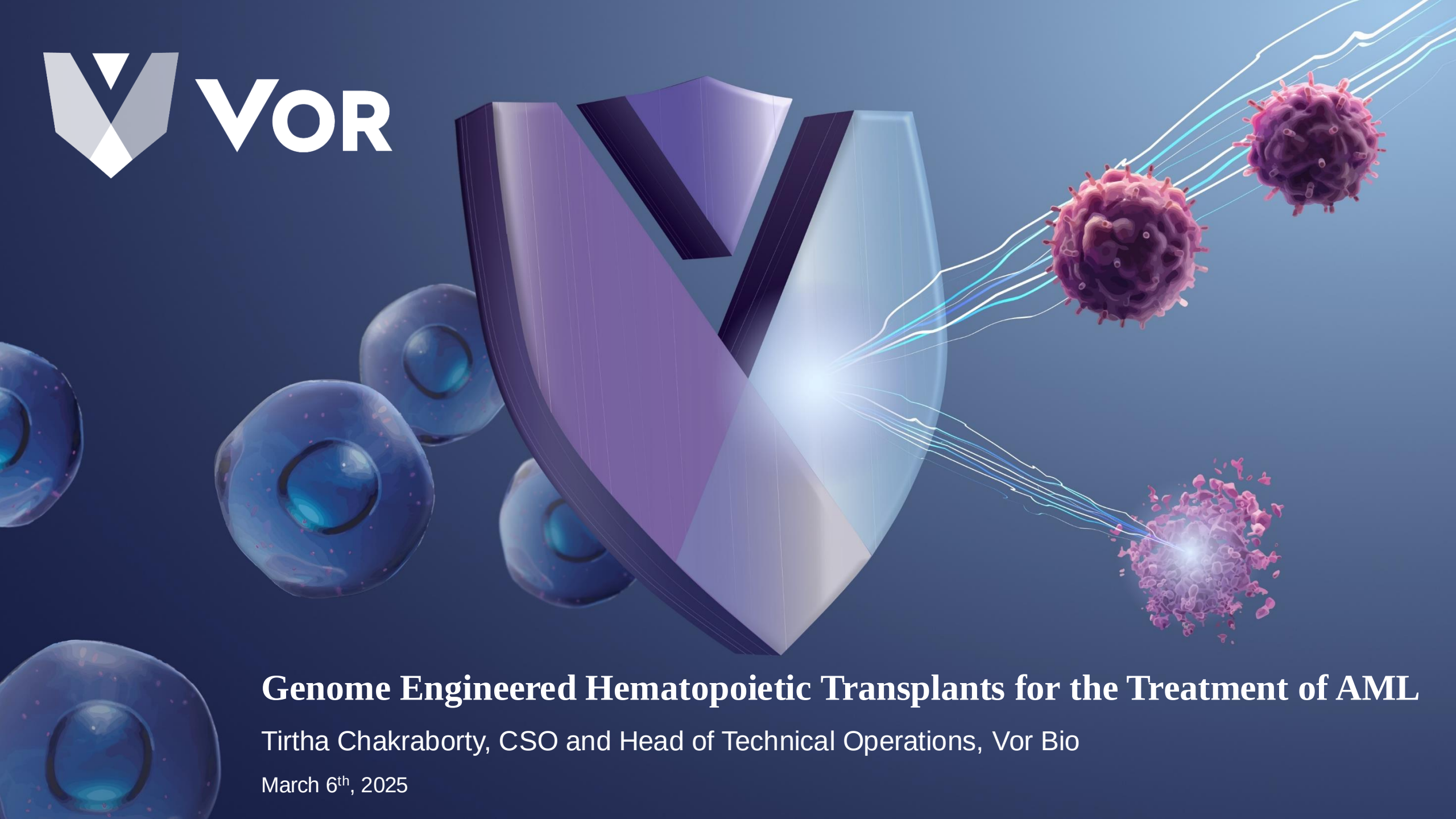
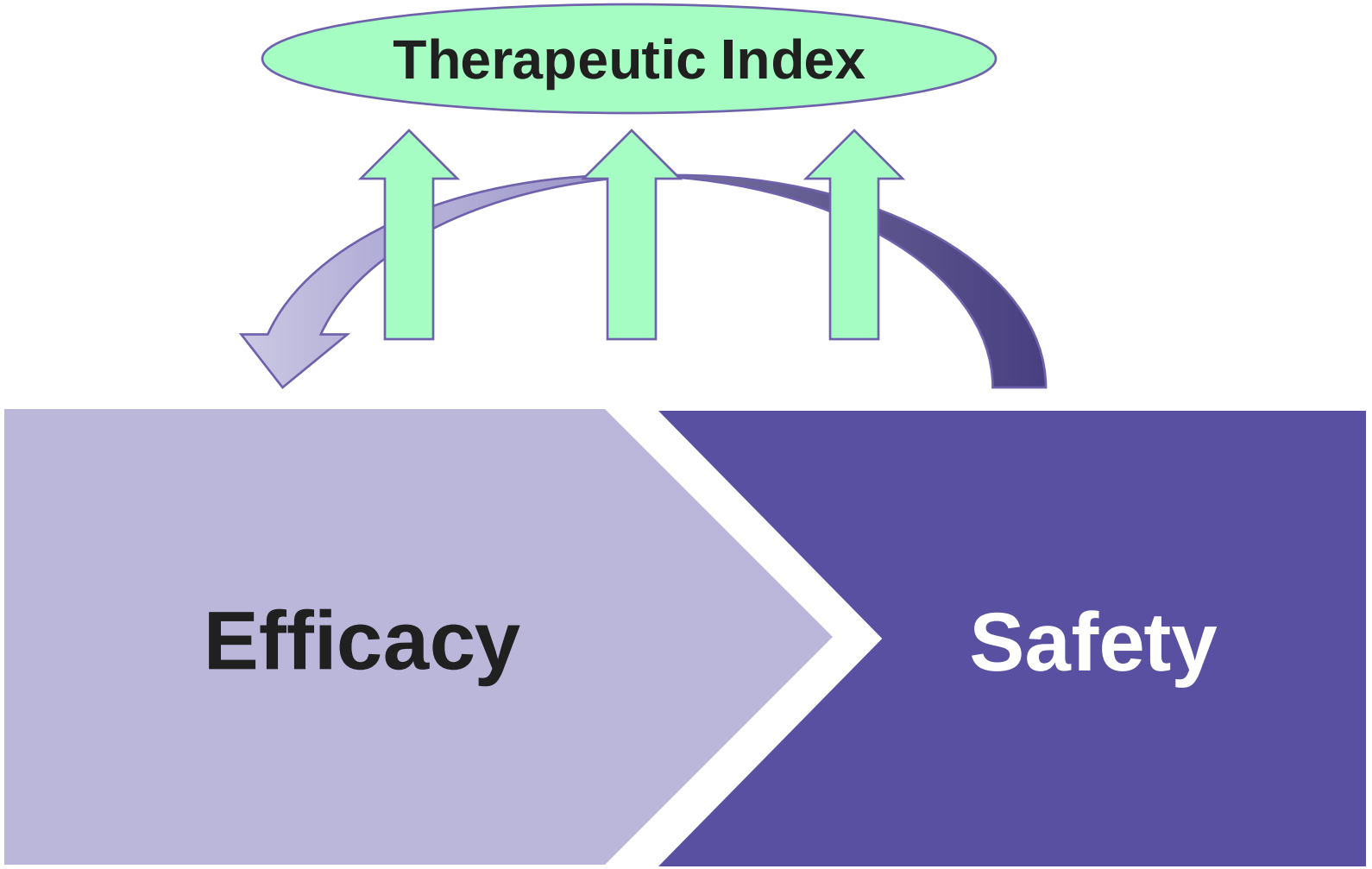


