Adoptive Cell Therapy vs. Bispecific Antibodies

Society for Immunotherapy of Cancer 2016

Crystal L Mackall MD
Professor of Pediatrics and Medicine
Associate Director, Stanford Cancer Institute

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Presenter Disclosure Information

Crystal L Mackall MD

The following relationships exist related to this presentation:

Consulting: Adaptimmune, Glaxo-Smith-Kline, Servier/Pfizer, Unum, Vor; Ownership interest: Unum; Royalties: Juno

Antibody Based Immunotherapies: B Cell Malignancies

- First antibody to demonstrate unequivocal antitumor activity was Rituximab in NHL (Blood 1997)

RAPID COMMUNICATION

IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma

By David G. Maloney, Antonio J. Grillo-López, Christine A. White, David Bodkin, Russell J. Schilder, James A. Neidhart, Nalini Janakiraman, Kenneth A. Foon, Tina-Marie Liles, Brian K. Dallaire, Ken Wey, Ivor Royston, Thomas Davis, and Ronald Levy

- First bispecific antibody to demonstrate unequivocal antitumor activity was Blinatumomab in B-ALL (Topp et al, J Clin Onc 2011)

VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

- First chimeric antigen receptor based therapy to demonstrate unequivocal antitumor activity was CD19-CAR in NHL (Blood 2010)

Plenary paper

B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells

James N. Kochenderfer,[1] Mark E. Dudley,[2] Steven A. Feldman,[2] Wyndham H. Wilson,[3] David E. Spaner,[4] Irina Maric,[5] Maryalice Stetler-Stevenson,[6] Giao Q. Phan,[2] Marybeth S. Hughes,[2] Richard M. Sherry,[2] James C. Yang,[2] Udai S. Kammula,[2] Laura Devillier,[2] Robert Carpenter,[1] Debbie-Ann N. Nathan,[2] Richard A. Morgan,[2] Carolyn Laurencot,[2] and Steven A. Rosenberg[2]

Factors Enabling Effective Mab Based Immunotherapy for B Cell Malignancies

- Exquisite knowledge of the cell surface landscape
- Several developmental antigens with high level cell surface expression expressed homogeneously on the malignant population
- Tolerable off-tumor, on-target effects
- ? Permissive microenvironment
  - Speculation fueled by higher response rates with CAR-T cells for B-ALL compared to lymphoma
  - We know very little about the microenvironment of leukemia or lymphoma and how it compares to solid tumors

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Which Immunotherapy Agent? Blinatumomab vs CD19-CAR T Cells

- **TOTAL ABSENCE OF RANDOMIZED CONTROLLED TRIALS THEREFORE CLEAR DATA IS NOT AVAILABLE**
- Toxicity: no clear distinction between modalities
  - Cytokine Release Syndrome
    - Largely related to disease burden
    - Managed safely in most cases using standardized grading and treatment algorithms
    - Emerging data suggest that prevention or preemptive strategies may diminish risk
    - Less risk when CD19 directed immunotherapy in the setting of low burden
  - Neurotoxicity
    - Usually reversible
    - Biology remains poorly understood
    - 3 Fatal events reported with CAR were restricted to specific combination of a unique preparative regimen with a unique CAR
- Ease of administration/availability: Blinatumomab
  - Short half-life is amenable to controlling delivery in the response to toxicity

CD19-Targeted Immunotherapies for B-ALL: Response Rates Across Trials

Agent	Population	N	CR Rate	MRD Only Enrolled	Reference
BLINA	Ph-, primary refractory or relapsed ALL adult	189	43%	Unknown	Topp et al., Lancet Oncology 2014[24]
BLINA	Adults >65 R/R B-ALL	261	47%	Unknown	Kantarjian et al., Cancer 2016[9]
BLINA	Pediatric R/R ALL	31	31%	Unknown	Gore et al. ASH abstract 2014[4]
BLINA	Pediatric R ALL	9	44%*	Unknown	Schlegel et al., Hematologica 2014[3]
BLINA	Primary refractory or relapsed ALL adult	36	69%	No	Topp et al., JCO 2014[25]
CAR-T 4-1BB	Pediatric and adult, R/R ALL	30	90%	Yes	Maude et al., NEJM 2014[19]
CAR-T CD28	Pediatric R/R ALL	20	70%	Yes	Lee et al., Lancet 2015[2]
CAR-T CD28	R/R B cell ALL	16	88%	Yes	Davila et al., STM 2014[5]
CAR-T 4-1BB	Adults R/R B cell ALL	29	93%	Yes	Turtle et al., JCI 2016[26]
CAR-T	Adults R/R B-ALL	32	91%	Yes	Park et al, ASCO abstract 2015[28]
CAR-T	Pediatric R/R B-ALL	37	91%	Unknown	Turtle et al., ASCO abstract 2015[29]
CAR-T 4-1BB (HUMANIZED)	Pediatric R/R B-ALL	6	50%	Unknown	Maude S, ASH abstract, 2015 [27]

INTENT-TO-TREAT

Davis and Mackall, 2016

Which Immunotherapy Agent? Blinatumomab vs CD19-CAR T Cells

- Toxicity: likely equivalent
- Ease of administration/availability: Blinatumomab
- Response rate
  - Data incomplete due to lack of randomized trials
  - Higher reported response rates to CD19-CAR in single arm studies
  - Care must be taken interpreting response rates reported that are not intent-to-treat
- Tissue trafficking
  - CAR-T cells traffic efficiently to CNS
  - CAR-T may also traffic to testes
  - Tissue trafficking of Blinatumomab less clear
- Durability of effect
  - Blinatumomab has very short half life
  - No clear evidence of induction of persisting anti-leukemic immune responses?
  - How durable are CAR based responses?

