UCSF Helen Diller Family Comprehensive Cancer Center

Developing a Dual-Targeting Anti-CD70/Active Integrin β2 CAR-T Therapy for Acute Myeloid Leukemia

National Academies Workshop on Cancer Engineering

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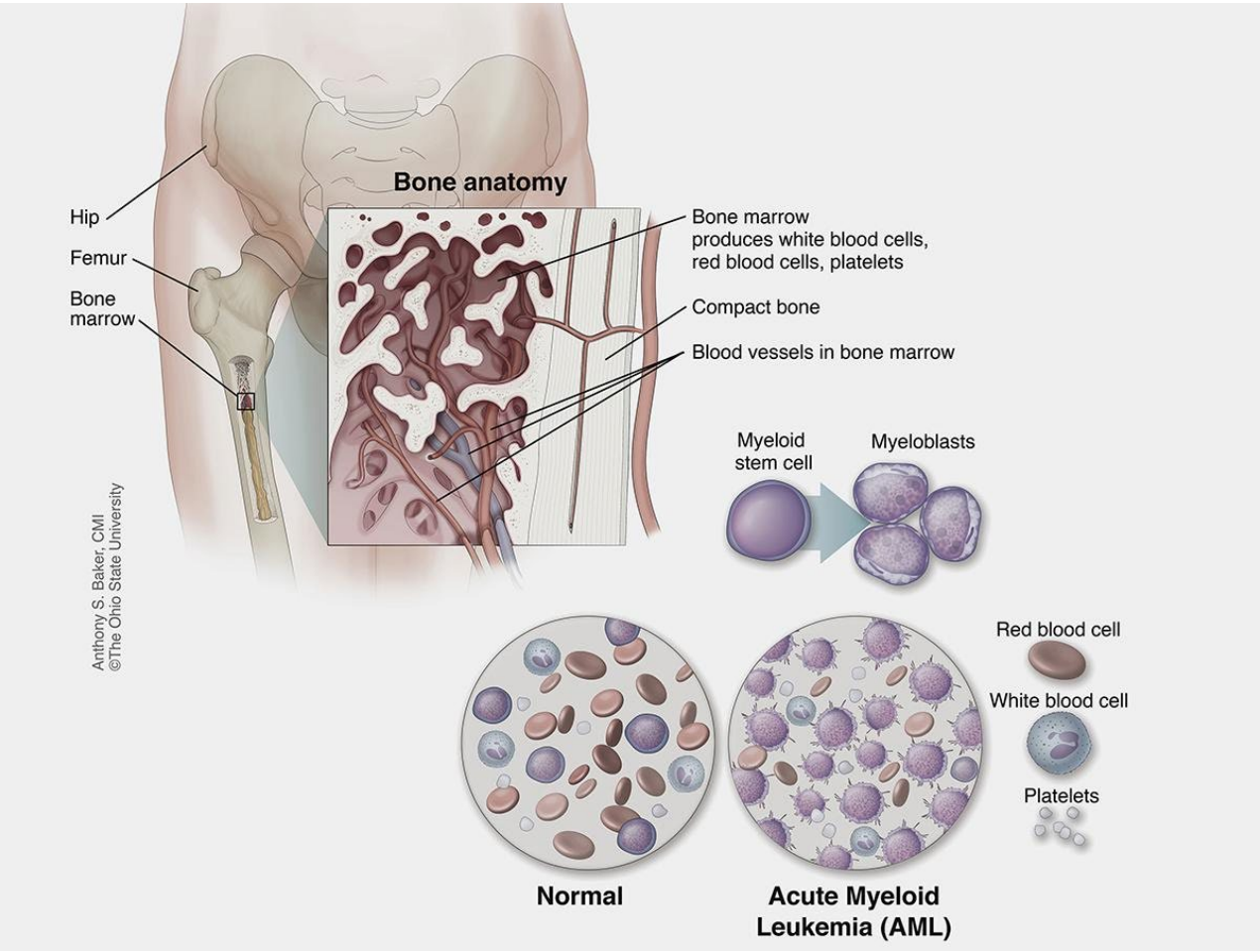
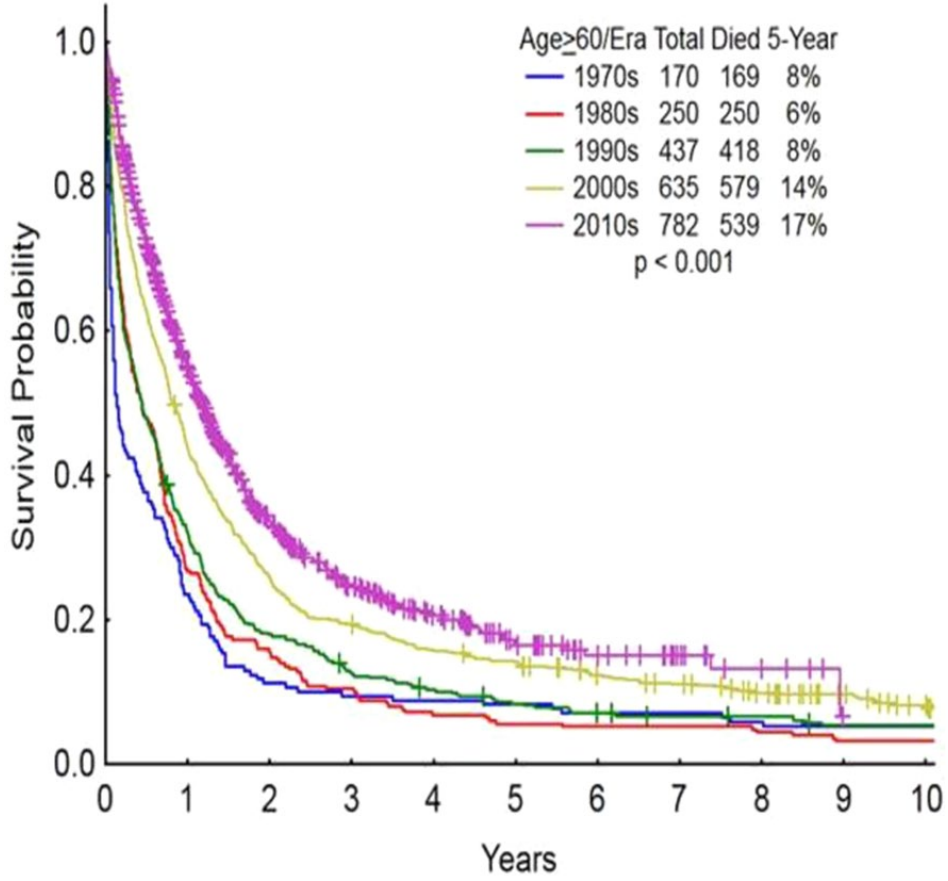
Acute Myeloid Leukemia has a High Clinical Need for New Therapies