Genome Engineered Hematopoietic Transplants for the Treatment of AML

Tirtha Chakraborty, CSO and Head of Technical Operations, Vor Bio

March 6th, 2025

Vor's approach to Hematopoietic Malignancies



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Most tumor antigens are not tumor specific

Targeted Tx???

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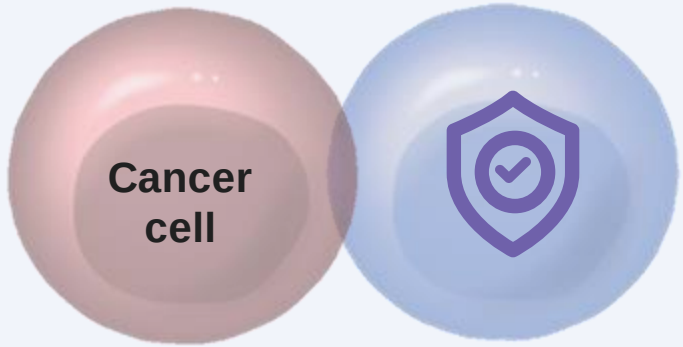
Changing the Thinking on Tumor Targeting to cure AML

Real life Problem

Surface antigen overlap

Vor's genome engineered HSPC transplant from a healthy donor

Vor Paradigm: Engineered HSCs (eHSCs)