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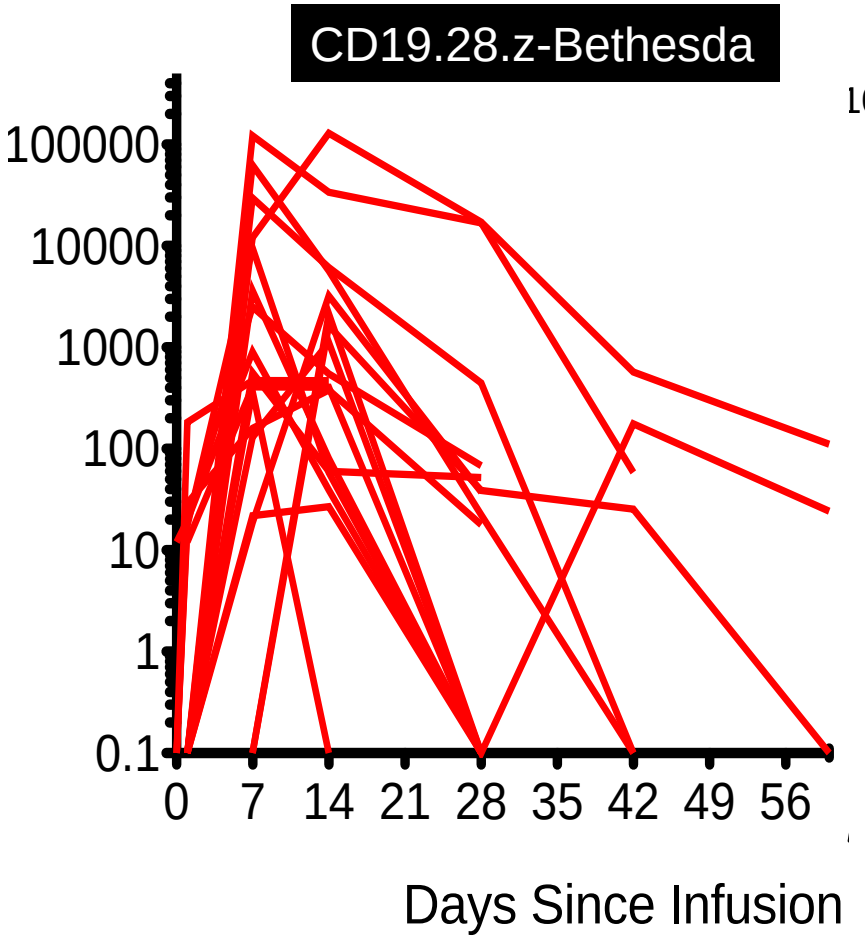
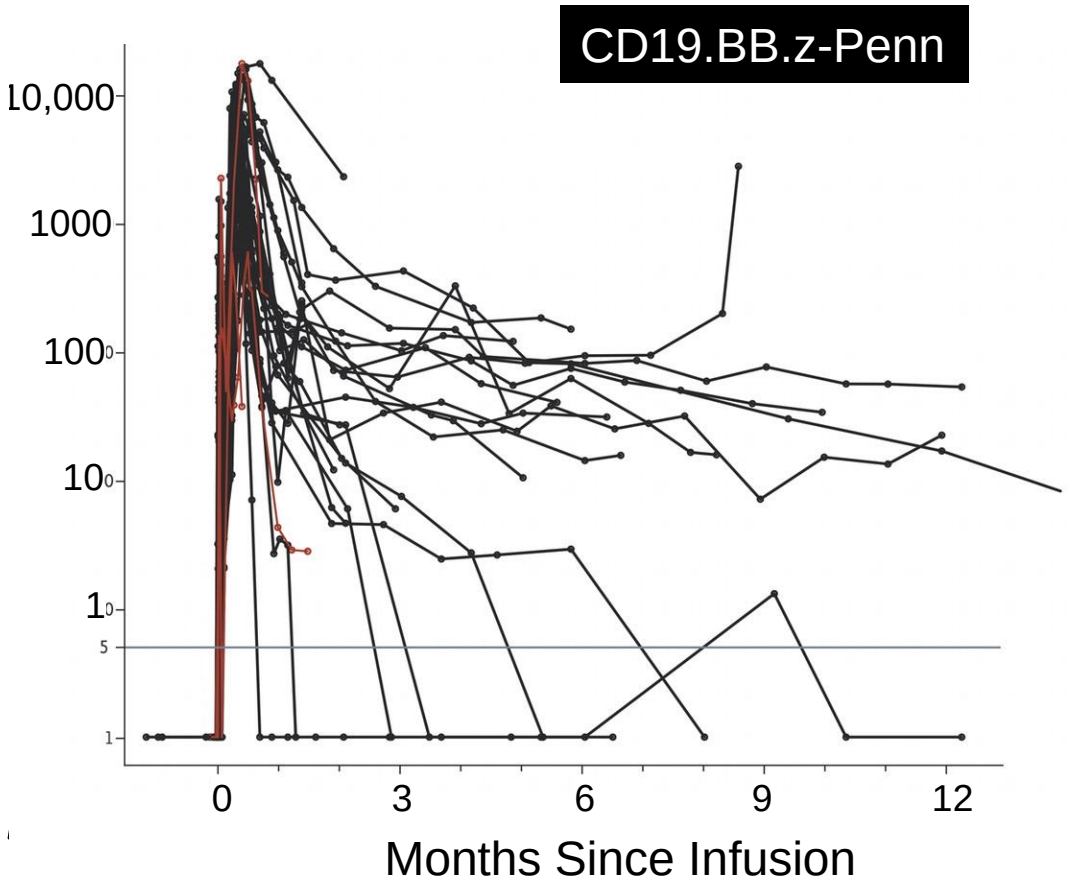
Differential Immunokinetics of CD19.28.z vs CD19.BB.z CAR in Clinical Trials