OHSU, Kantarjian et al. *Blood Cancer Journal* 2021

Major Challenges for AML CAR-T Therapy

1. High tumor heterogeneity- target selection is difficult
2. High risk of on-target, off-tumor toxicity
3. Immunosuppressive tumor microenvironment

BIOTECH

Death triggers pause of 2seventy CAR-T cell therapy leukemia trial

By **Nick Paul Taylor** · Jun 14, 2023 8:30am

2seventy bio | acute myeloid leukemia (AML) | cell therapy | Cell & Gene Therapy

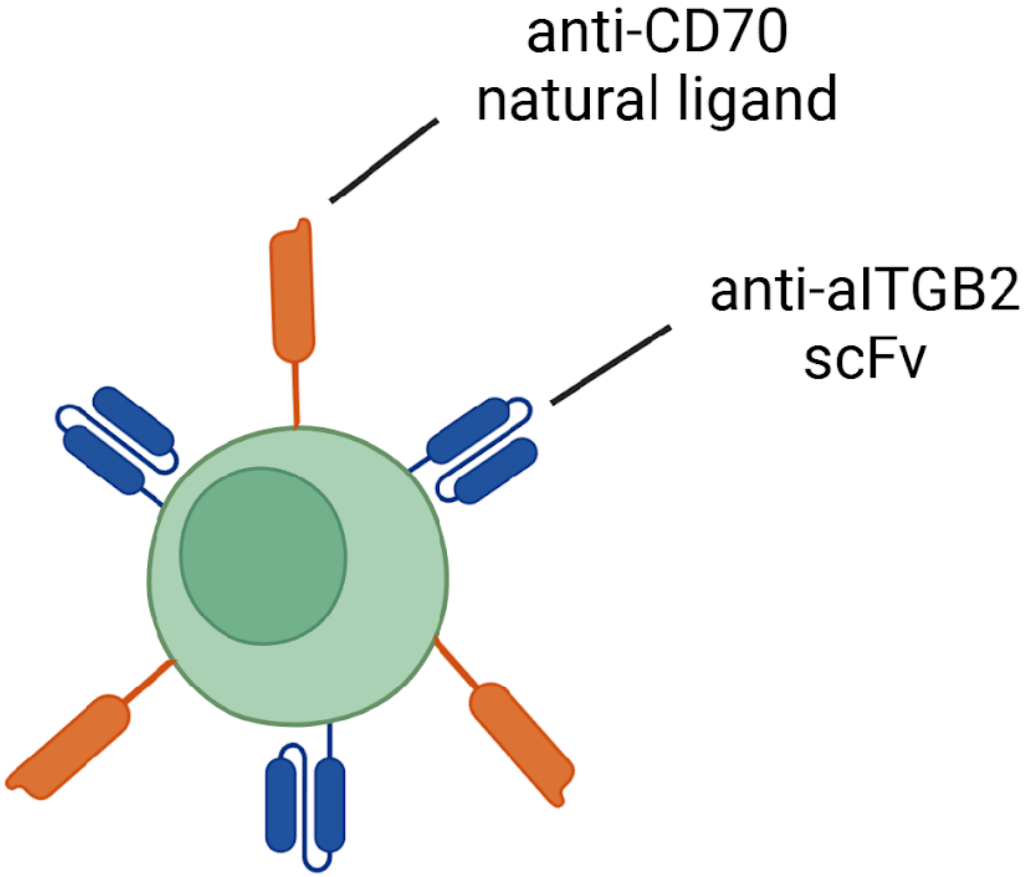
FDA Suspends UCART123 Trials After Patient Death

SEPTEMBER 7, 2017 BY ALICE MELÃO IN NEWS.

