

NIH Myelodysplastic Syndromes Symposium

CAR-T Cell Therapy in Pediatric Leukemia

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Friday, July 12, 2019



Disclosures

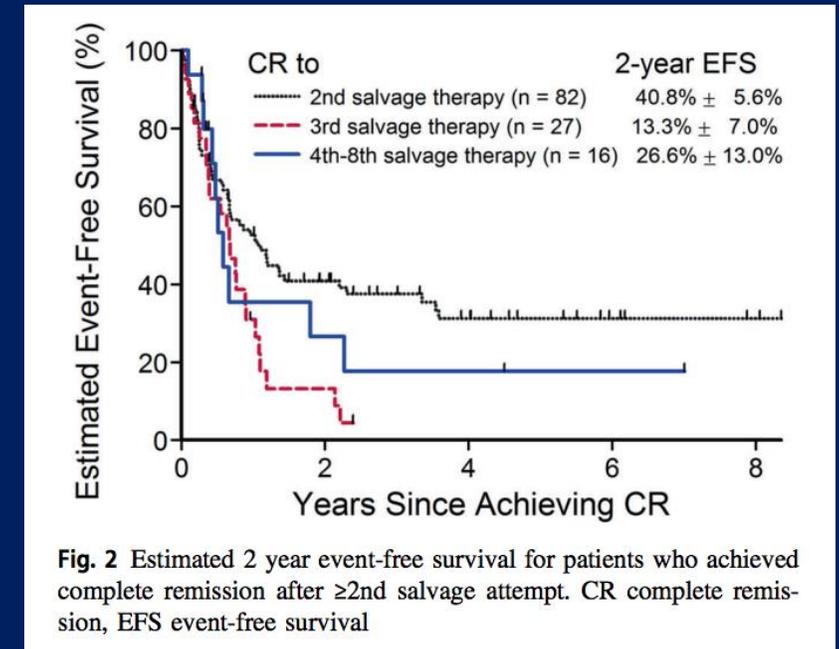
- No disclosures to report
- I will be discussing utilization of novel (non-FDA approved) CAR-T cell approaches in pediatric leukemia

Educational Objectives

- Provide a general overview of CAR-T Cell therapy in pediatric acute lymphoblastic leukemia (ALL)
- Discuss future directions and challenges in immunotherapy for hematologic malignancies

Childhood Acute Lymphoblastic Leukemia (ALL)

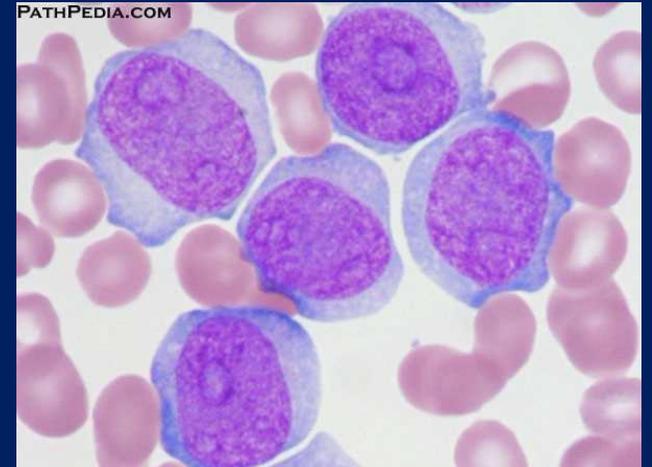
- Most common cancer diagnosed in children.
 - 41 cases/million in children aged < 14
 - 17 cases/million in teens between ages 15-19
 - 25% of all new cancer diagnosis
- 85-90% of patients will be cured.
- “Poster-child” for efficacy and importance of cooperative groups and clinical trial participation.



Outcomes for relapsed/refractory disease remain poor

Acute Myelogenous Leukemia (AML)

- 20% of Childhood leukemia
- > 20,000 new cases annually in adults
- 50-70% complete remission rate; cure rates lower in adults
- 30-40% relapse rate
- Intensive therapy associated with high-risk of infectious complications
- 5-7% treatment related mortality