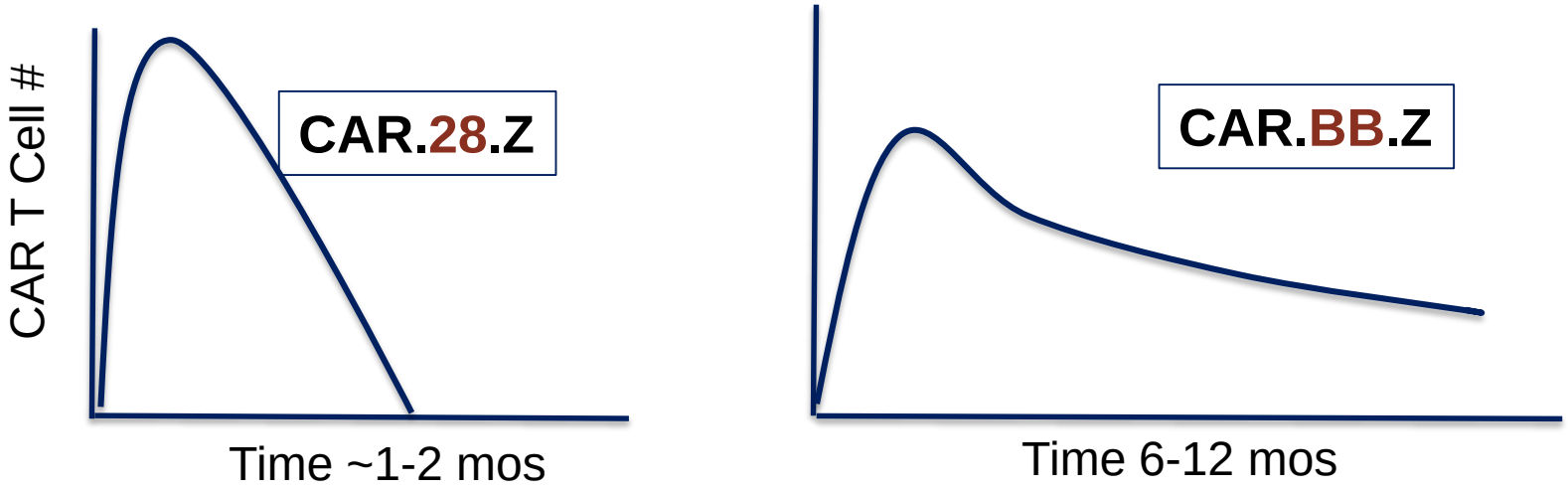




Lee, Lancet, 2014

Maude, NEJM, 2014

4-1BB Containing CARs Not Infrequently Persist for Several Months



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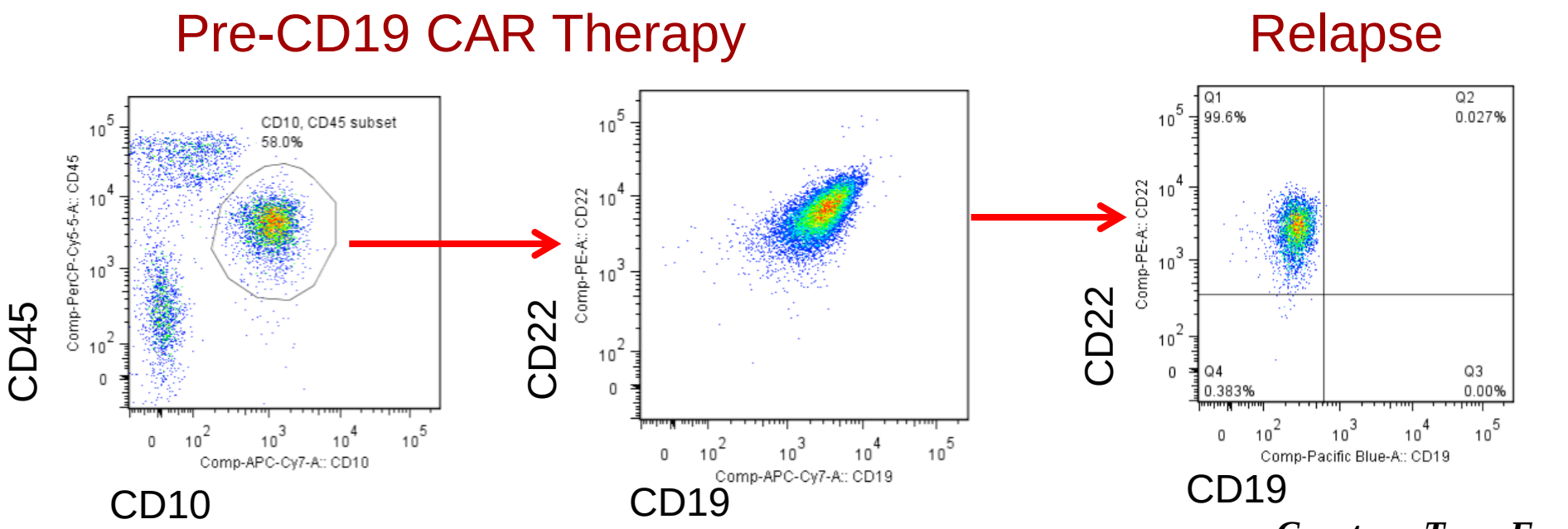
Immunotherapy for B-ALL: State-of-the-Field 2016

- Successes have already resulted in FDA approval of blinatumomab for adult and pediatric B-ALL. Approvals expected for CD19-CAR in 2017.
- Patterns of clinical usage will emerge as treating physicians develop more experience with these agents, larger studies become available and CAR-T cells become more widely available.
- How best to incorporate these therapeutics into up front or second-line therapies?
  - Require large studies primarily driven by disease-specific experts and/or cooperative groups
- Success of Immunotherapy for B cell malignancies has provided a treasure trove of opportunities to advance the larger field of immunotherapy
  - Standardization of supportive care regimens for cytokine release syndrome
  - Development of approaches to commercialize cell therapies
  - What distinguishes responders from non-responders?
  - **What are the patterns of resistance?**

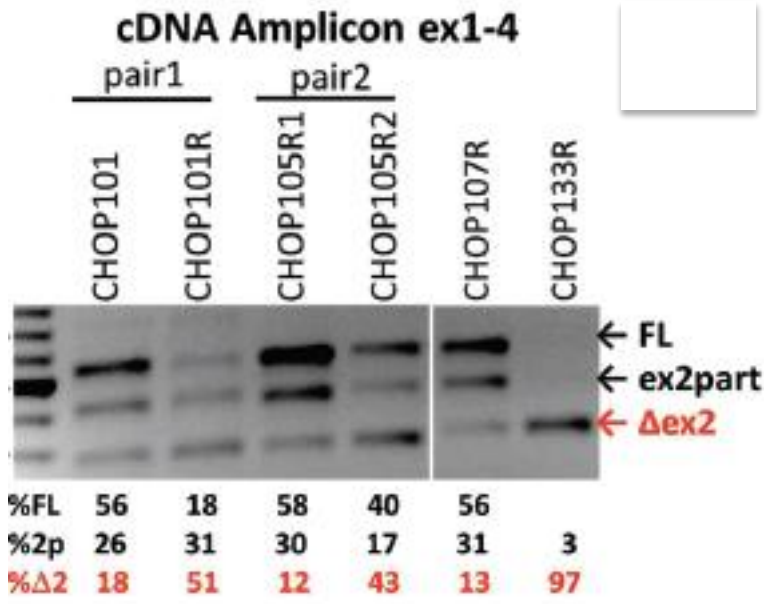
Antigen Loss Escape is a Primary Cause of Acquired Resistance Following CD19-Based Immunotherapy

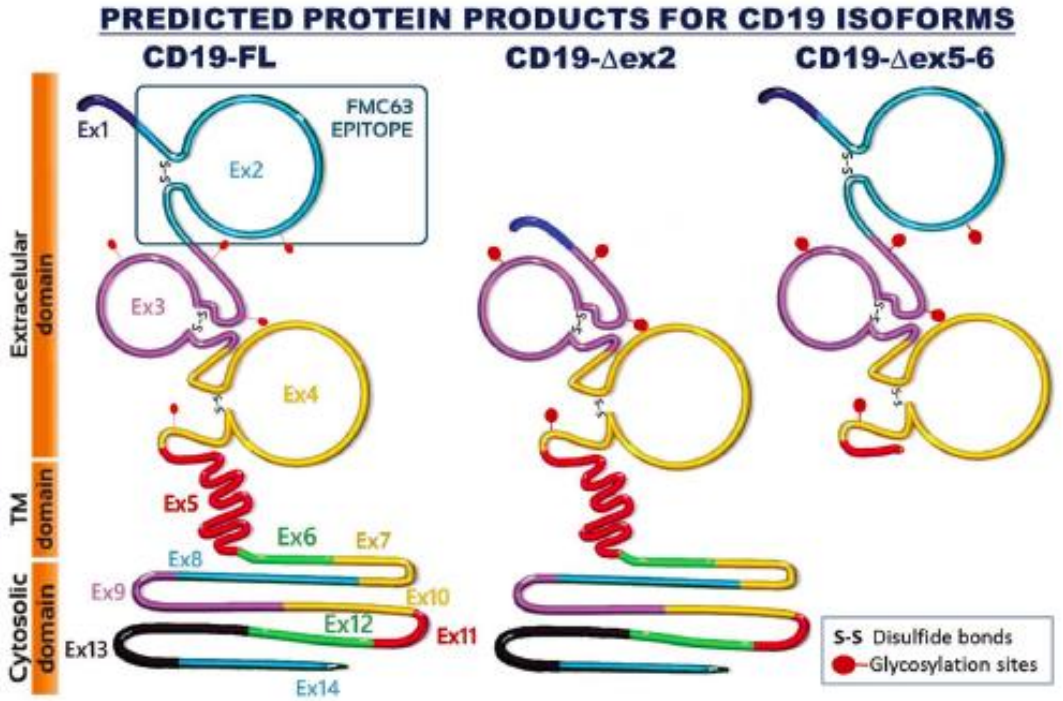


Courtesy Terry Fry
Mary Alice Stetler-Stevenson

- ✓ ***Observed following both Blinatumomab and CD19-CAR***
- ✓ ***Occurs in at least 30% of CD19-CAR responders***
- ✓ ***Most common cause of relapse following 4-1BB containing CD19-CARs***

Resistance via Isoform Switch
Increased CD19 Isoforms Lacking the Immune Targeted Epitope





Sotillo et al, Cancer Discovery, 2015

- ✓ *true incidence unknown due to short follow-up*
- ✓ *incidence increases as therapeutic potency of the T cells is increased*
- ✓ *unknown whether patients predisposed to this can be identified pre-therapy*
- ✓ *unknown whether CD19– B-ALL has increased therapeutic vulnerability*