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES | NOVEMBER 2, 2023

Cytokine Release Syndrome Results in Reduced AML Killing By CD123 CAR T Cells

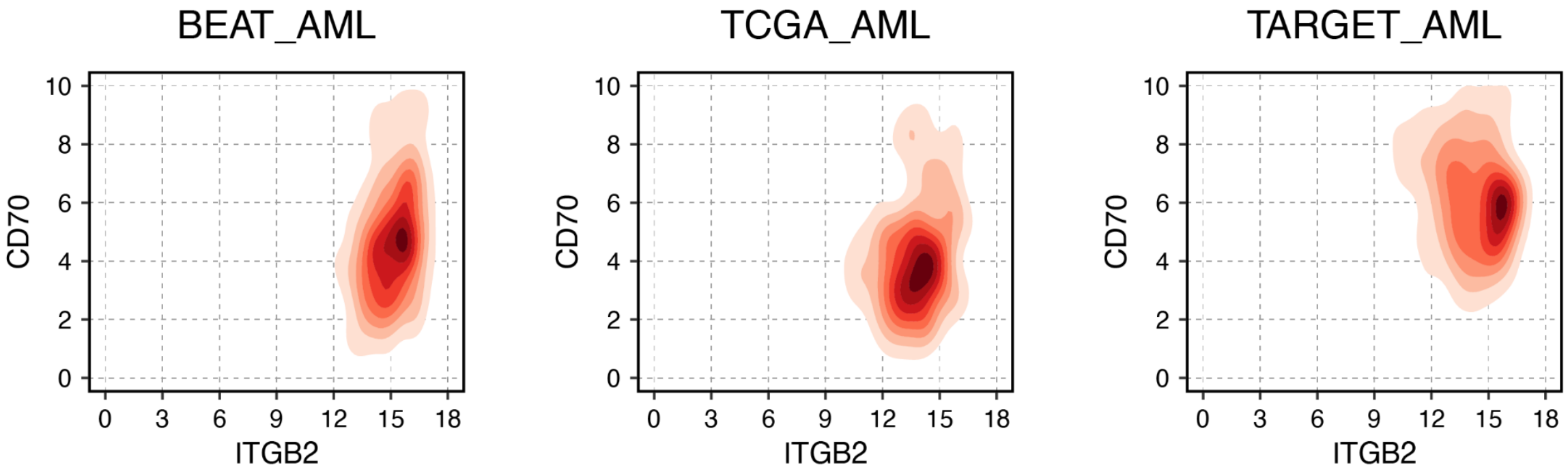
Anand S Bhagwat, Leonel Torres, Olga Shestova, Maksim Shestov, Noelle V. Frey, Elizabeth O Hexner, Selina M Luger, Alison W Loren, Mary Ellen Martin, Shannon R McCurdy, Alexander Perl, Edward A. Stadtmauer, James K. Mangan, Jennifer Brogdon, Joseph A Fraietta, Wei-Ting Hwang, Don L. Siegel, Saad S. Kenderian, David L. Porter, Carl June, Saar Gill