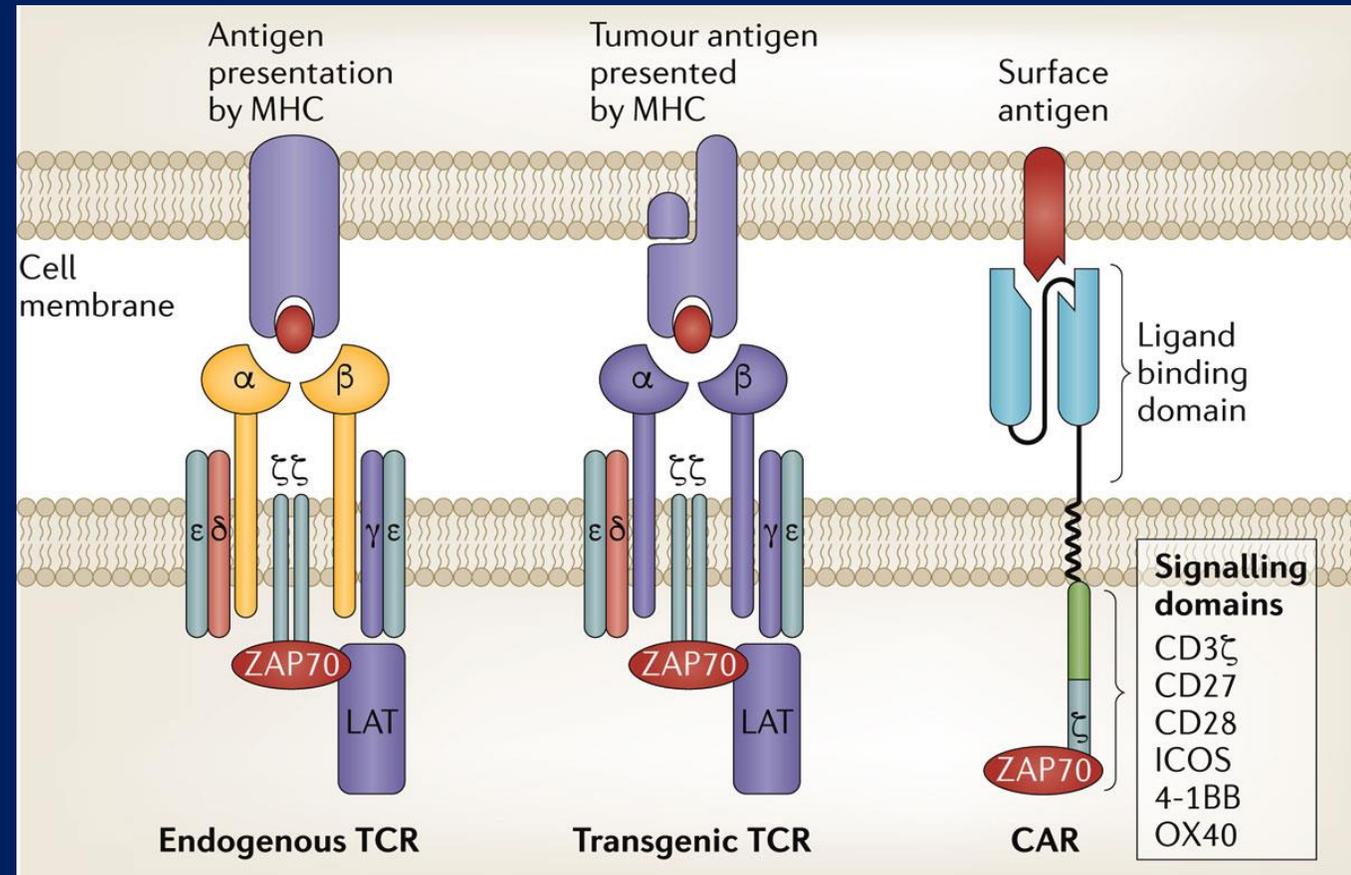
Challenges

- Curative options for relapsed/refractory disease remains a therapeutic challenge
- Outcomes for the adolescent young adult (AYA) population remain particularly poor
- Toxicity from cumulative therapy not insignificant
- Novel therapies are needed

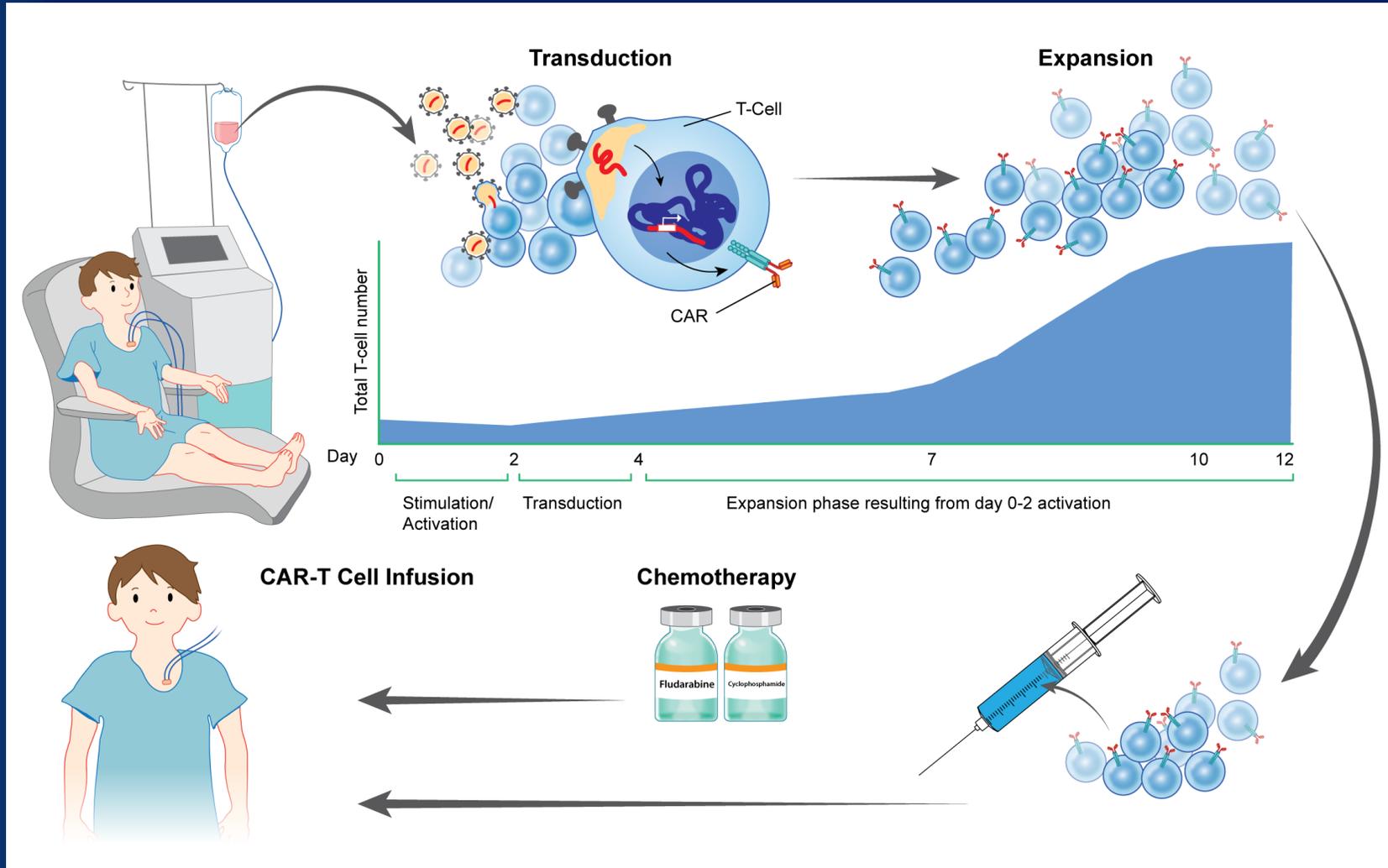
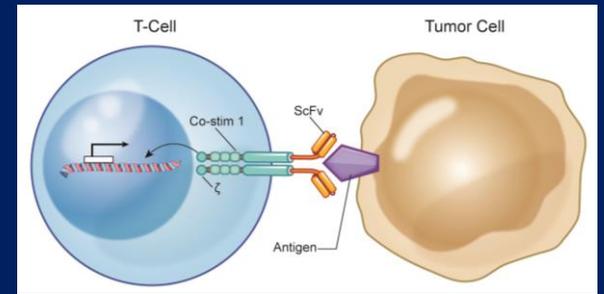
TCRs and CARs

