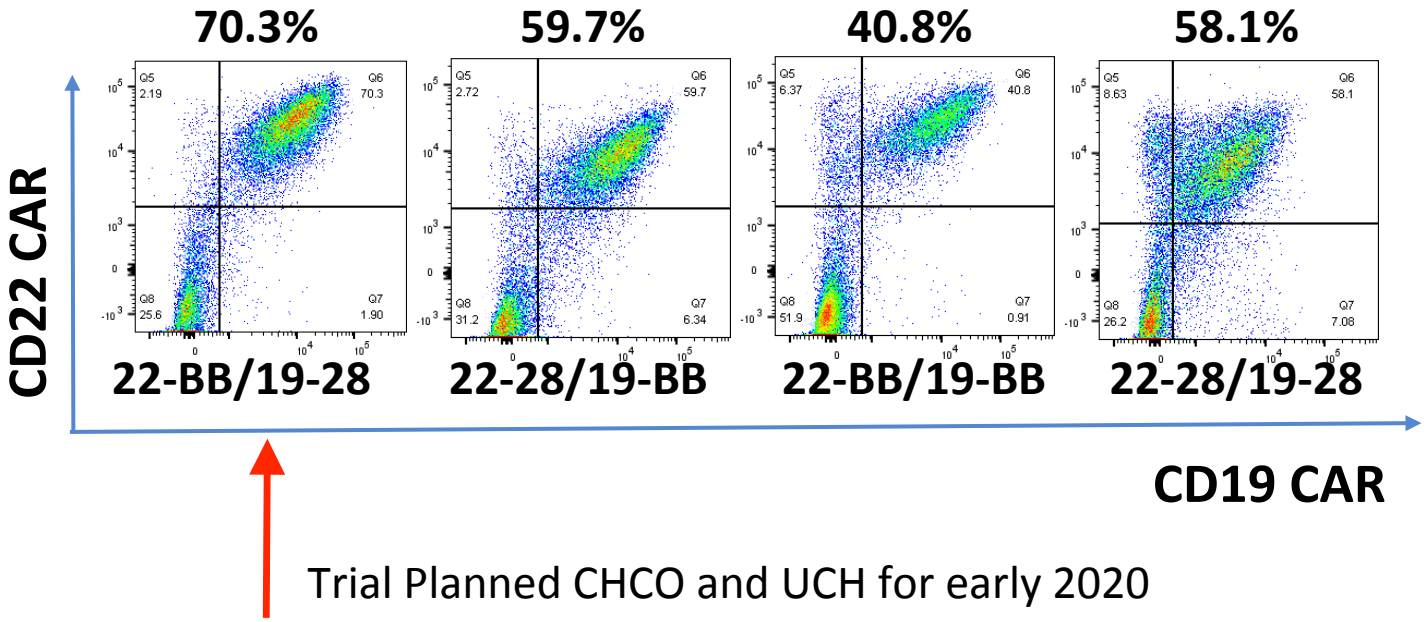
Hossain et al, ASH 2018, Abstract 490.
Schultz et al, ASH 2018, Abstract 898.