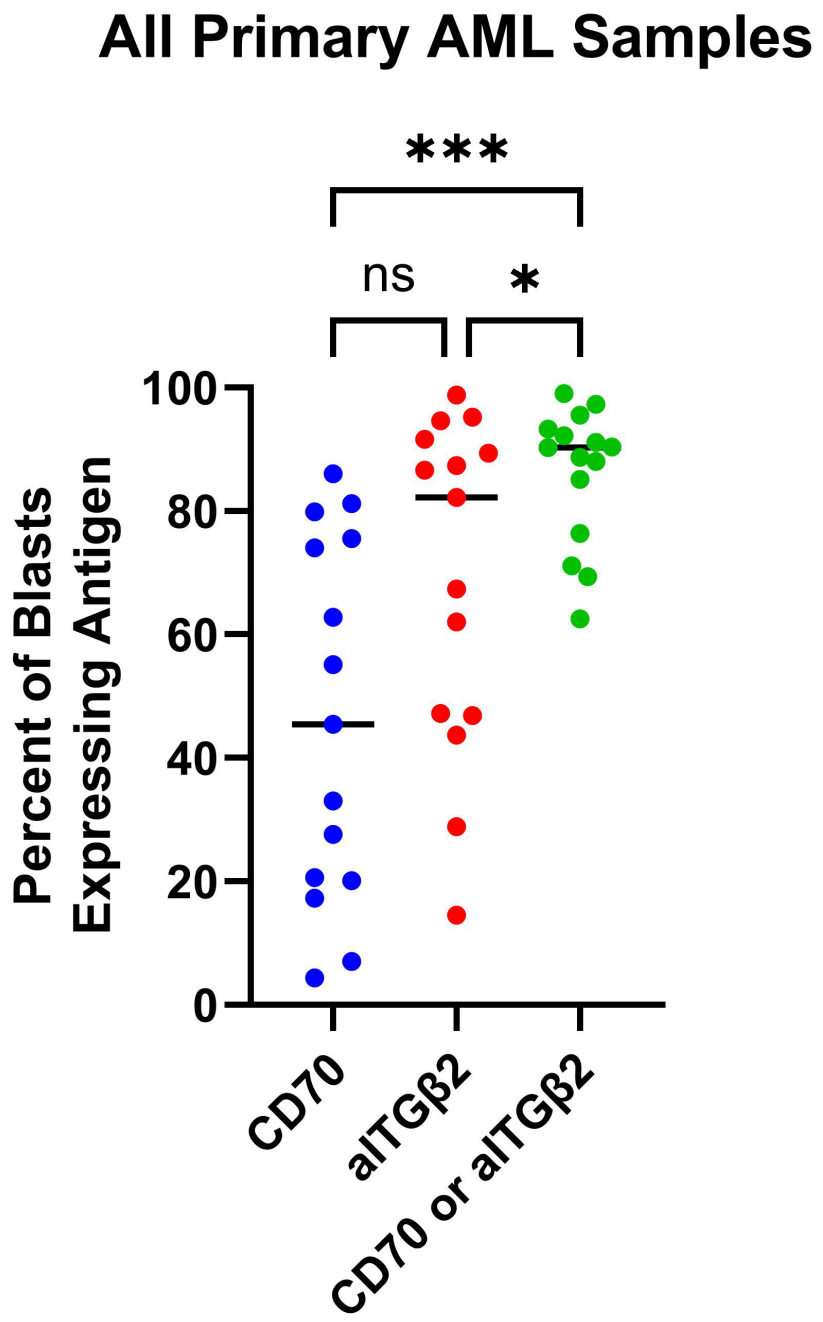
Bicistronic OR-gated CAR Rationale

- Both CD70 and Integrin β2 have low off-tumor toxicity profiles
- Both expressed on most, but not all, AML cells
- OR-gated CAR could increase coverage with minimal off-tumor toxicity

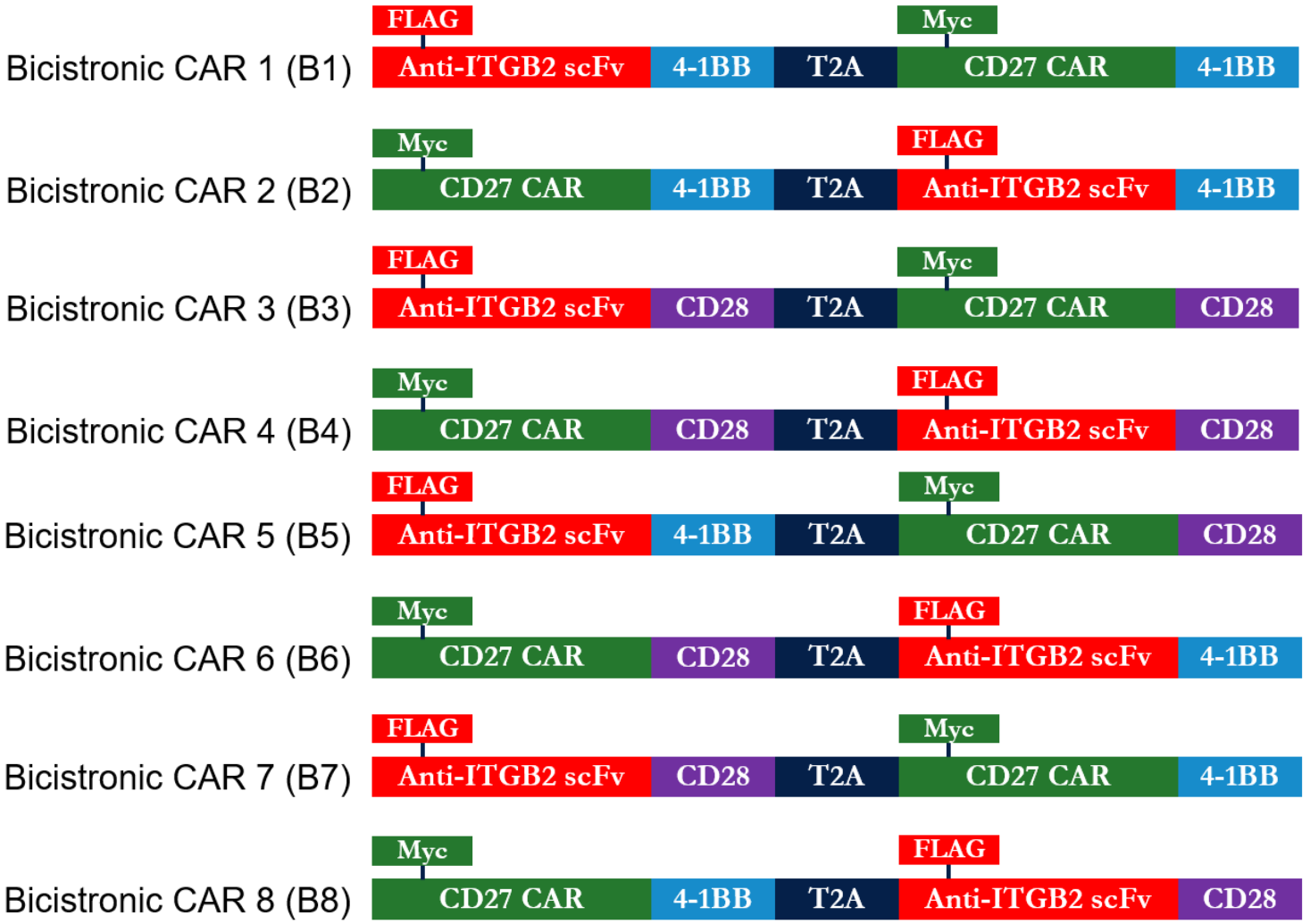
RNA-seq data for *CD70* & *ITGB2* co-expression