- TCR: T-cell receptor
 - Recognize processed antigens and are MHC dependent, and require co-stimulatory signals for T-cell activation
- CAR-T cell: chimeric antigen receptor T-cell
 - Recognize cell surface antigens independent of MHC, have co-stimulatory signals integrated
 - Retains the functionality of a T-cell with the antigen recognition properties of antibody

TCR vs CAR-T Cell Structure



Making a CAR-T Cell

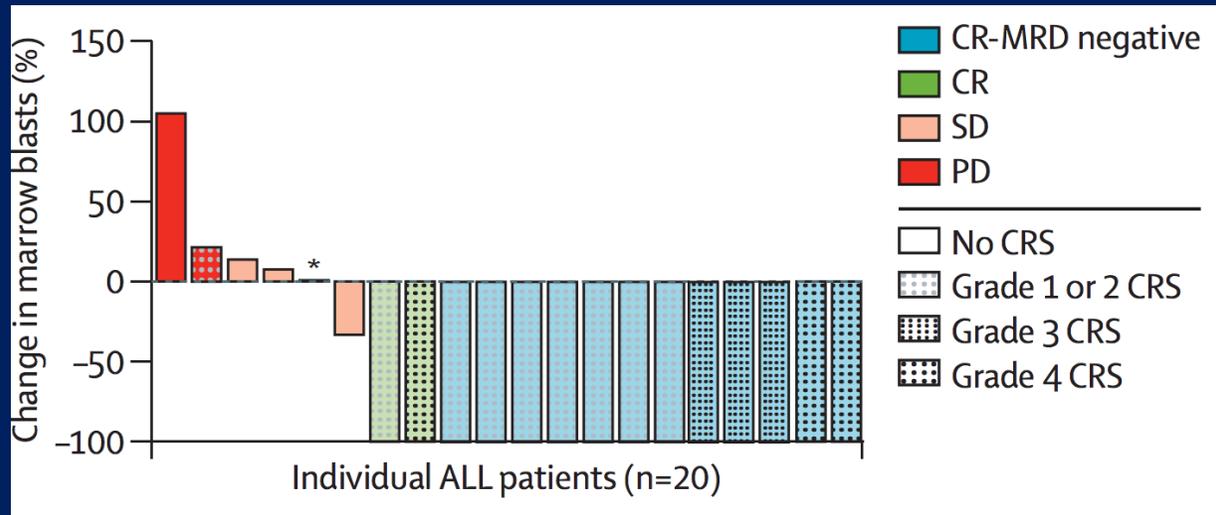


1. Apheresis
2. Stimulation and Transduction
3. Expansion
4. Lymphodepletion
5. Infusion

CD19 CAR Clinical Updates (NCI-POB)

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Nirali N Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall



Lee et al. Lancet 2015
67% CR rate (ITT)
All responders with CRS

CD19 CAR Clinical Updates (Novartis)

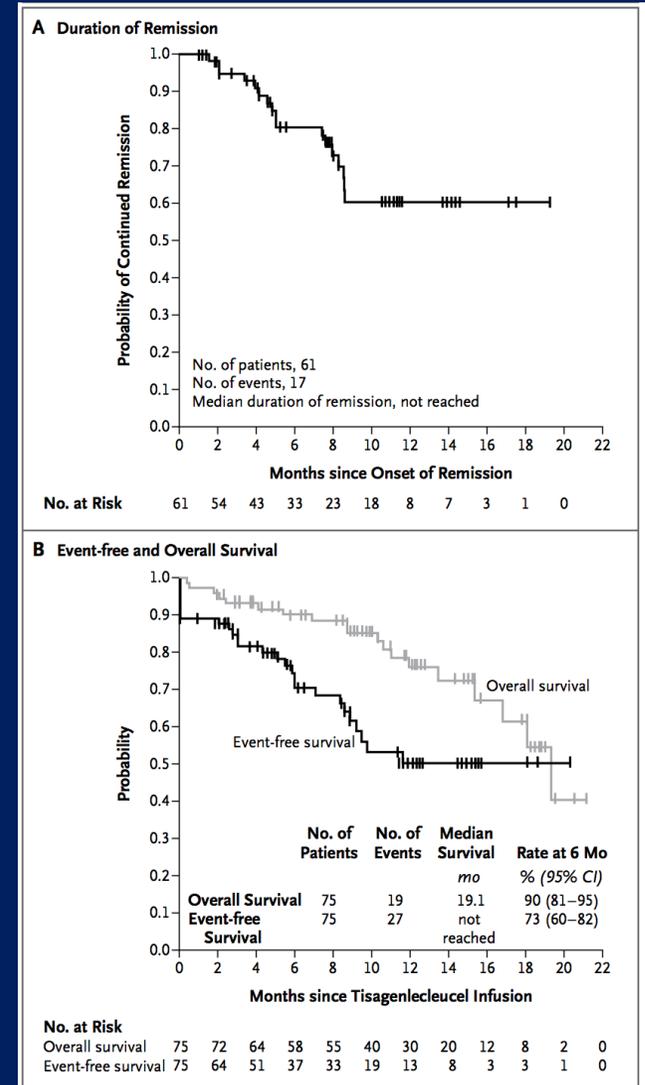
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