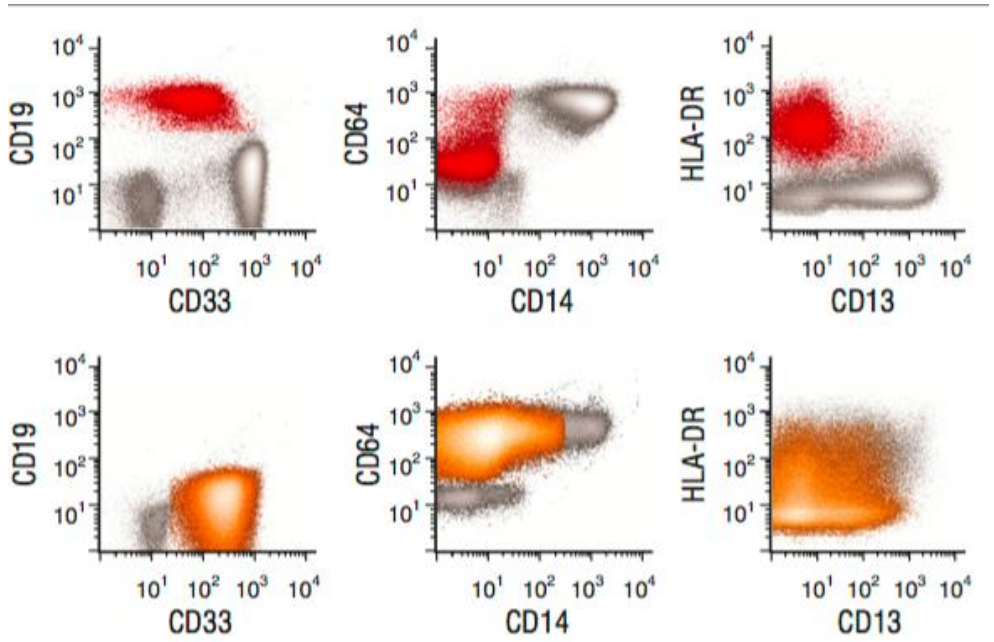
Resistance via Lineage Switch: Emergence of Myeloid Leukemia Following CD19-CAR

May 2016

Acquisition of a CD19-negative myeloid phenotype allows immune escape of *MLL*-rearranged B-ALL from CD19 CAR-T-cell therapy

Rebecca Gardner,[1,2] David Wu,[3] Sindhu Cherian,[3] Min Fang,[3] Laïla-Aïcha Hanafi,[4] Olivia Finney,[1] Hannah Smithers,[1] Michael C. Jensen,[1,2] Stanley R. Riddell,[4,5] David G. Maloney,[4,5] and Cameron J. Turtle[4,5]

[1]Seattle Children's Research Institute, [2]Department of Pediatrics, and [3]Department of Laboratory Medicine, University of Washington, Seattle, WA; [4]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; and [5]Department of Medicine, University of Washington, Seattle, WA

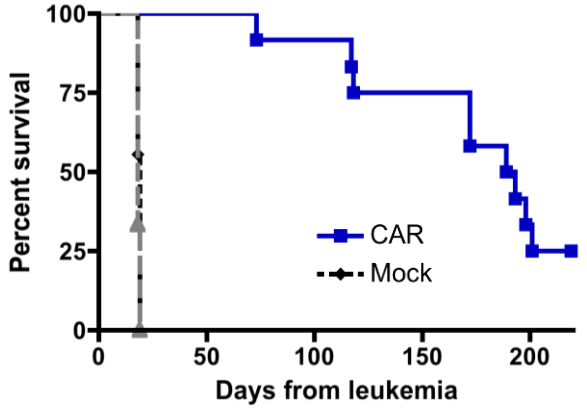


Red: Pre-CD19-CAR
Orange: Post-CD19-CAR

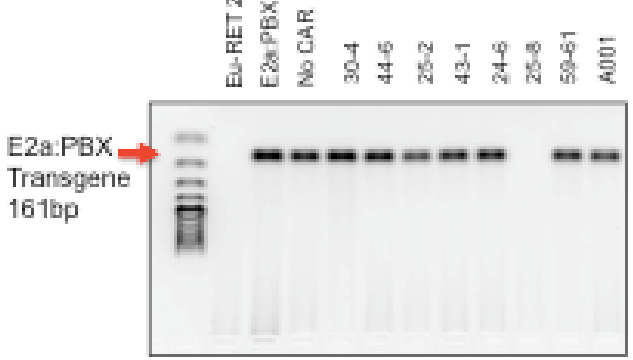
- *appears less common than isoform switch*
- *likely occurs with higher frequency in more primitive B-ALL subtypes (e.g. MLL rearranged)*

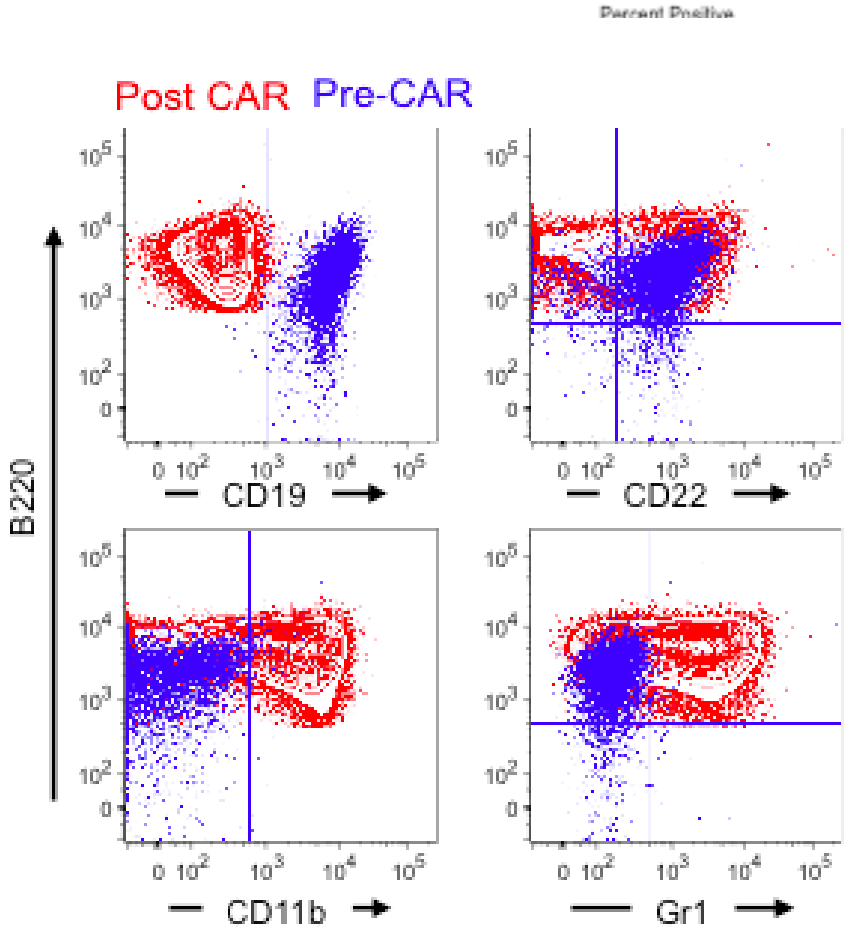
Resistance via Lineage Switch: CD19-CAR in Murine Model of B-ALL Drives Emergence of Myeloid Leukemia Following CD19-CAR

E2A-PBX Model of Murine ALL Treated with Murine CD19-CAR



All Mice Eventually Die Due to E2A-PBX+ Leukemia





Jacoby et al, Nat Comm, 2016

CD19 Loss Escape in B-ALL: The Canary In the Coal Mine

- CD19 is a near perfect target for mAb based therapy
  - ✓ Pro: Expressed at high density
  - ✓ Pro: Expressed on 99.9999% of cells
  - ✓ Pro: Not expressed on other vital tissues
  - ✓ Con: Not required for cell survival
- Immune pressure on one antigen alone will lead to selection of antigen negative variants with high frequency, over time
- Antigens targeted thus far in solid tumors show greater heterogeneity in antigen expression
  - ✓ Typically expressed at lower densities across a greater range
  - ✓ Often not expressed in 99.9% of cells
- As mAb based therapeutics become more potent (mAbs, bispecifics, CARs), multi-antigen targeting will become increasingly important for effective disease control