Translation

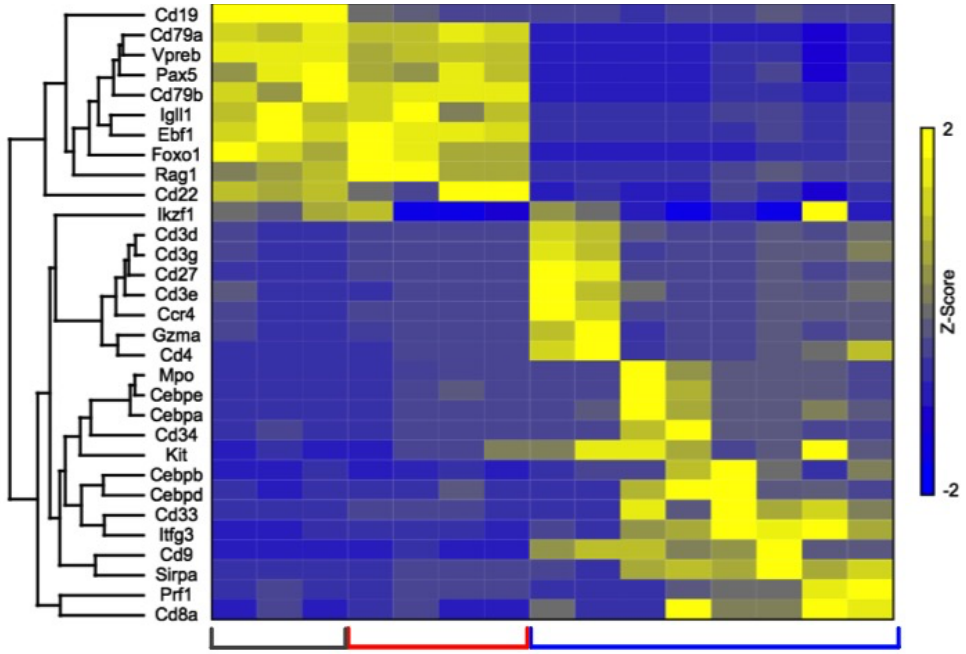


Signal Integration

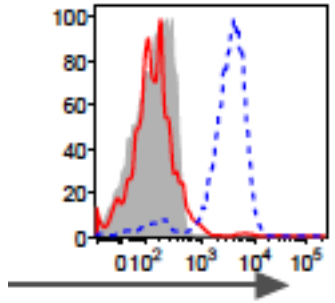


Trial Planned CHCO and UCH for early 2020

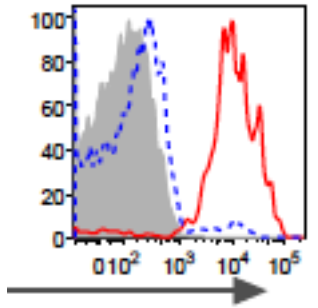
Leukemic evolution in the context of targeted Immunotherapy can be complex