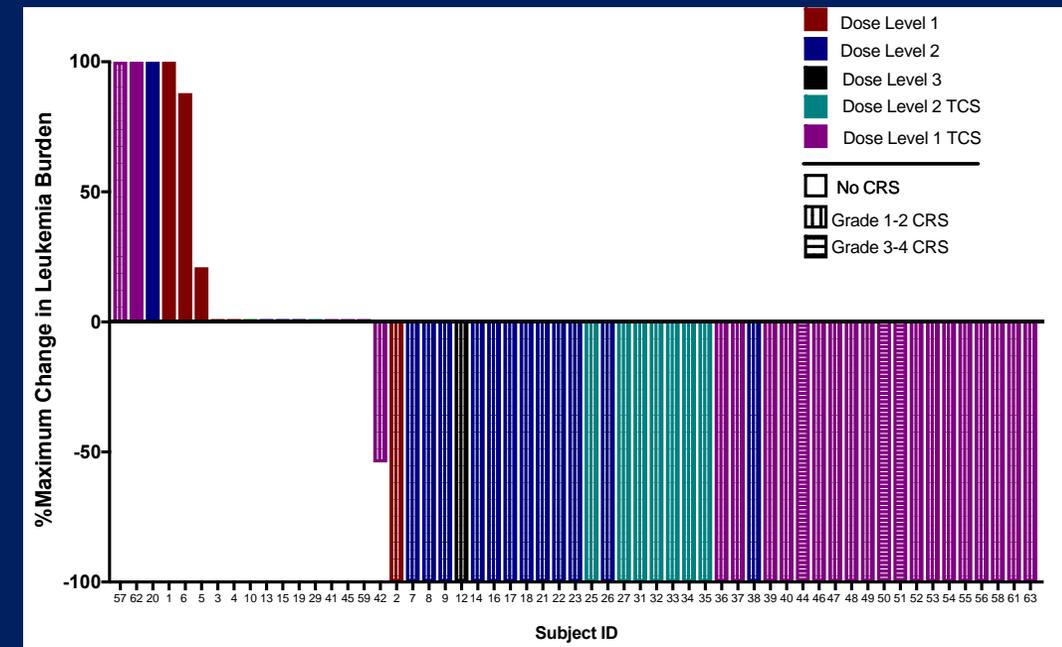
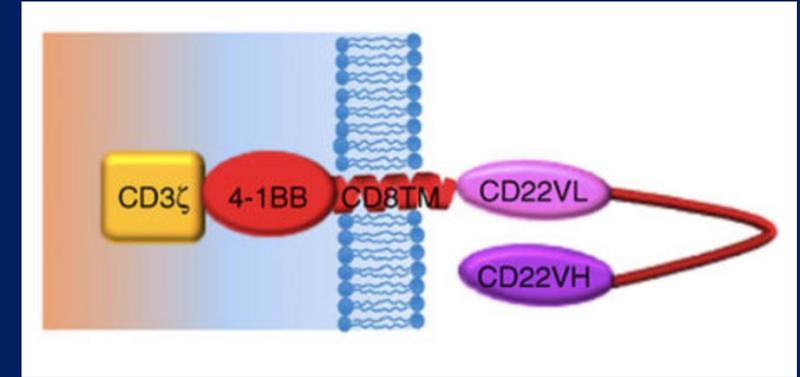
S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, 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