Makes surface antigens cancer-specific

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Acute Myeloid Leukemia

the most common adult acute leukemia

Annual incidence
USA: 25,000 and EU: 25,000

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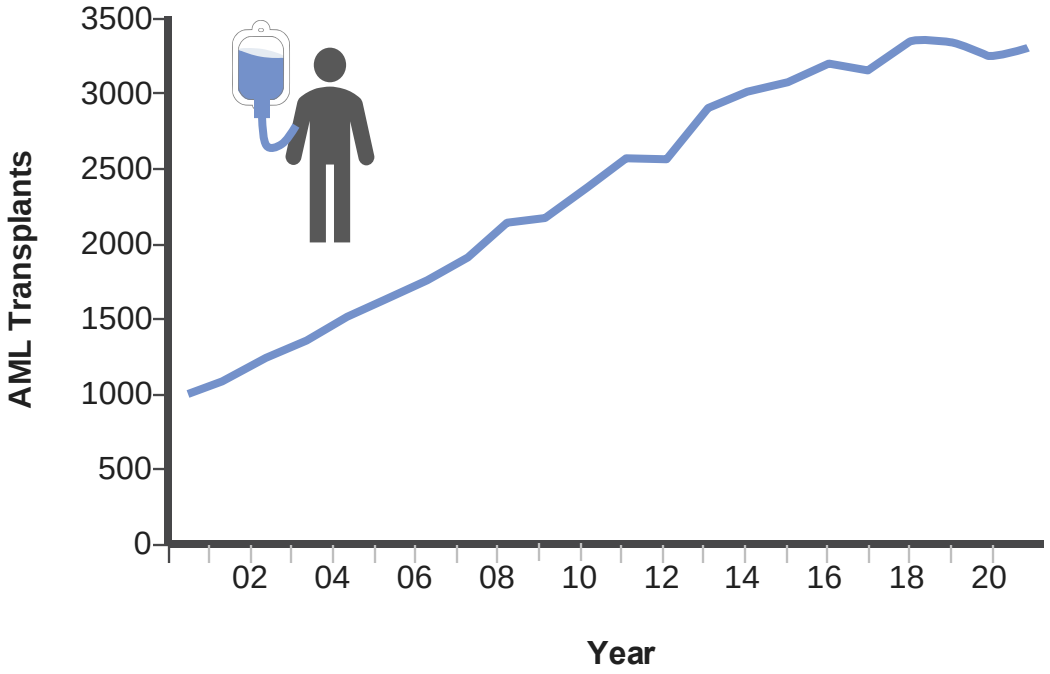
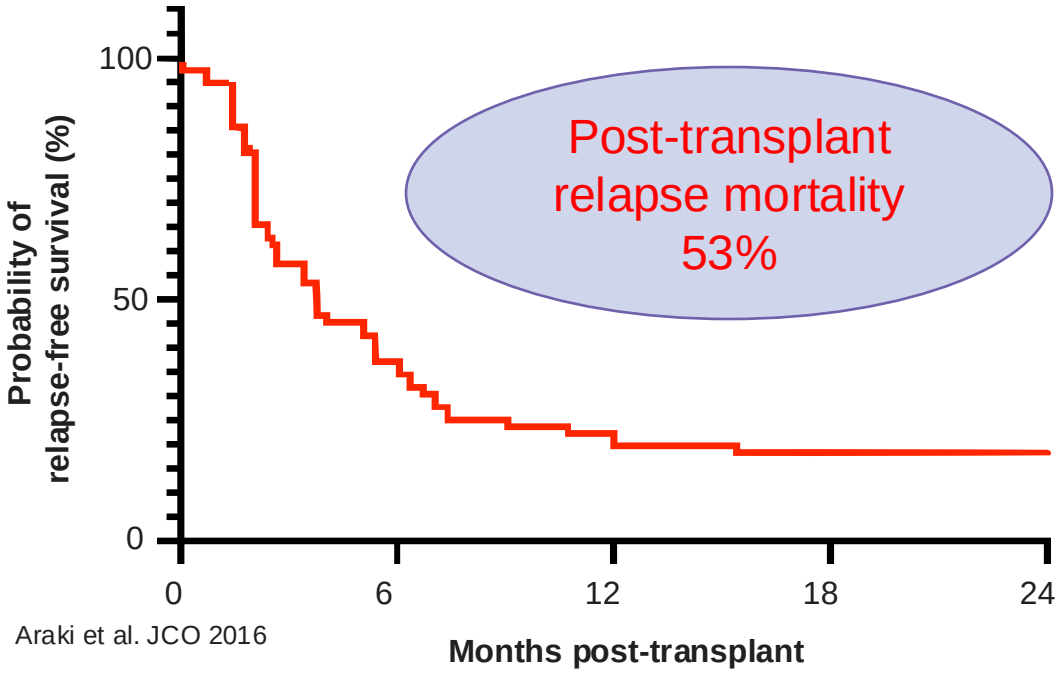
Even After SoC Allo Transplant, High-Risk AML Has Poor Outcomes