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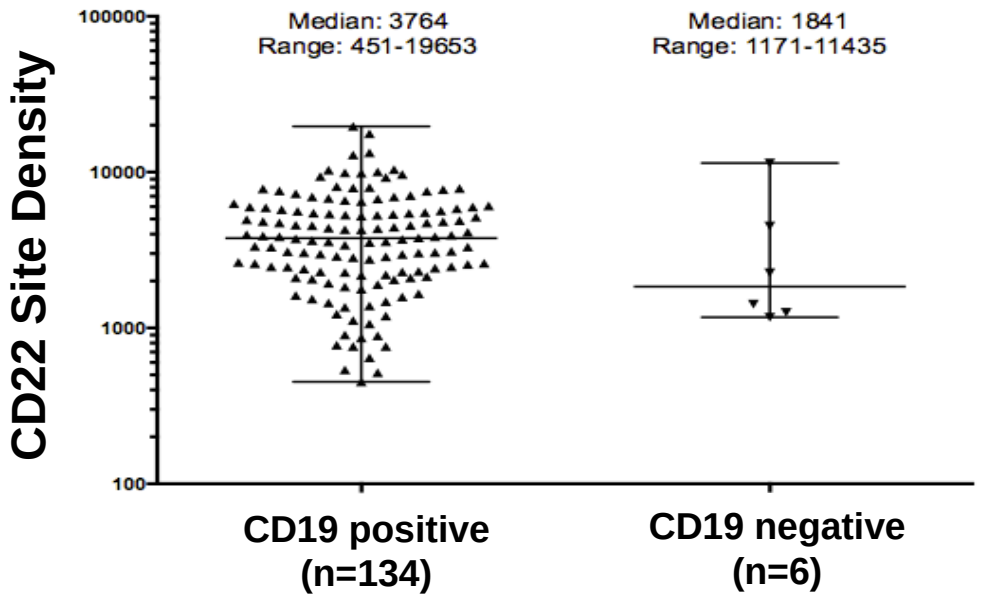
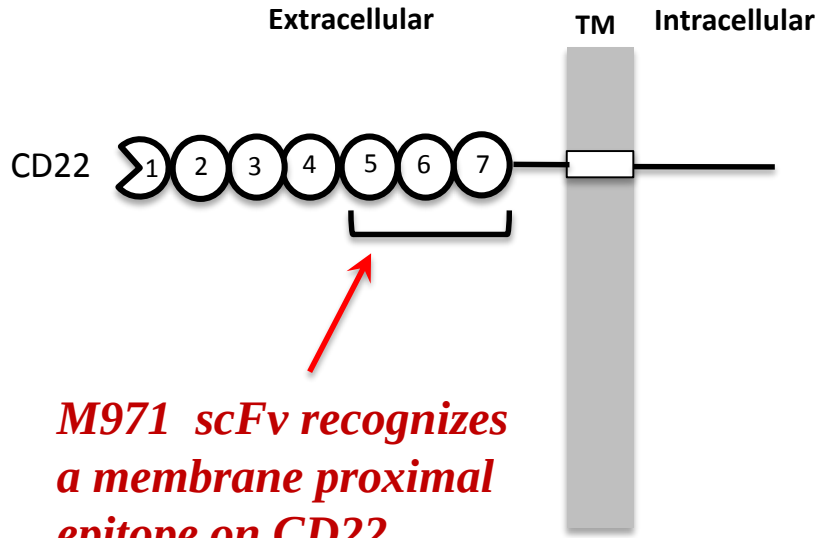
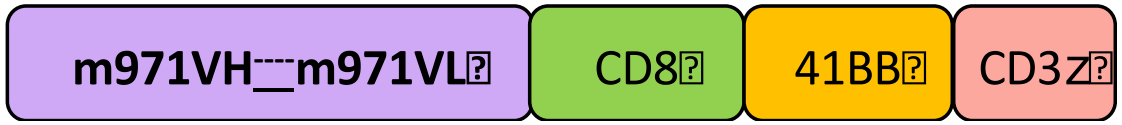
CD22 Is Ubiquitously Expressed on B-ALL, Including Most CD19⁻ Leukemias Emerging Following Immunotherapy