81% Complete remission rate (not ITT)

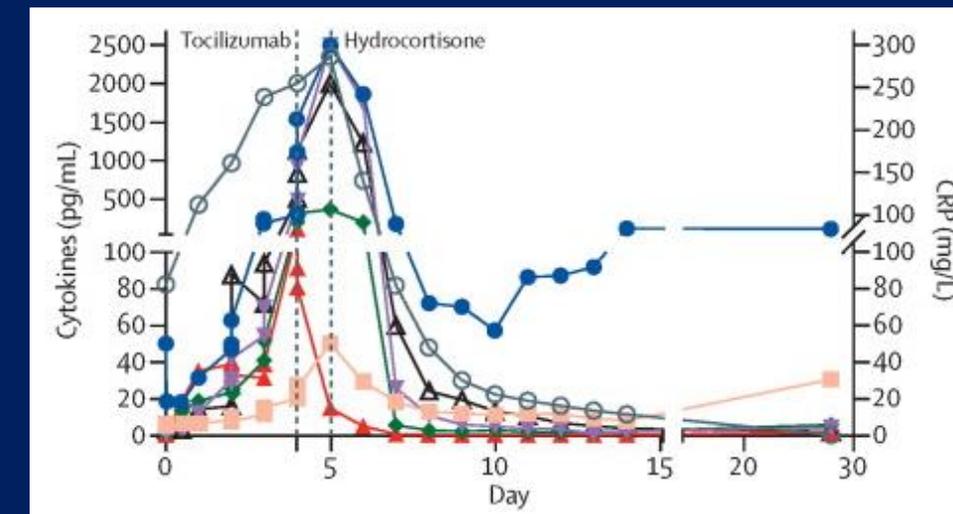
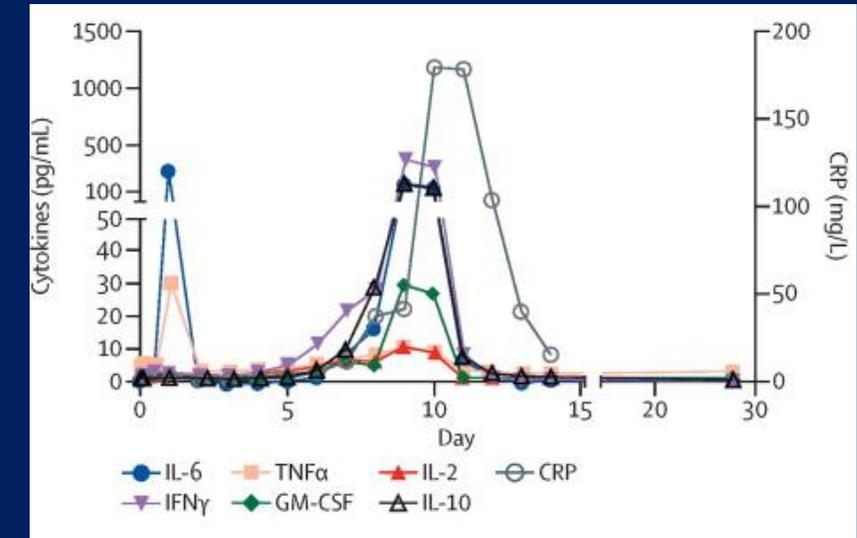
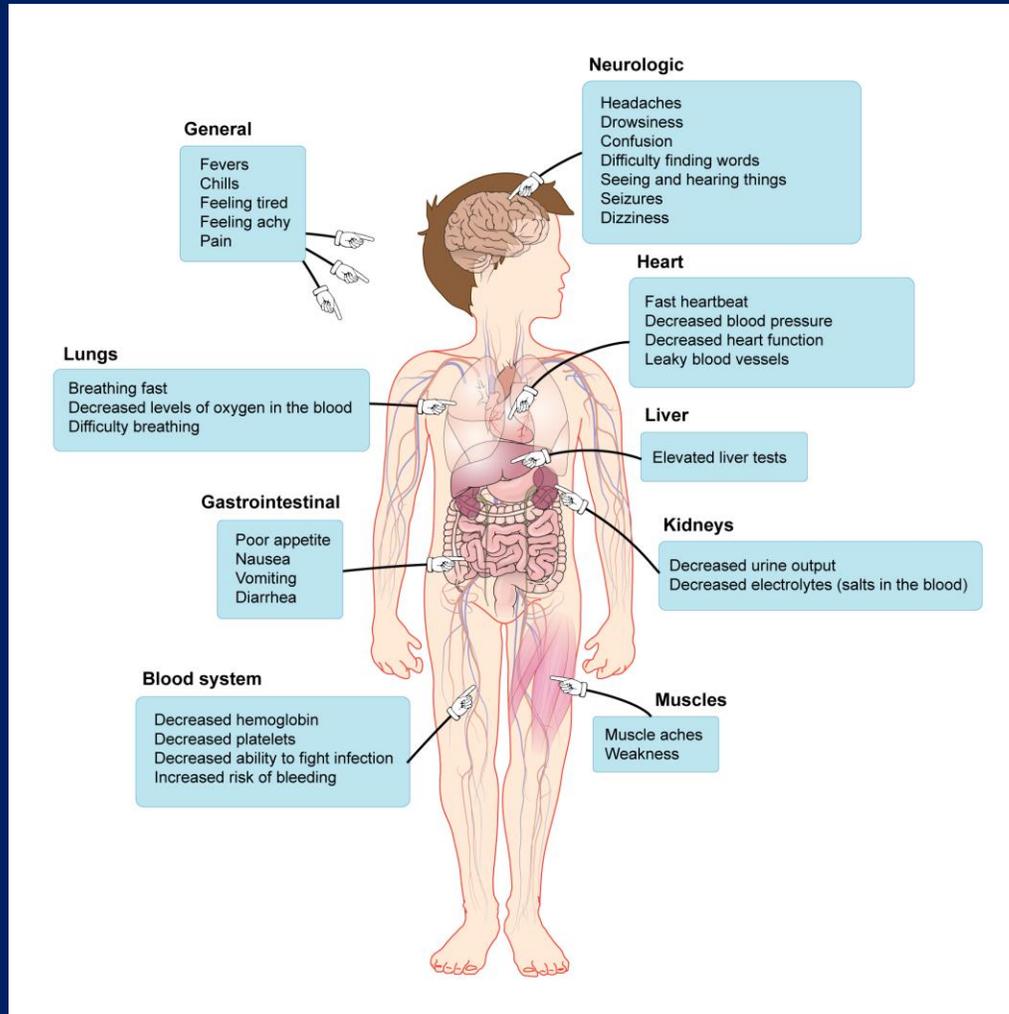