Transplant Volume is **Increasing**…



Transplant remains the only potentially curative treatment

…but Relapse Rates **Remain High**



Araki et al. JCO 2016

Limited treatment options post-transplant due to on-target toxicity

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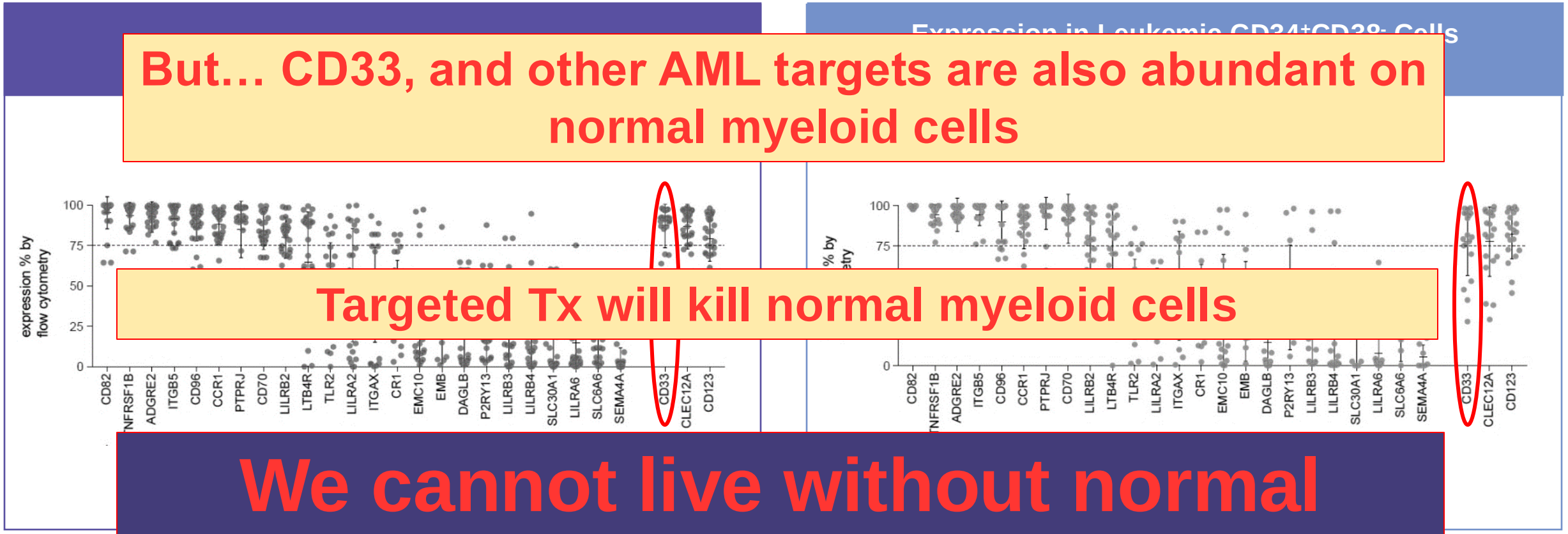
CD33 Among the Most conspicuous Targets in AML

But… CD33, and other AML targets are also abundant on normal myeloid cells



Targeted Tx will kill normal myeloid cells

We cannot live without normal myeloid cells

Perna, Sadelain et al, Cancer Cell 2017

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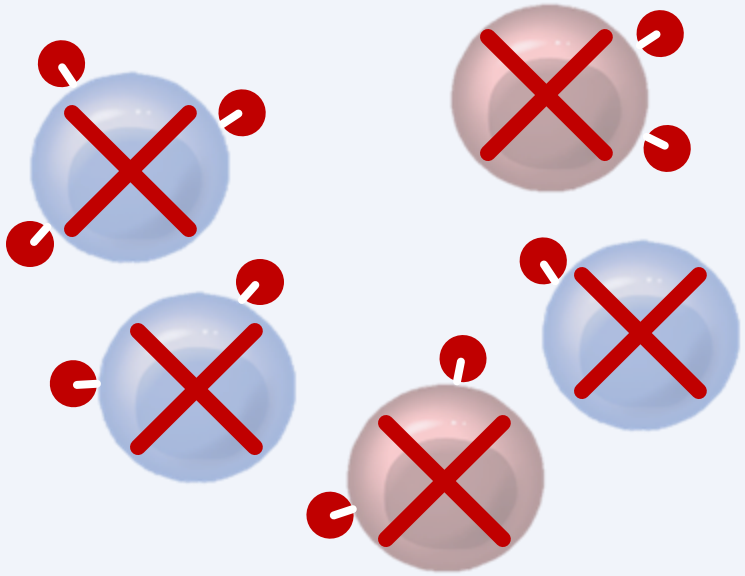
Vor Transplant: Make engineered graft 'Invisible' to Targeted Tx