Jacoby et al, Nature Communications, 2016



CD19



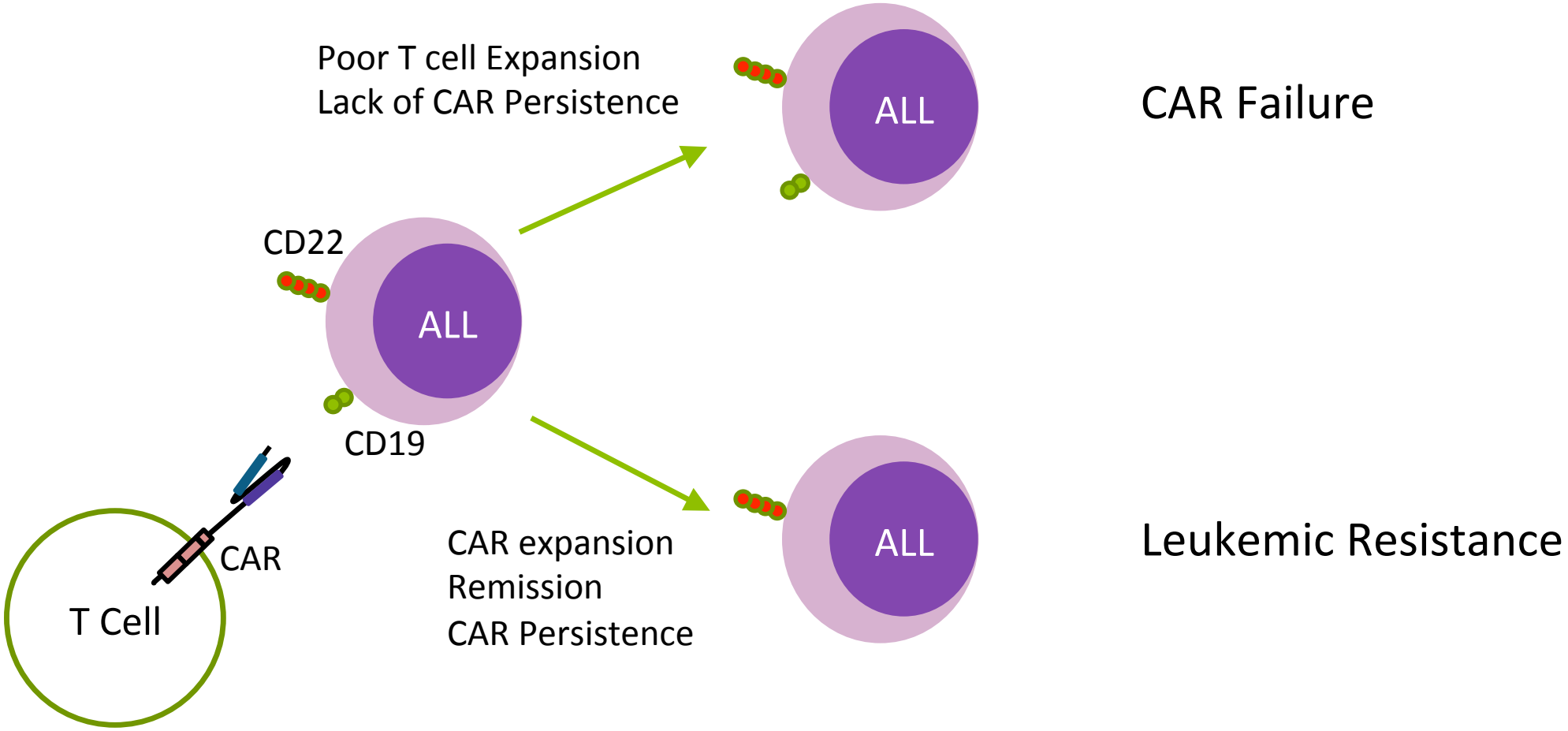
CD11b

Pre-CD19 CAR

Post-CD19 CAR

Gardner et al, Blood, 2016

Patterns of Failure after CAR T cell Therapy

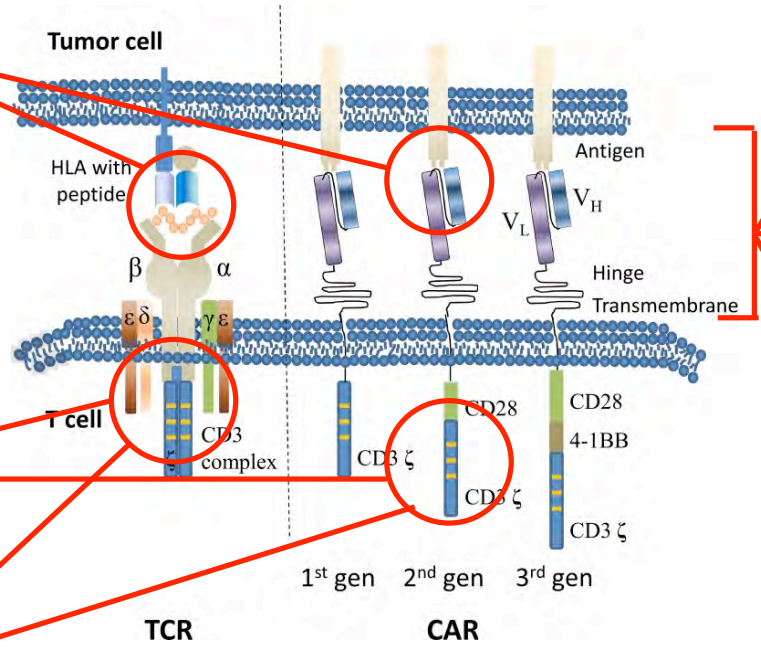


Chimeric Receptors are Not the Same as the native TCR