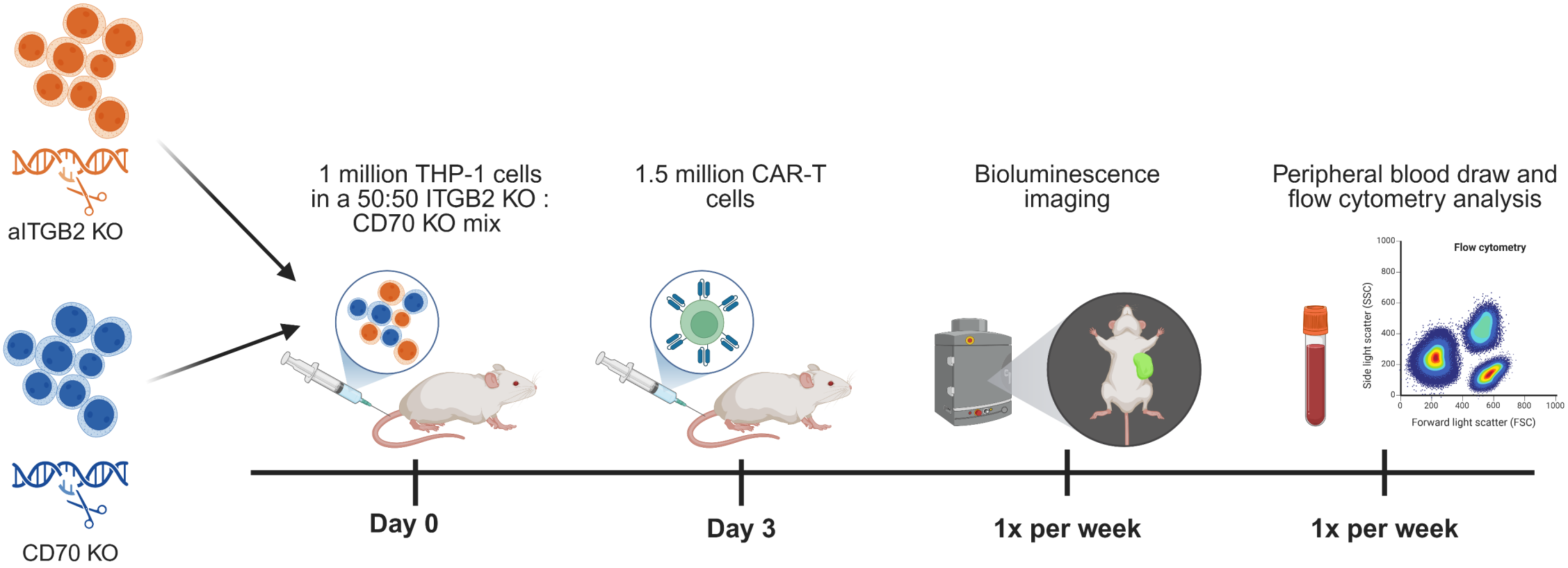
Flow Cytometry Shows Improved AML Targeting in OR-gated Approach