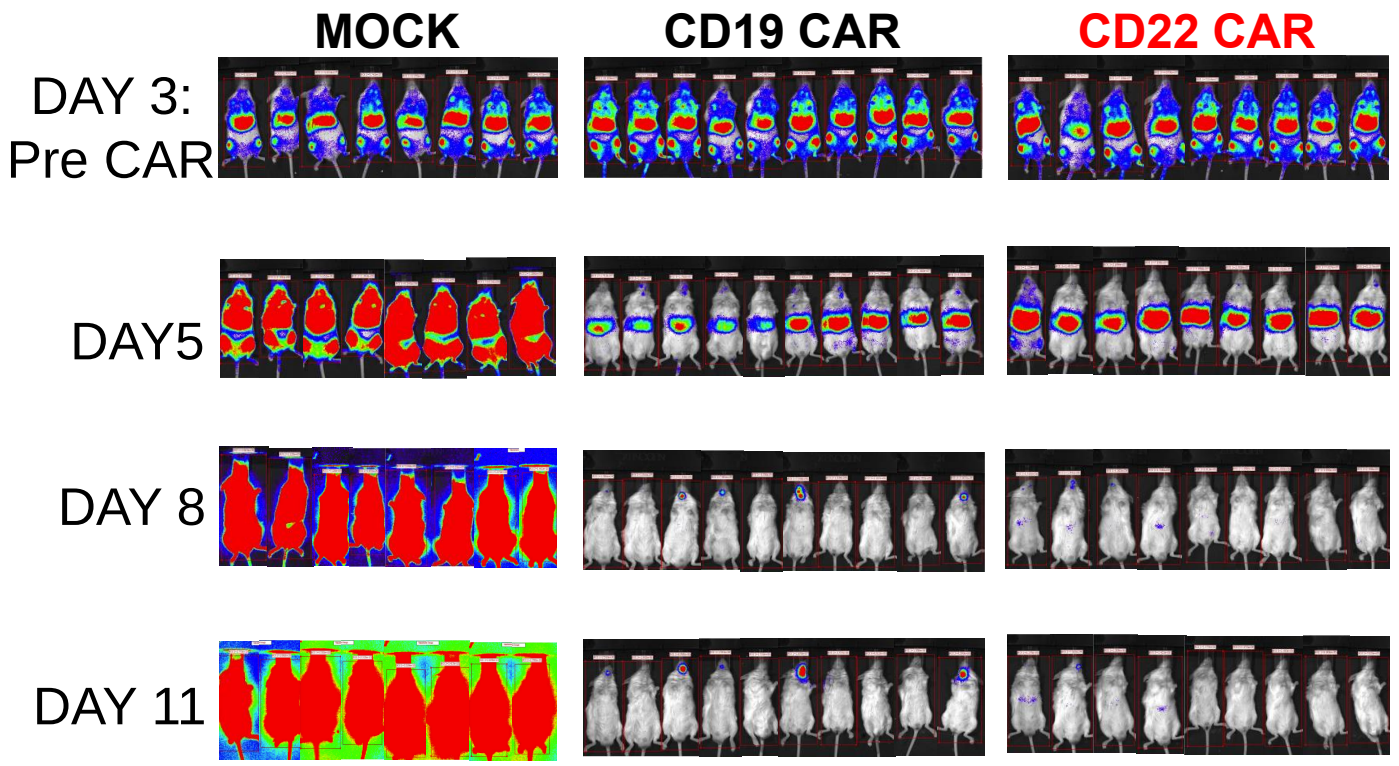




Generation and Optimization of a CD22 CAR, Haso et al, Blood 2013



CD22-CAR Displays Similar Potency as CD19-CAR Against B-ALL



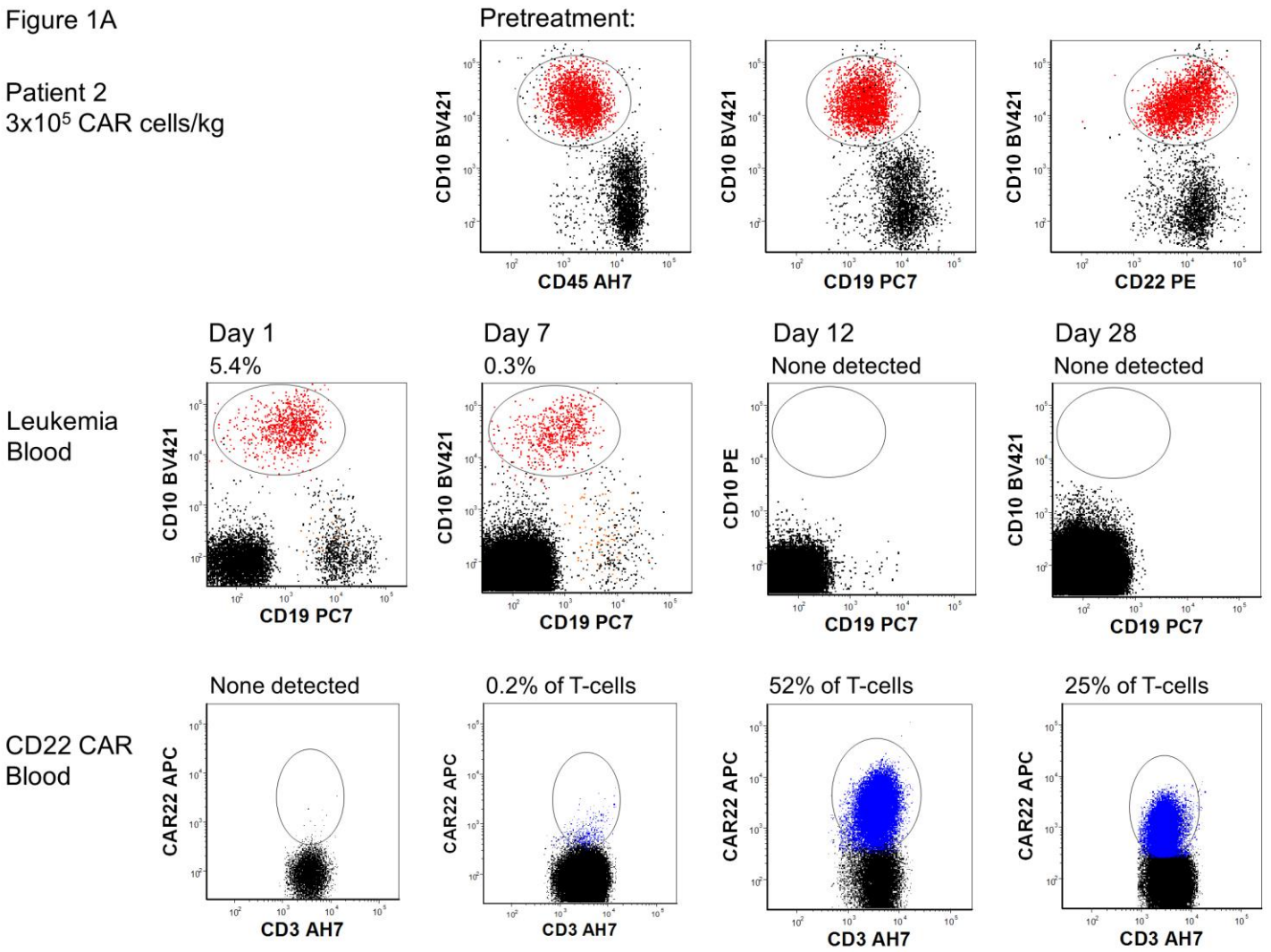
Clinical Trial Initiated At NIH Clinical Center, December 2014

PI: Terry Fry MD

CD22-CAR Induces Remission in CD19-CAR Resistant B-ALL

Figure 1A

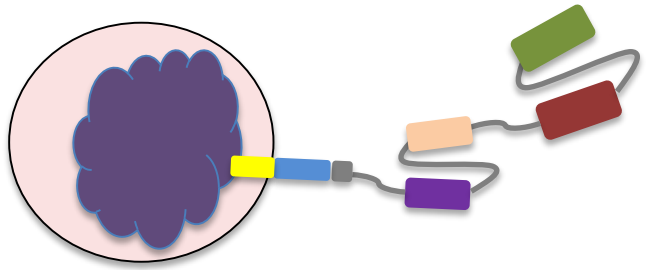
Patient 2
3x10^5 CAR cells/kg



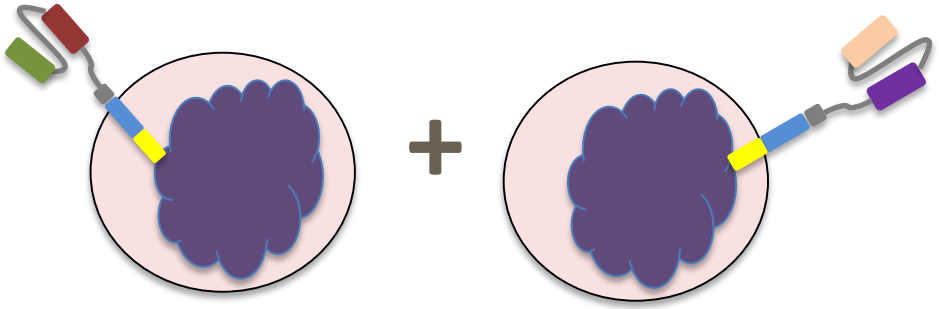
Beyond CD19: Potential Targets for B-ALL

- **CD22**
  - Generally retained on CD19– B-ALL
  - Significant response rate observed with CD22-CAR for CD19-naïve and CD19-resistant B-ALL
  - Full dataset will be presented at ASH 2016
- **TSLPR (*CRLF2*)**
  - Oncogene overexpressed in many high-risk B-ALL
  - CAR targeting TSLPR shows activity in murine models (Qin et al, Blood, 2015)
- **ROR1**
  - ROR1 CAR developed by Riddell and colleagues (Berger, Canc Immunol Res, 2015)
  - ROR1 expressed in ~45% of pediatric B-ALL (Dave, PLoS One, 2012)
- **CD123** (Ruella, J Clin Invest 2016)
  - CD123 expressed on CD19 B-ALL, with retention in most cases of CD19– B-ALL
  - CD123 CAR effectively targeted CD19– B-ALL in preclinical models
  - Mixed populations of CD19-CAR T cells plus CD123-CAR T cells prevented CD19– escape in a murine model using
  - Dual expression of CD19-CAR and CD123-CAR on the same cell led to more potent activity against B-ALL in murine models
  - CD123-CAR previously demonstrated to mediate hematopoieiic toxicity in preclinical models (Gill, Blood, 2014)