Phase I Study of Anti-CD22 CAR

- Novel CAR construct targeting CD22
- Heavily pre-treated population
- CRS was less severe (Grades 1 and 2)
- Limited neurotoxicity
- Unique toxicities:
 - Capillary leak
 - Coagulopathy
 - Hemolytic uremic syndrome
- 70% Complete remission rate



Cytokine Release Syndrome



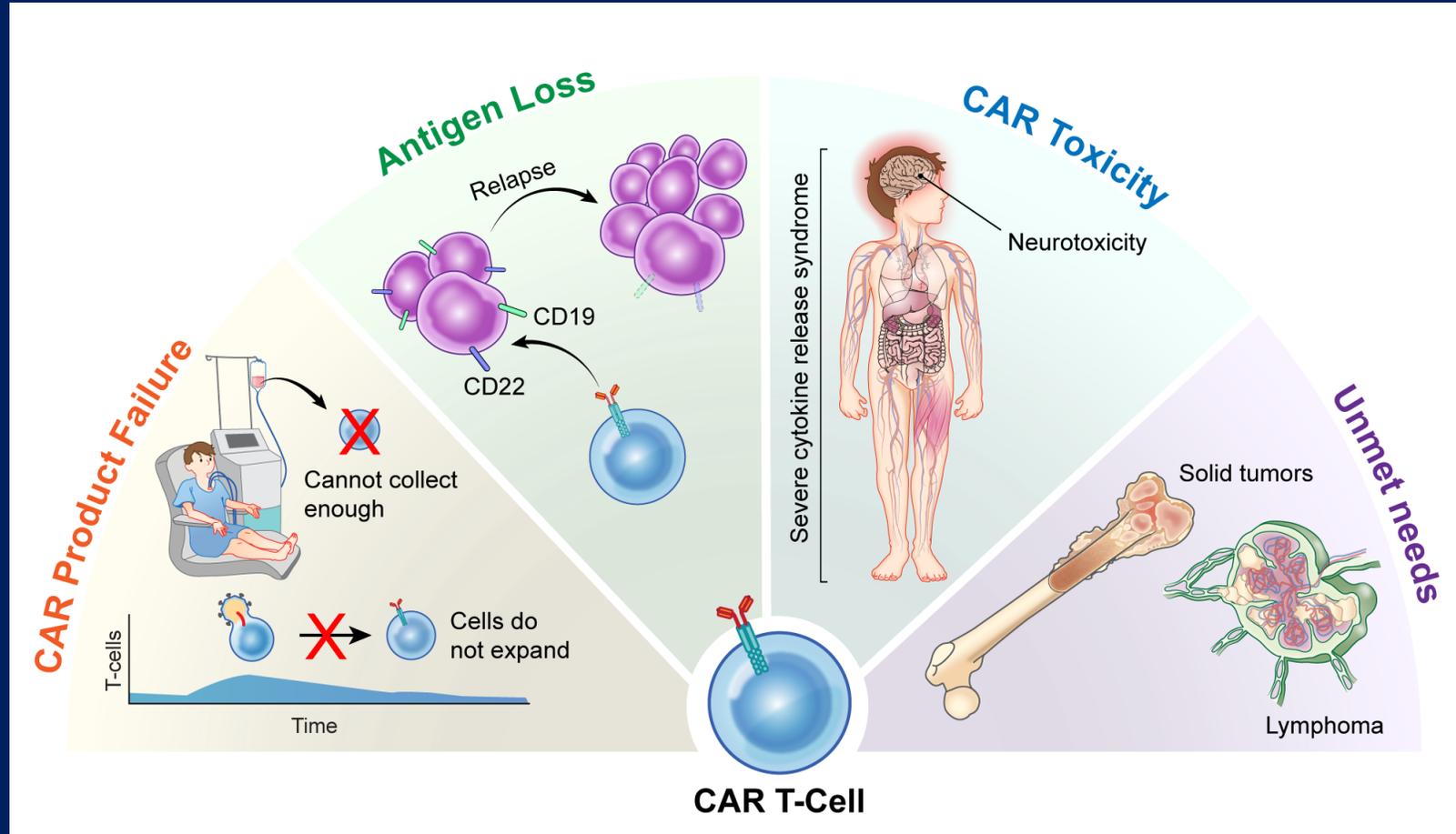
Images, Courtesy of NIH Medical Arts

Lee/Mackall Lancet 2015

CAR Therapies: FDA Approval

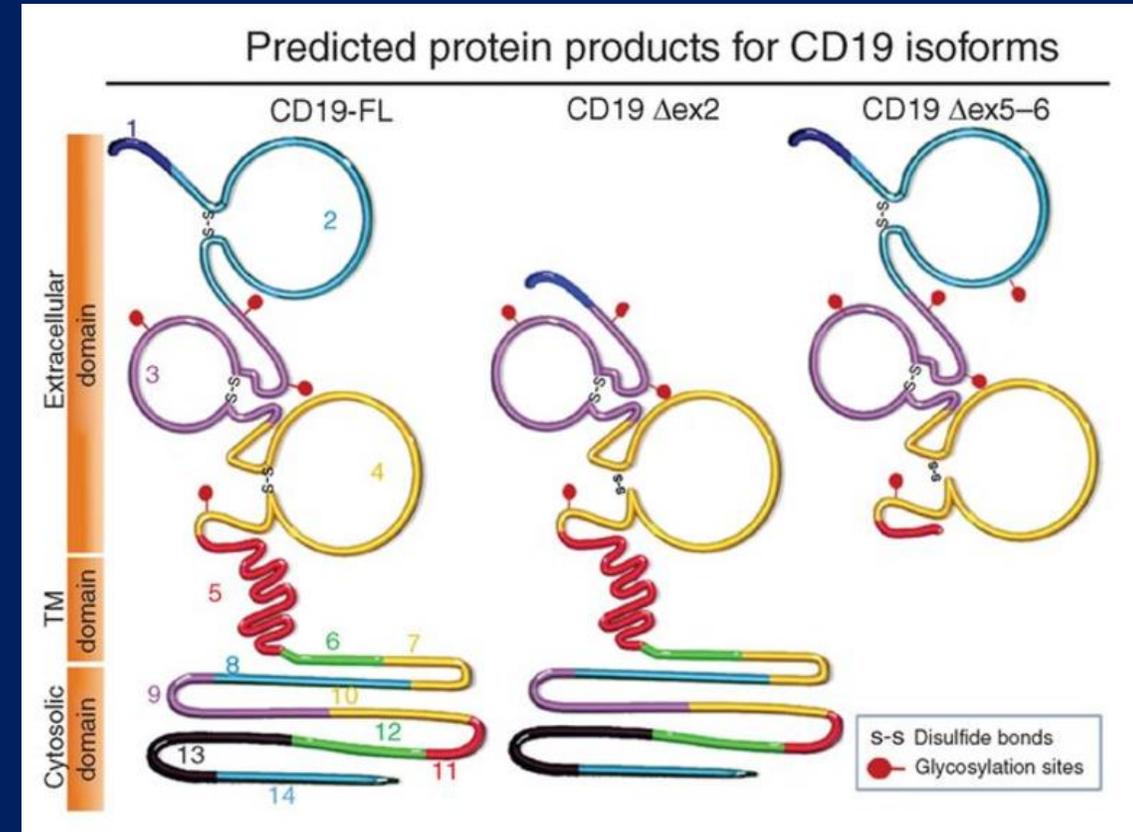
- Kymriah™ (tisagenlecleucel, Novartis): For children up to age 25 with ALL (August 2017)
- Tocilizumab: To treat CAR T-cell related CRS (August 2017)
- Yescarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)
- **Complete remission rates: +/- 50-80%**

Limitations to Durable Remissions



Oh Where... Oh Where... Has my CD19 gone?

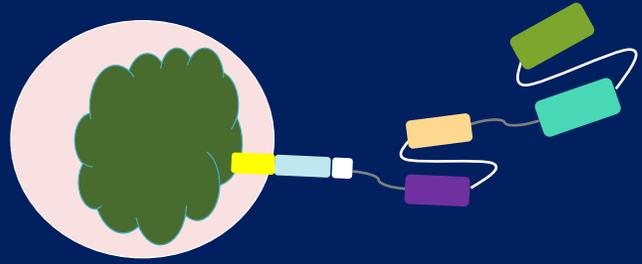
- At least ONE identified mechanism:
 - Loss of the surface epitope, but retention of the target protein (in part)
 - Due to clustering of nonsense and missense mutations in exon 2 of CD19
 - Specific frameshift mutation eliminates full-length CD19 but allows expression of an isoform
 - Mostly cytosolic and hidden from T cells
 - Hallmark of relapsed leukemia post CAR was lack of the full-length isoform



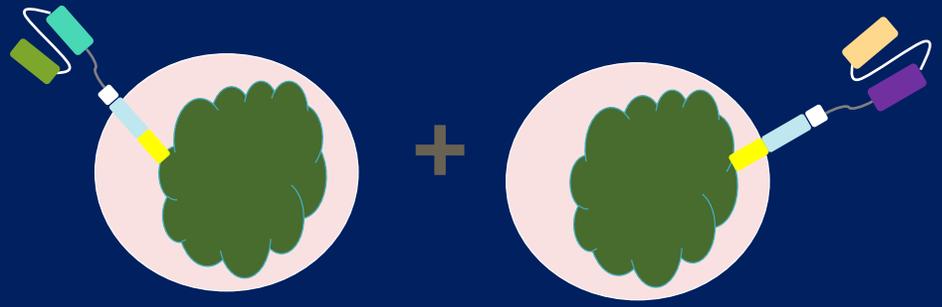
Lineage Switch (ALL → AML)