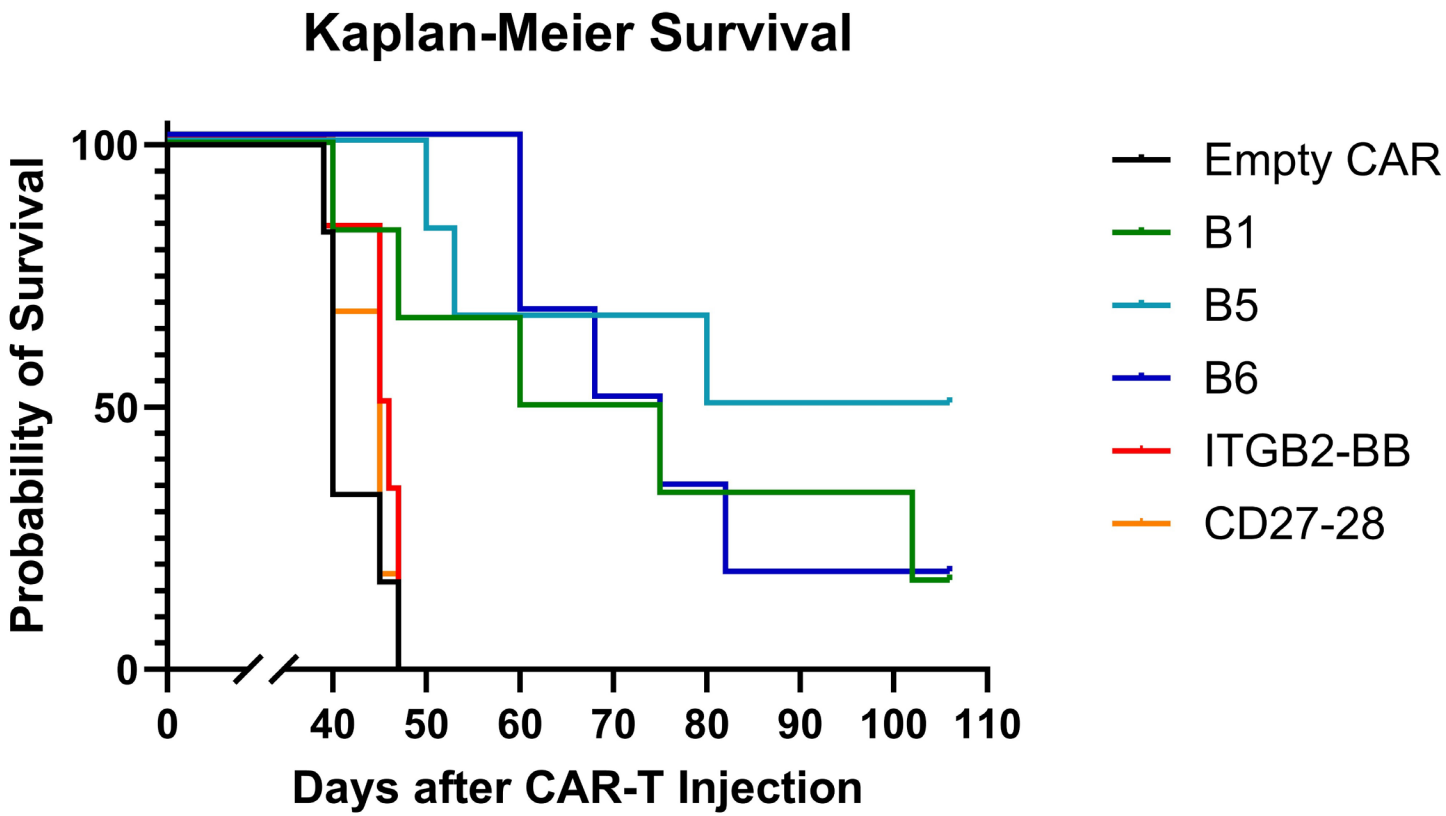
Designing Bicistronic CARs



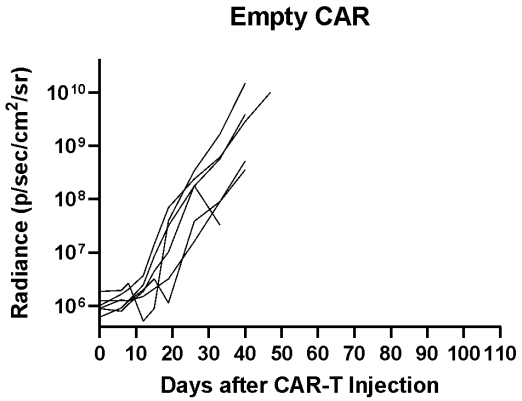
AML Antigen Heterogeneity in vivo Xenograft Model

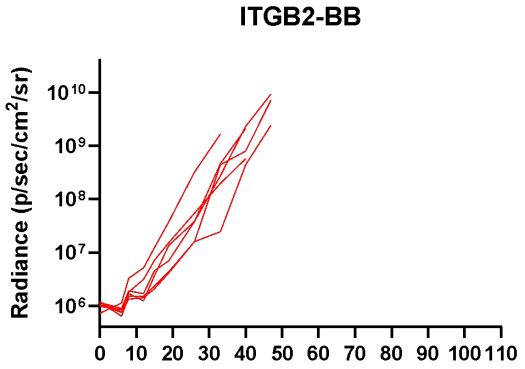


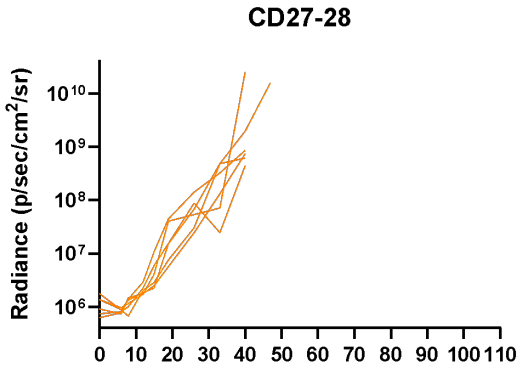
Bicistronic Design #5 Shows Superior *In Vivo* Efficacy

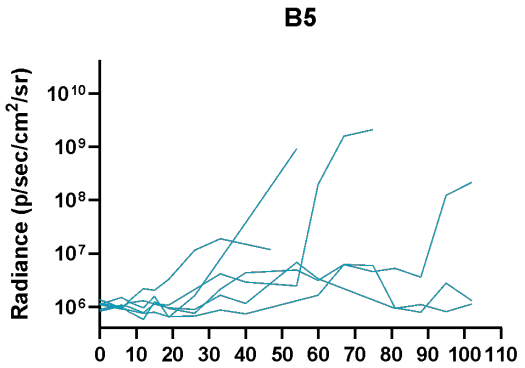


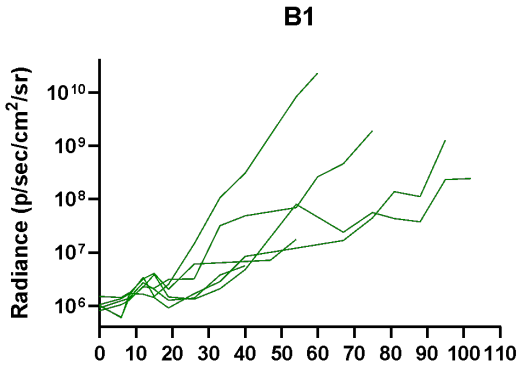
Bicistronic Design #5 shows superior tumor burden control