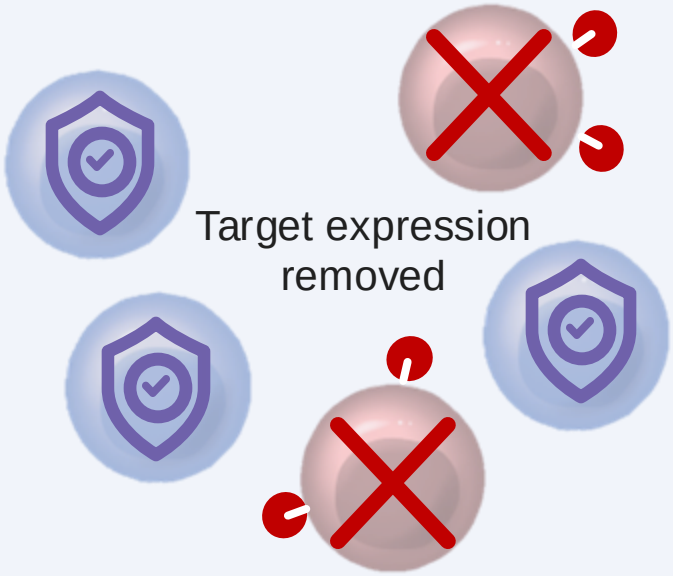
Current Targeted Therapies



On-target Off-tumor toxicity

CRISPR KO of target antigen from the transplant

Protected invisible eHSCs



Cancer-specific killing by the targeted Tx

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Dispensability of CD33: Human genetic evidence

65 individuals with homozygous loss-of-function mutations in the CD33 gene have no obvious defects

gnomAD database

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Lead Program: CD33^{Del} HSPC transplant in AML (VOR33)

Vor Scientific Founder
Dr. Siddhartha Mukherjee

- Associate Professor of Medicine in the Division of Hematology and Oncology at Columbia University
- Chair of Vor Biopharma Scientific Advisory Board

Pulitzer prize: Emperor of All Maladies

	Vor	Independent validation from two labs	
	Mukherjee lab	Gill lab	Kiem lab
	Columbia University	Penn Medicine	Fred Hutch
Robust POC w/ Primary Cells	✓	✓	✓
Killing Cancer in Humanized Mice	✓	✓	✓
Engraftment & Safety in Rodents	✓	✓	✓
Safety in Non-Human Primates	N/A	✓	N/A
	Borot et al, PNAS 2019	*Kim et al, Cell 2018*	*Humbert et al, Leukemia 2018*

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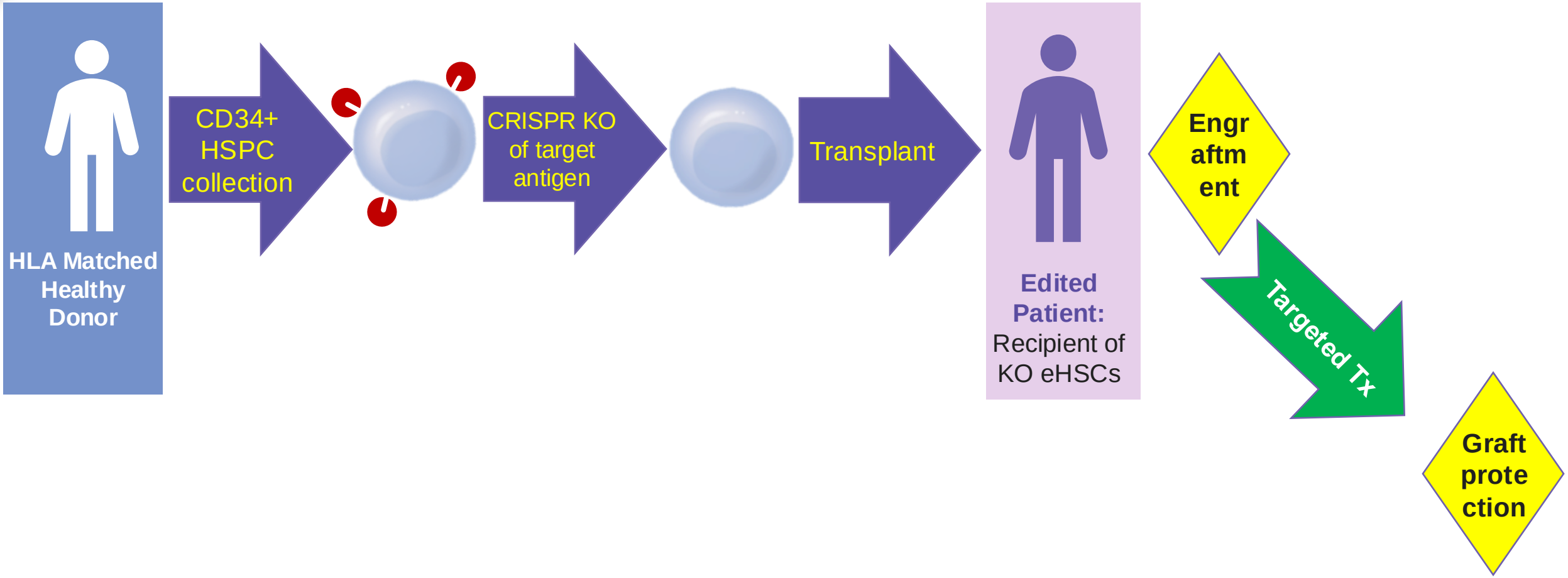
Vor Transplant: The Treatment Paradigm