Affinity for antigen is ~1000 fold higher in CARs

10 ITAMs per receptor

CAR contains in-line co-stimulatory signaling

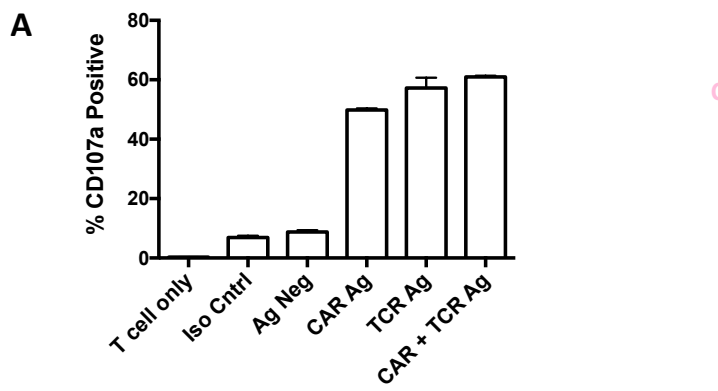


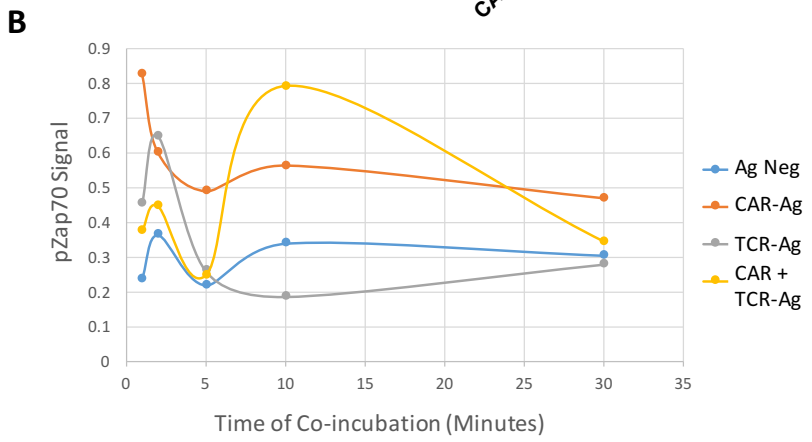
Unknown if CAR activation results in organized synapse

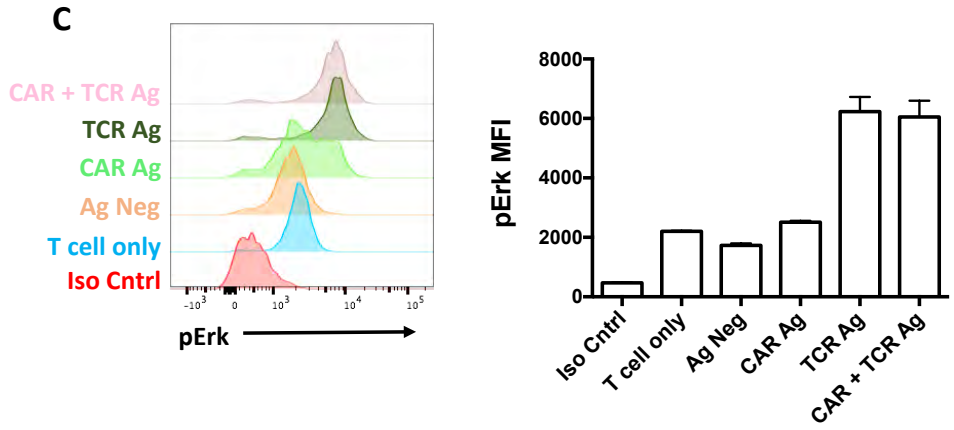
Distance between cells variable with CARs