- *MLL*-rearranged B-ALL (11q23) rearrangement
 - “Infant” ALL → VERY poor prognosis
- Gardner et al.
 - 7 of 7 with *MLLr*-ALL attained MRD neg CR post –CD19 CAR
 - Relapses seen in 2 with myeloid phenotype
- Similar experience seen in *MLLr*-ALL treated with blinatumomab
- Jacoby et al.
 - CD19 CAR immune pressure induces lineage switch

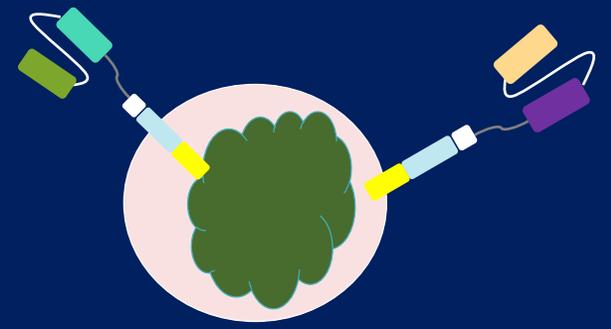
Options for Simultaneous Targeting of CD19 and CD22 (Fry Lab)



Bivalent-Bispecific Receptor



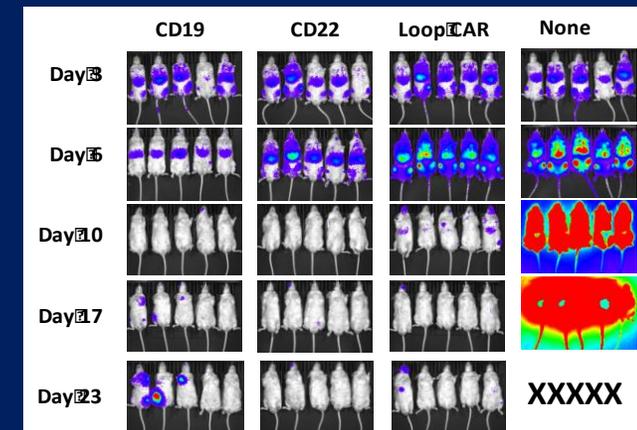
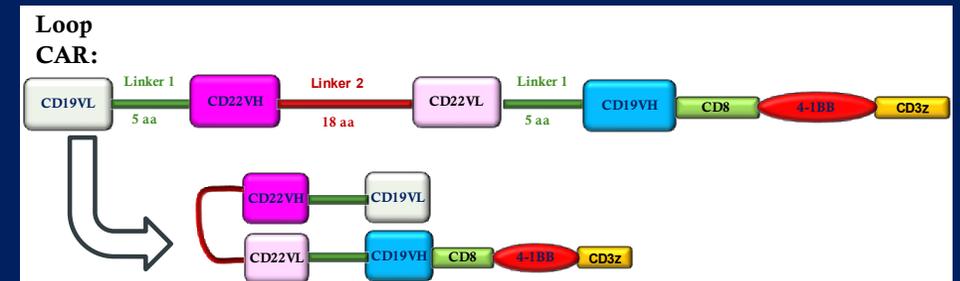
Co-administration



Co-expression

Phase 1 Dose Escalation Study of Anti-CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B Cell Malignancies

- Hypothesis: Simultaneous targeting of CD19 and CD22 could diminish the risk of antigen loss escape
- Novel bivalent, bispecific CAR to be tested in the clinic
- Actively enrolling