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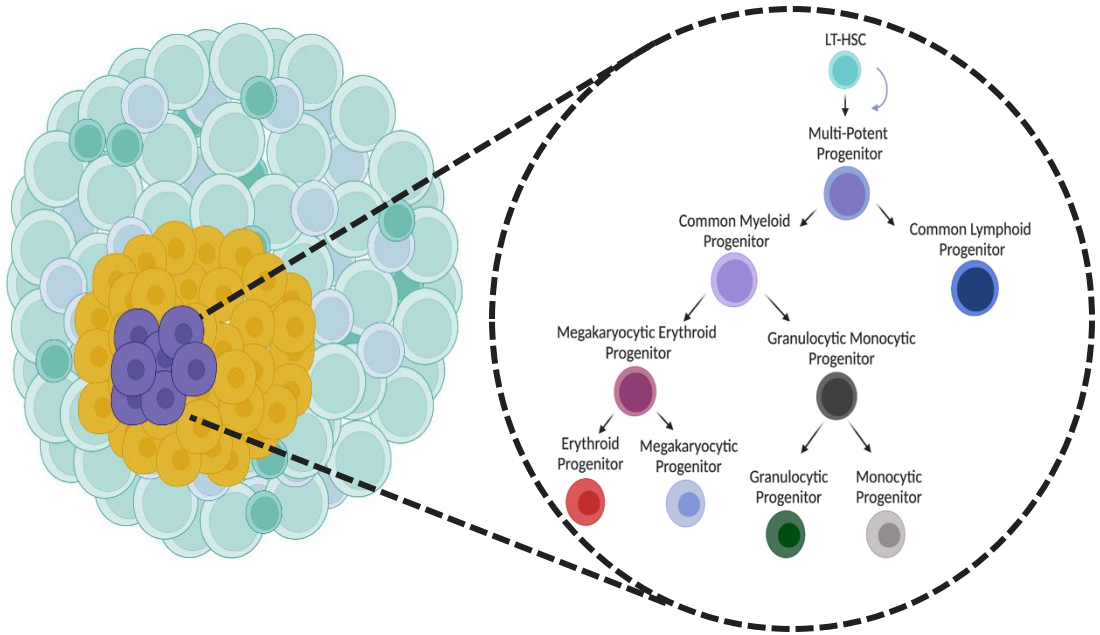
A Primer: Human Hematopoietic Stem (and Progenitor) Cells

CD34+ HSPCs are Heterogenous



True LT-HSCs (~1/20,000 WBC)

- Extremely small population
- Poorly defined
- Difficult to identify
- Impossible to purify
- Do not proliferate
- Differentiate easily, losing stemness
- Delicate, difficult to manipulate