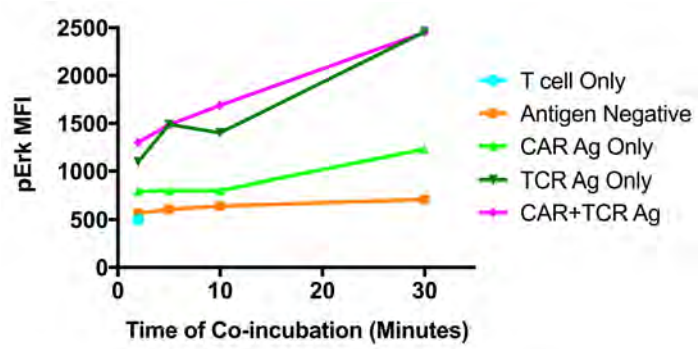
CD4/CD8 co-receptors not recruited by CARs

Signaling through the mCD19-28z CAR leads to prolonged Zap70 phosphorylation and decreased phosphorylation of Erk relative to TCR



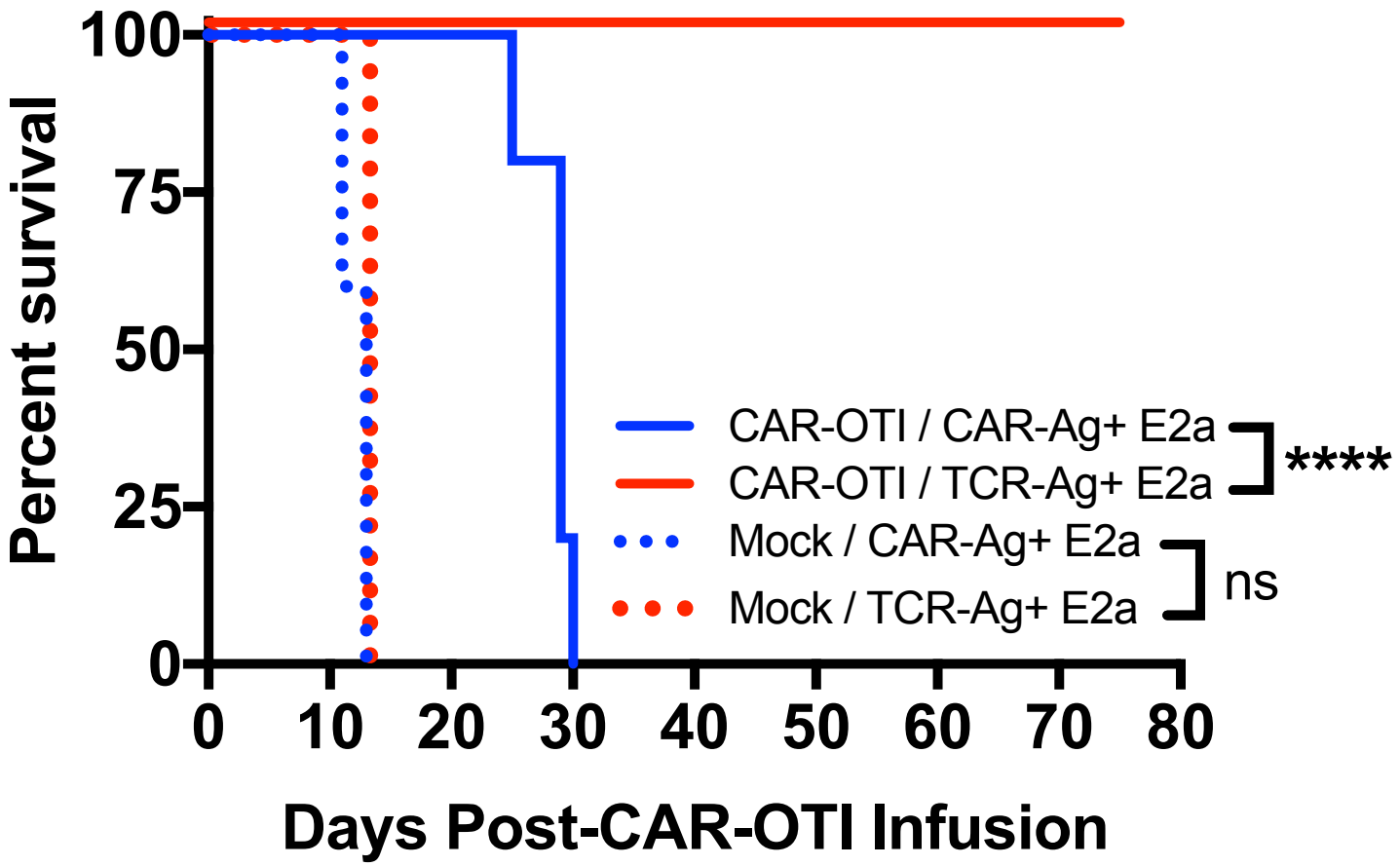




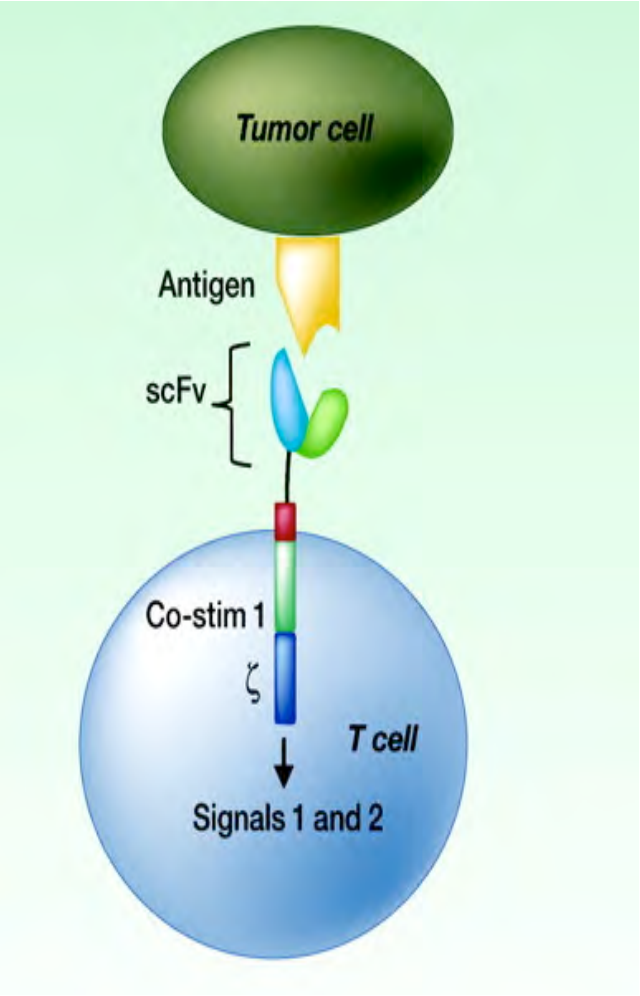


CAR-mediated anti-leukemic potency inferior to TCR

CAR-OTI Dose: 50,000/mouse



So, what have we learned?



- Single antigens comparable to CD19 will be difficult to find
- Details of CAR T cell products matter
- Antigen modulation as well as more complex patterns of cancer resistance will frequently emerge
- Current CAR formats do not fully recapitulate T cell biology
- As synthetic receptors, the ability to modify is almost endless
  - Binding domains, signaling domains, multiplexing

COST of and ACCESS to complex therapeutics will be a challenge

Acknowledgments

Pediatric Oncology Branch

- Nirali Shah
- Cindy Delbrook
- Bonnie Yates
- Sharon Mavroukakis
- Haneen Salabi
- POB Fellows

Hematologic Malignancy Section

- Haiying Qin
- Lila Yang
- Amy Yang
- Chris Chien
- Sneha Ramakrishna
- Eric Kohler
- Zach Walsh

Denver Lab

- Eric Kohler
- Savannah Ross
- Jen Cimons
- Zach Walsh
- Lillie Leach
- Christine Meadows
- Michael Yarnell

Patients and Families