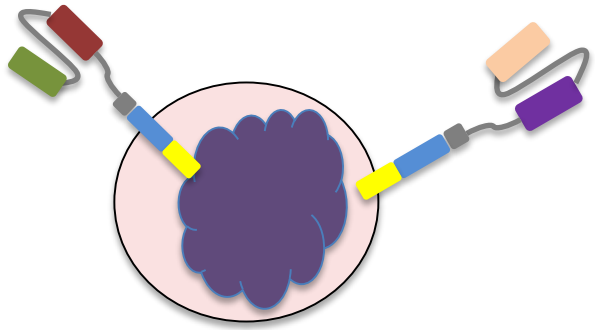
Options for Simultaneous Targeting: Multispecific CARs



Bivalent-Bispecific Receptor



Co-administration



Co-expression

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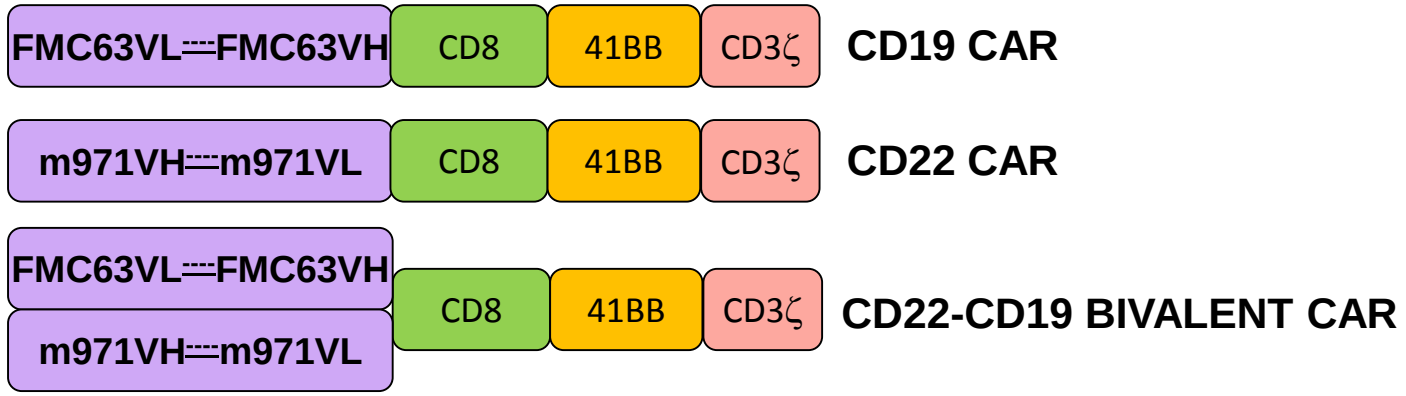
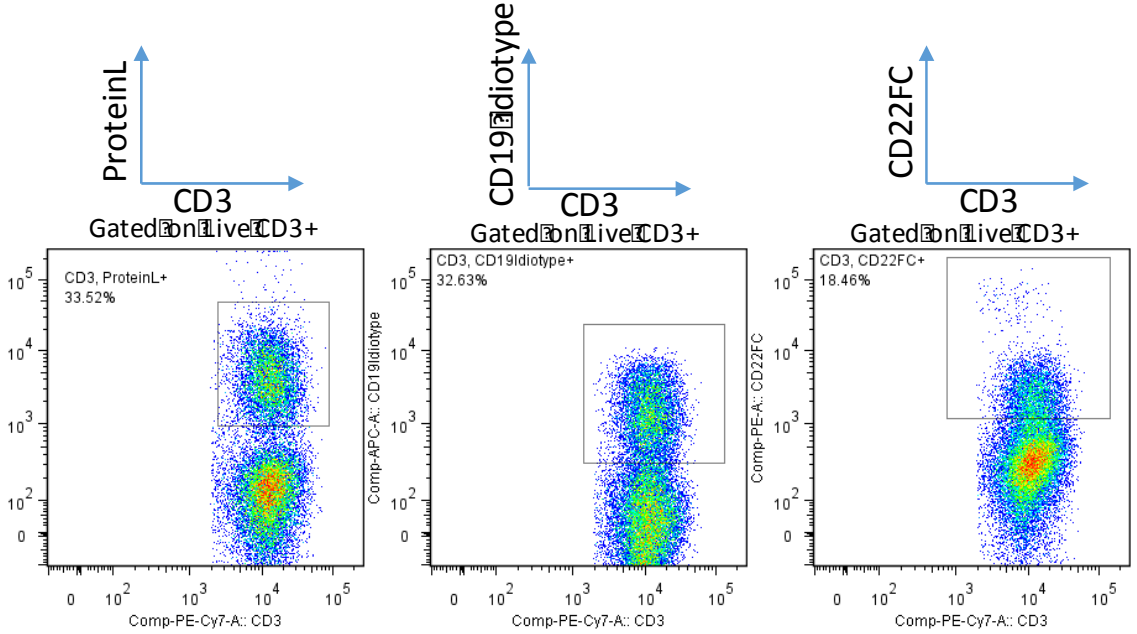
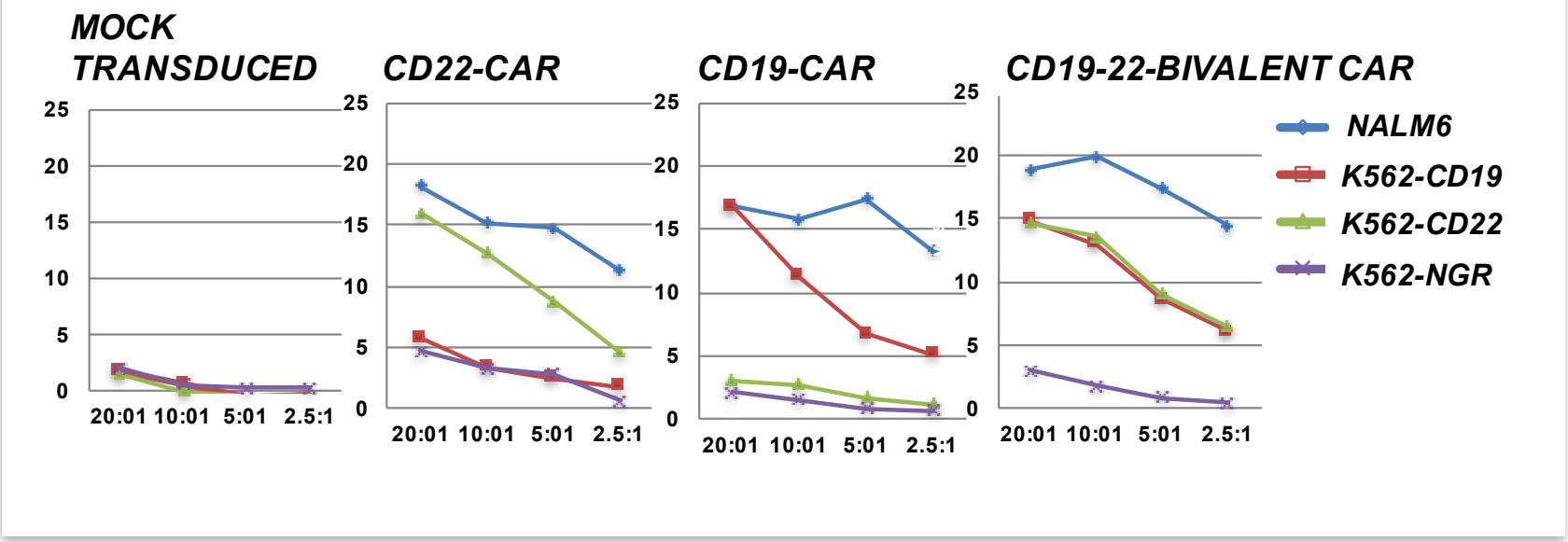
Generation and Optimization of a Bivalent CAR Targeting CD19 and/or CD22