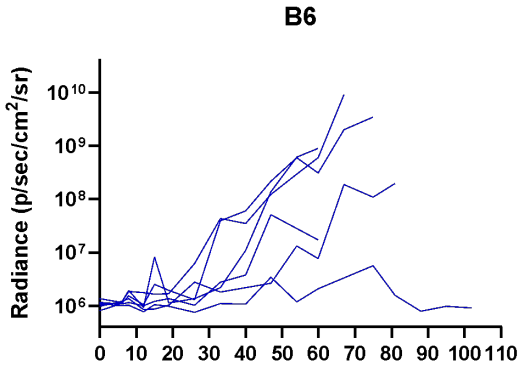




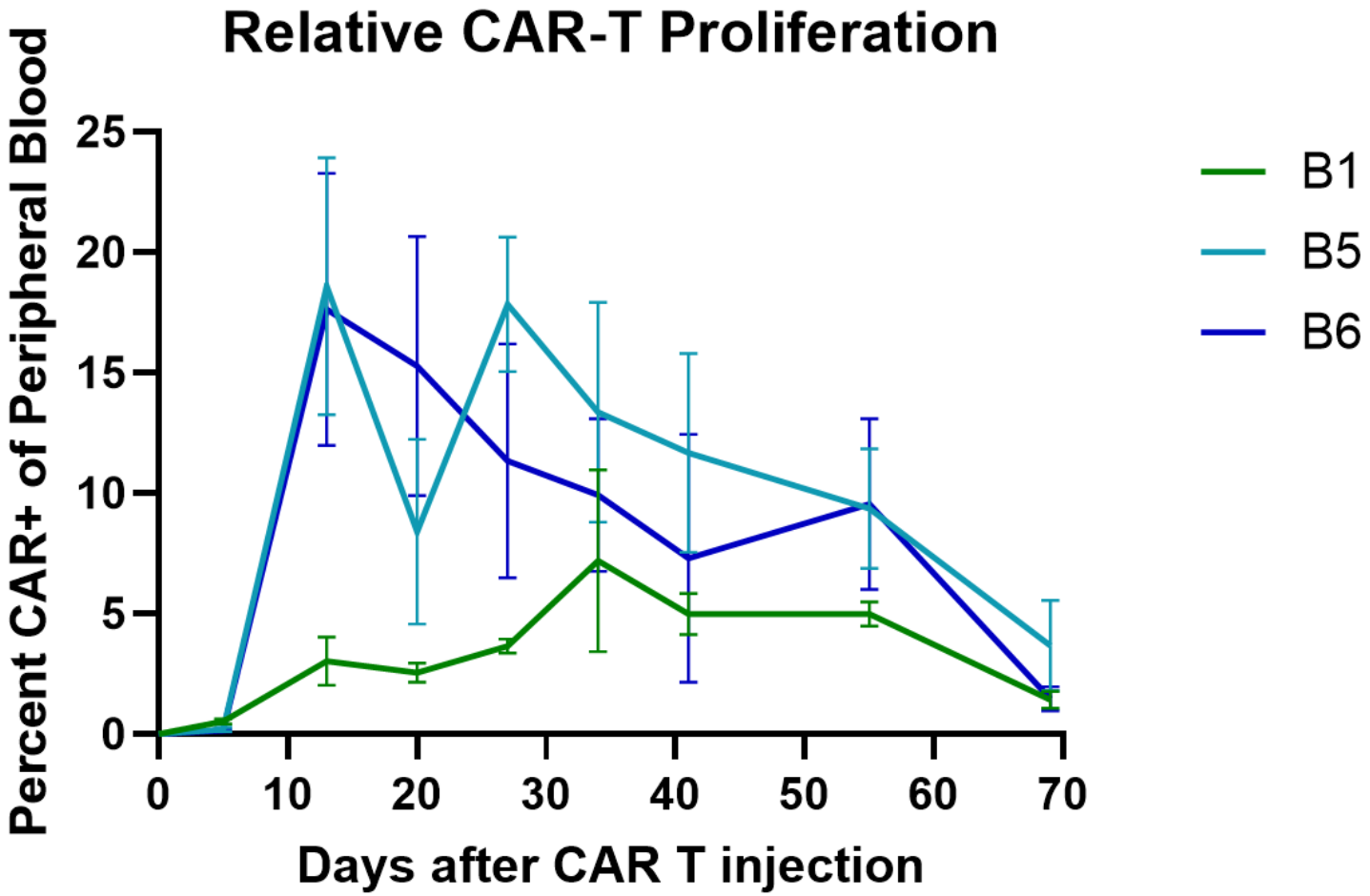




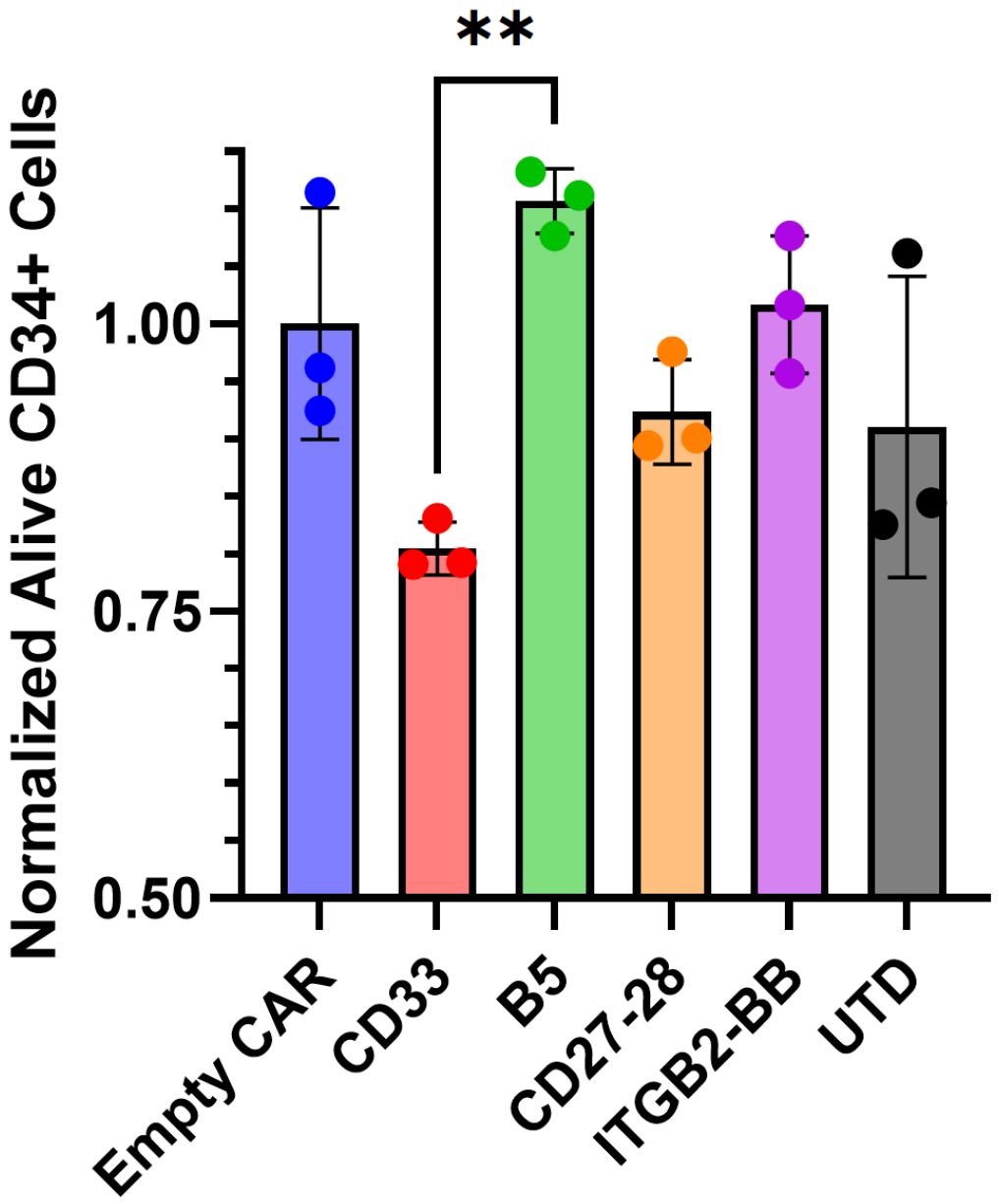




Bicistronic Design #5 Has Superior Persistence in Peripheral Blood



Bicistronic Design 5 Maintains Safety Against CD34+ HSPCs



Conclusions

The combination of CD70 and ITGB2 targeting is promising for AML treatment

A bicistronic CAR approach can be effective in treating AML xenograft models of AML

Our lead bicistronic CAR expands the relative percentage of AML blasts targetable while maintaining no observed HSPC toxicity

Acknowledgements

Wiita Lab

- Arun Wiita
- Abhilash Barpanda
- Nikhil Chilakapati
- Bonell Patiño Escobar
- Adila Izgutdina
- Haley Johnson
- Tom Li
- Corynn Kasap
- Chloe Kong
- Audrey Kishishita
- Ruyan Rahnama
- Sham Rampersaud
- Tasfia Rashid
- Dan Waller
- Sujata Walunj

Eyquem Lab

- Justin Eyquem
- Vincent Allain
- Pierre-Louis Bernard
- Mahmoud Elwakil
- Jae Hyung Jung
- Gabriella Kimmerly
- Joseph Muldoon
- William Nyberg
- Gabi Reeder
- Allison Rothrock
- Luis Sandoval
- Charlotte Wang
- William Xie
- Pierre-Louis Bernard
- Emilie Kono

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