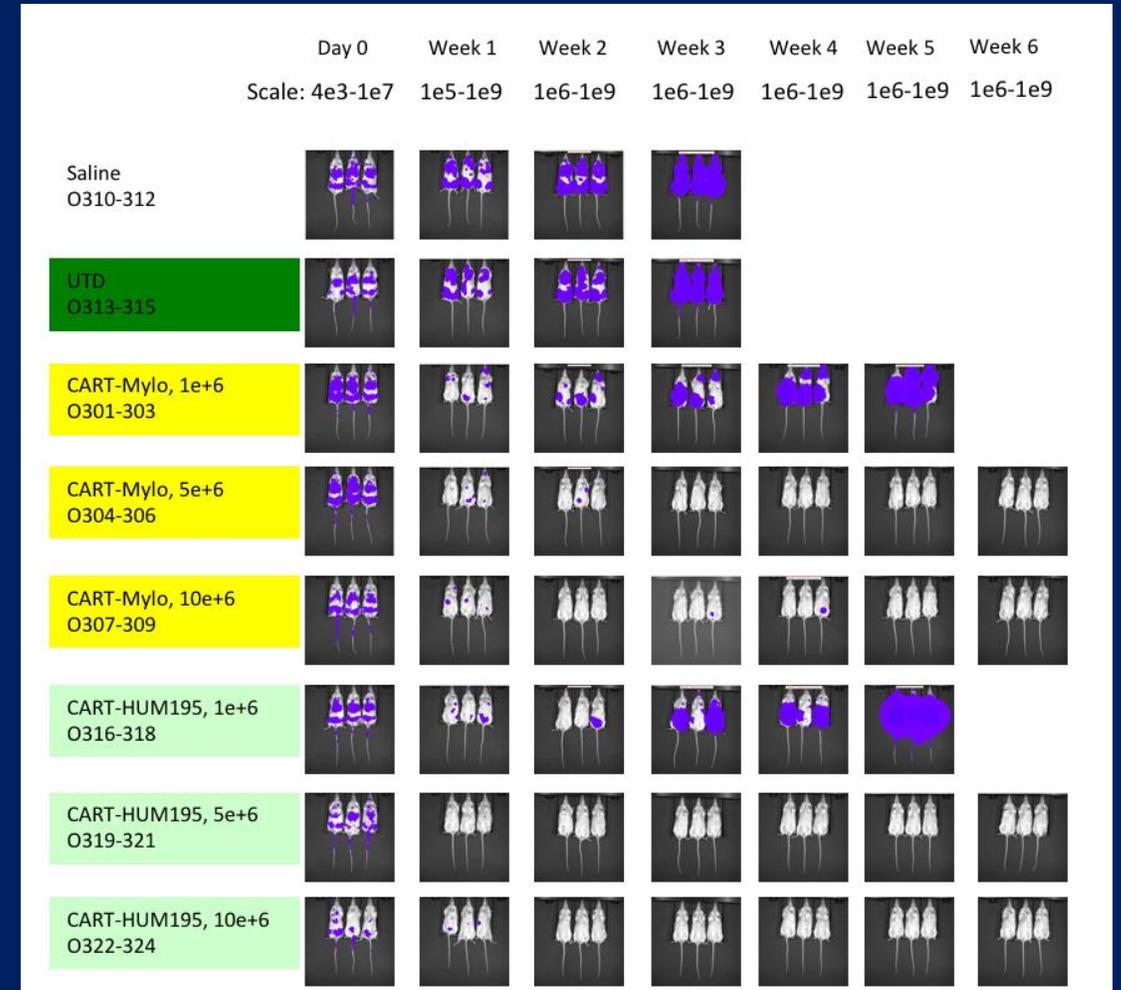
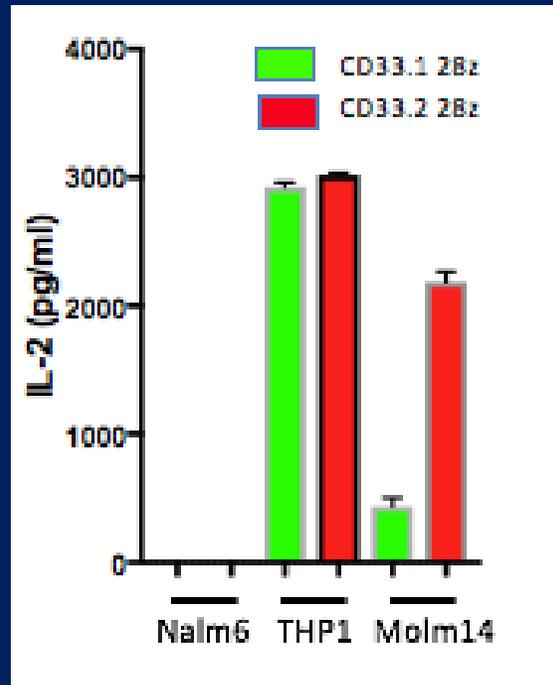
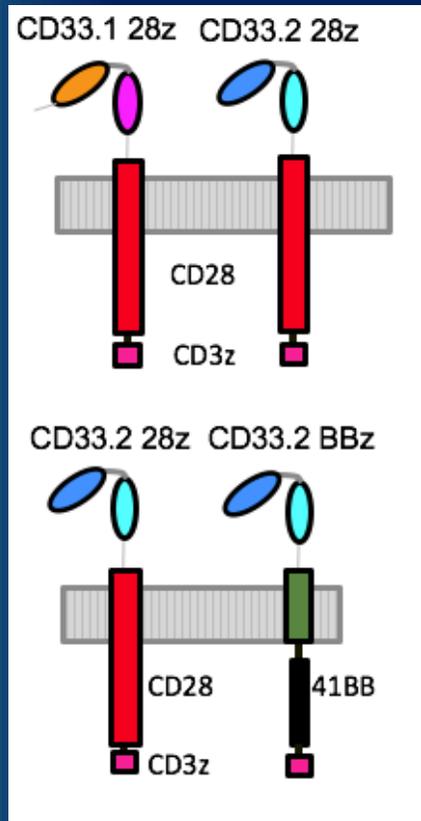
Activity of Bispecific CAR:
In vivo activity against CD19+/22+ B-ALL

CD33 Validated Target in AML

- Gemtuzumab ozogamicin: FDA approved anti-CD33 conjugated antibody
 - Highly effective in AML
 - Risk of sinusoidal obstruction syndrome
- Lintuzumab: Anti-CD33 monoclonal antibody (SGN-33)
- Pre-clinical development for CAR construct performed in the Fry Lab

Pre-Clinical Data for CD33 CAR

(Fry Lab-NCI/Tasian Lab-CHOP)



Protocol Proposal and Logistics

- CD33 CAR as a bridge to HSCT
- Limited Site Multi-Center Study
 - NCI POB
 - Children's Hospital of Philadelphia
 - (+ CHLA, Seattle, Denver, Boston)
- Scientific Collaboration
 - Vector funding and manufacturing provided by CHOP
 - Plan for Uo1 Application
 - Multi-center interest for correlative biology
- Phase I Dose Escalation Study
 - Utilizes 3+3 design
 - Slow accrual in first year
- IND to be held by RCI-BMT
 - Clinical trials infrastructure support of the CIBMTR
- Trial sponsored by the PBMTC with St. Baldrick's Funding
- **Anticipating Enrollment Fall 2019**



Future Directions

- Novel CAR constructs:
 - AML CAR
 - Bi-specific CAR
- Optimizing second infusions
- Improving CAR persistence
- Increasing tumor sensitivity by enhancing antigen expression
- Bringing CAR constructs earlier into the therapeutic plan
- Exploring response in lymphoma and CNS disease
- Decreasing toxicity
- Improving access to therapy

Acknowledgements

- Terry J. Fry
- Brigitte Widemann
- John Glod
- Haneen Shalabi
- Bonnie Yates
- Cindy Delbrook
- Maryalice Stetler-Stevenson
- Constance Yuan
- Leah Hoffman
- Pamela Wolters
- Crystal L. Mackall
- Daniel "Trey" Lee
- Rimas Orentas
- Richard Aplenc
- Sarah Tasian
- Steve Highfill
- David Stroncek
- Haiying Qin
- Naoza Collins-Johnson
- Staci Martin
- Lori Wiener
- Sima Zadeh
- Joan Galil
- Kamille West
- Cathy Cantilena
- Paul Jarosinski
- Nursing



A special thanks to all our patients, particularly those who are no longer with us, their families and referring teams. Their memory lives on in our work.