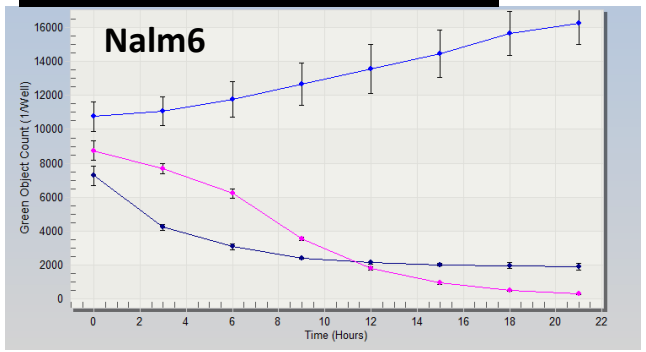


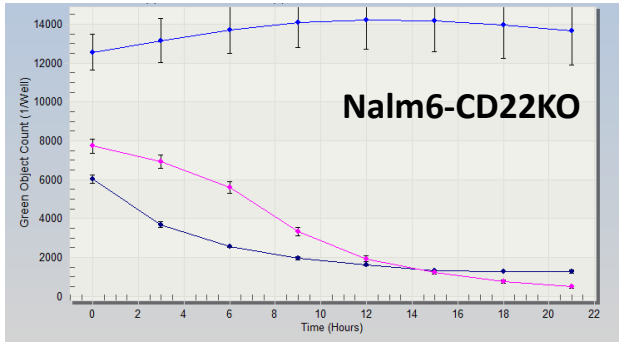
CD19/22 Bispecific CAR Shows Efficient Killing of CD19+CD22+; CD19-CD22+ and CD19+/CD22– B-ALL

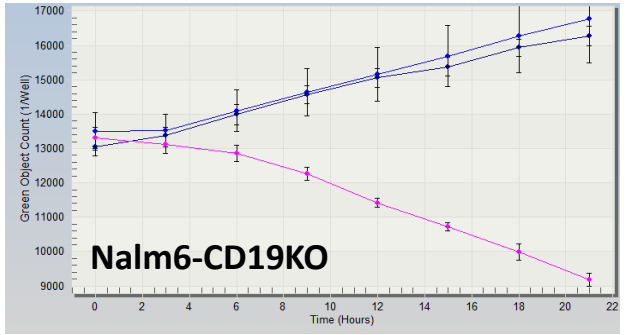
Chromium Release Assay



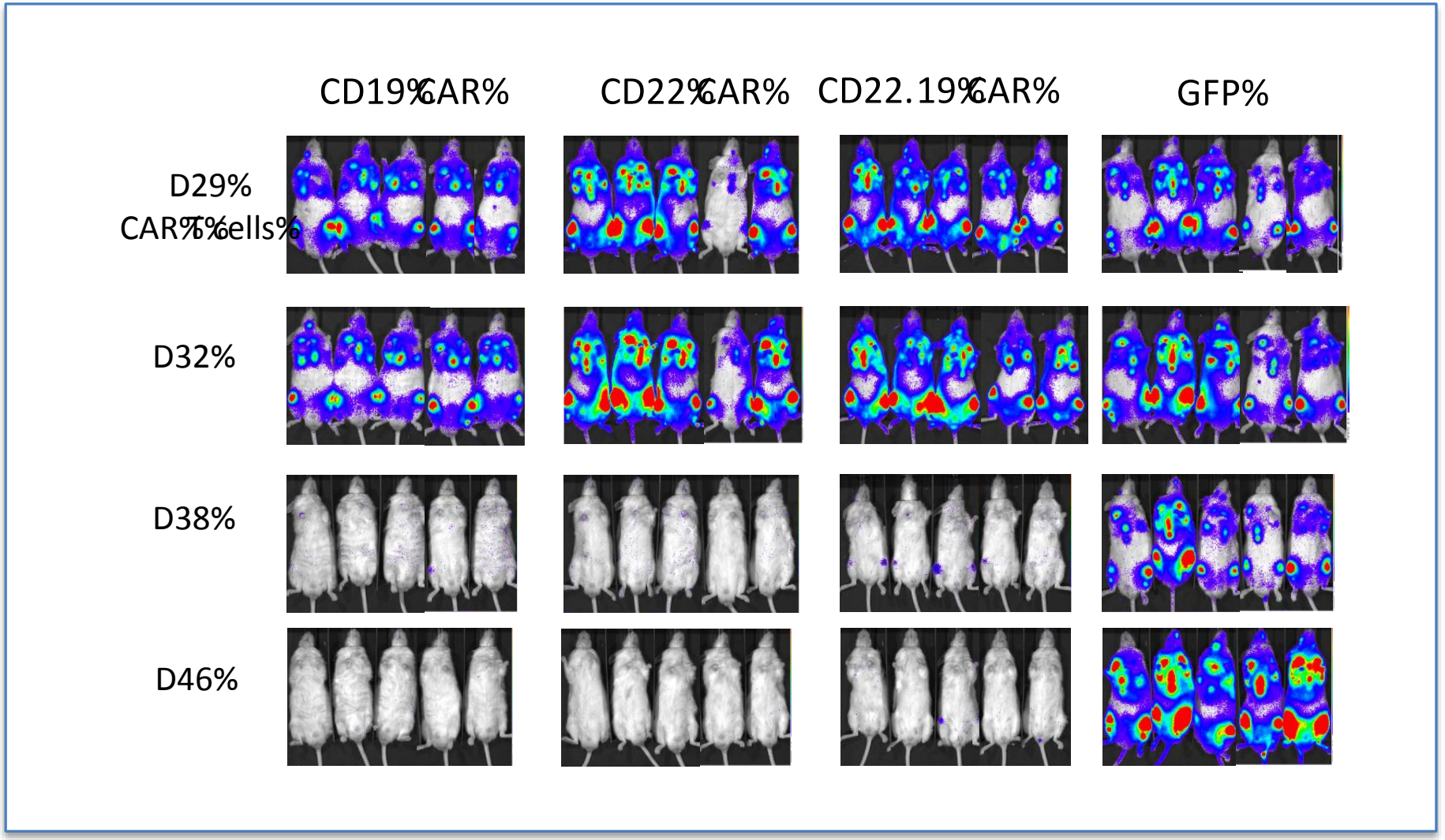
Incucyte Killing Assay







CD19/CD22-Bivalent CAR Mediates Potent Anti-Leukemia Activity in Preclinical Models



Conclusions

- Success of mAb based therapies for B cell malignancies is providing new options for clinical management of these diseases
- Absent randomized controlled trials, physicians are likely to soon be faced with decisions regarding which immunotherapy to deliver: bispecific mAbs vs CAR-T cells
- Antigen loss escape is emerging as a major cause of resistance to CD19-based immunotherapies
  - Likely enhanced by sequential CD19-based therapies
- Next generation CARs are under development that can simultaneously target two antigens
  - Optimal approach to do this is still being defined
- Trials are need to determine whether simultaneous dual antigen targeting can prevent or diminish antigen loss escape

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Acknowledgments

NCI

- Trey Lee
- Terry Fry
- Nirali Shah
- Haiying Qin
- Rimas Orentas
- Waleed Haso

Mackall Lab @ Stanford

- Robbie Majzner
- Samuel Haile
- Sabine Heitzeneder
- Evan Weber
- Rachel Lynn
- Meena Malipatlolla
- Peng Xu
- Kevin Chow
- Cynthia Klein
- Meena Kadapakkam
- Elena Sotillo-Pineiro

THE PATIENTS AND FAMILIES!