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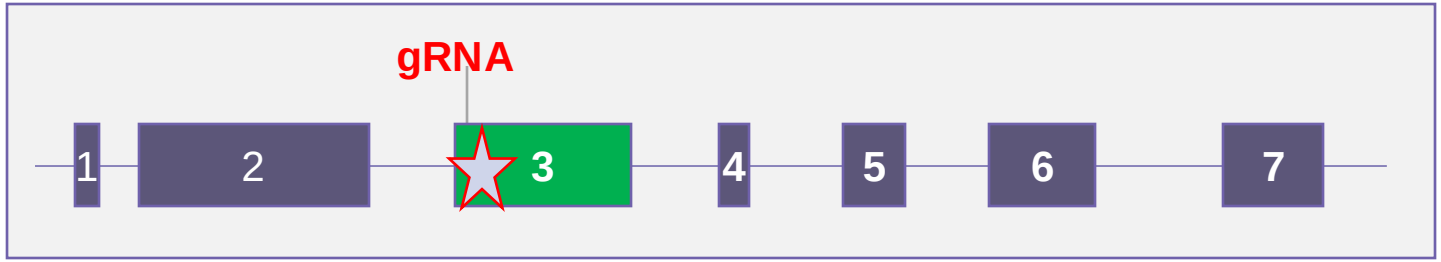
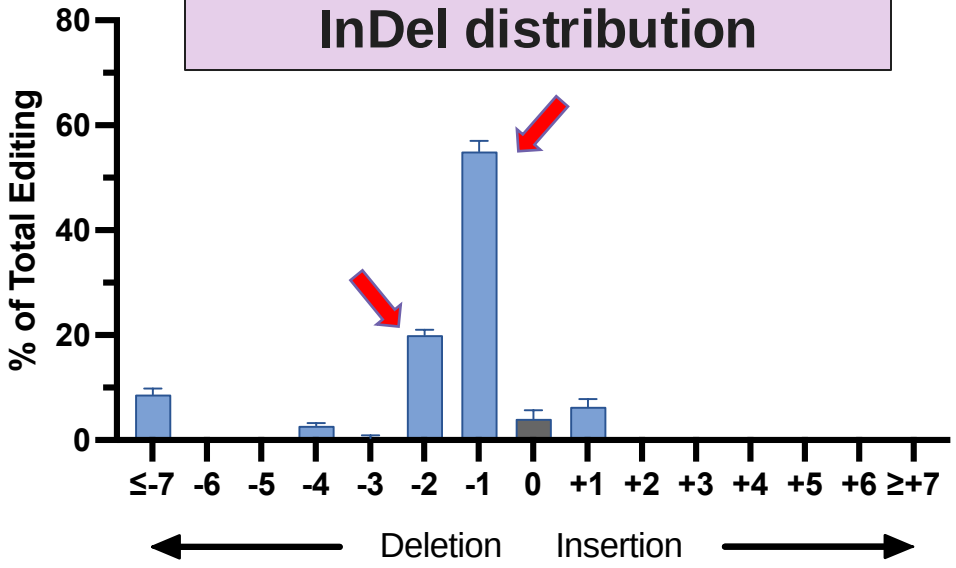
Molecular Mechanism of CD33 KO: Single guide NHEJ: Formation of a Premature STOP



InDel distribution



Impact on ORF

INDEL	Frequency %	DNA Sequence (gRNA + PAM) ± 5nt	Amino Acid Change	Consequence
0	4 ± 2	TTTCTCCTCACTAGACTTGACC CACAGGCCCAA	Full length	Full length
-1	55 ± 2	TTTCTCCTCACTAGACTTGACC -ACAGGCCCAA	His143Pro	Ter10
-2	20 ± 1	TTTCTCCTCACTAGACTTGAC- -ACAGGCCCAA	His143Glu	Ter26
+1	6 ± 2	TTTCTCCTCACTAGACTTGACCCCACAGGCCCAA	His143Pro	Ter27

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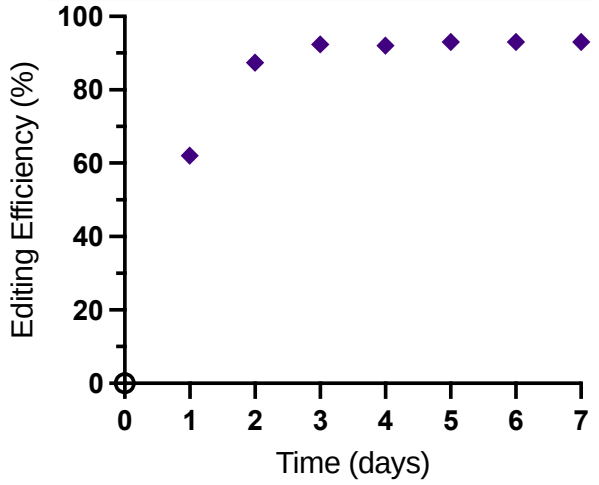
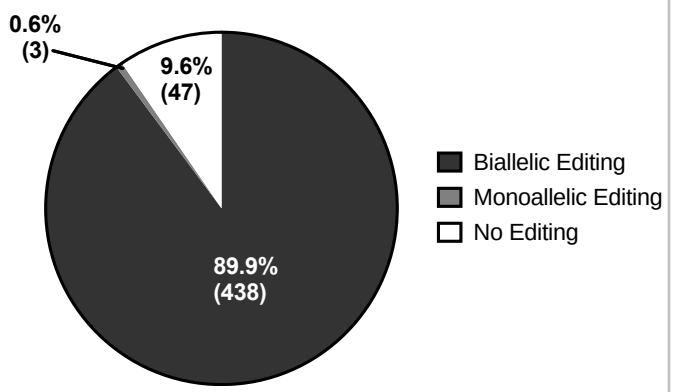
Molecular Characterization of CD33 KO HSPCs:

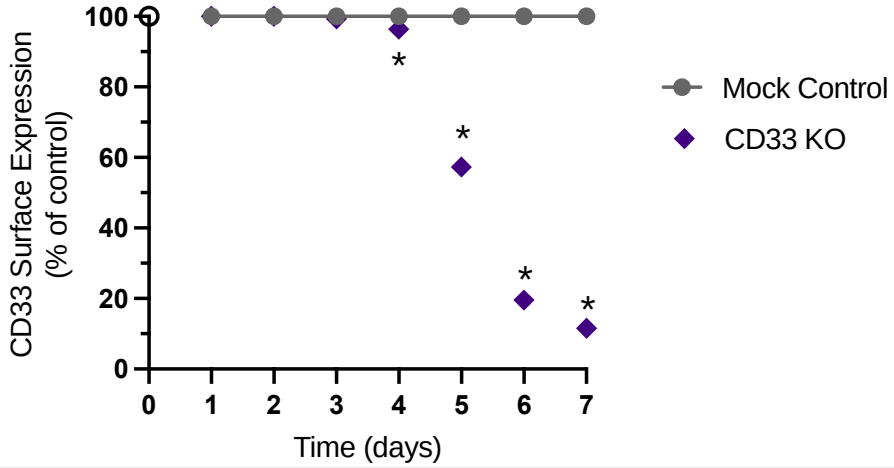
~90% Bulk CD33 Editing



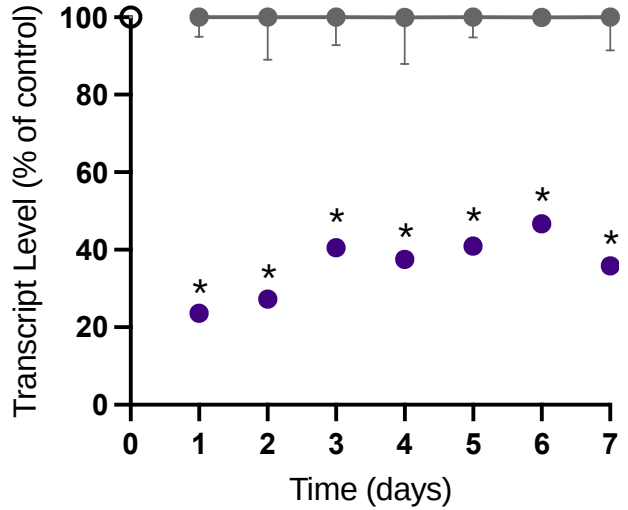
~90% Bi-allelic Editing



Loss of CD33 surface expression



Loss of CD33 transcript in AML cell line



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Pre-clinical investigation:

Is CD33 Dispensable for Human HSPC Biology?

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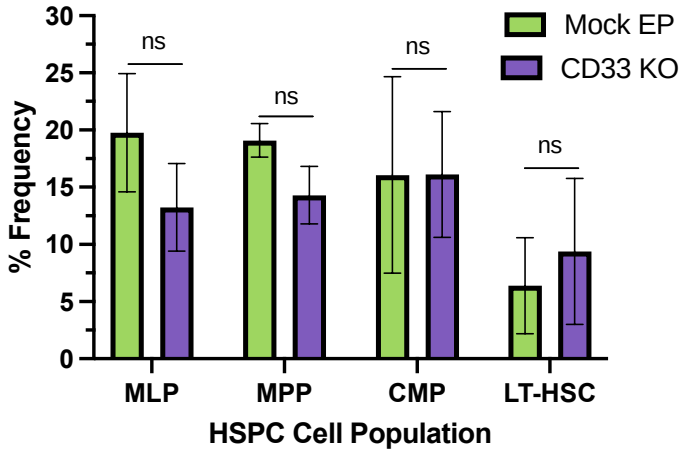
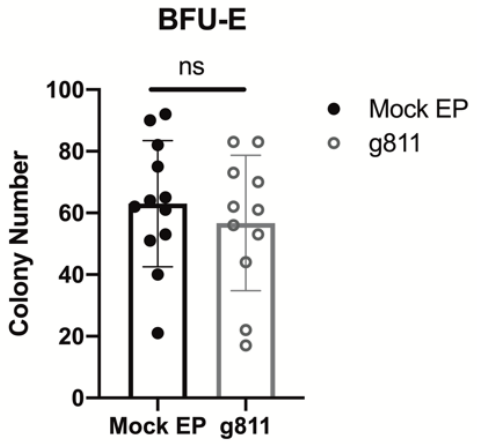
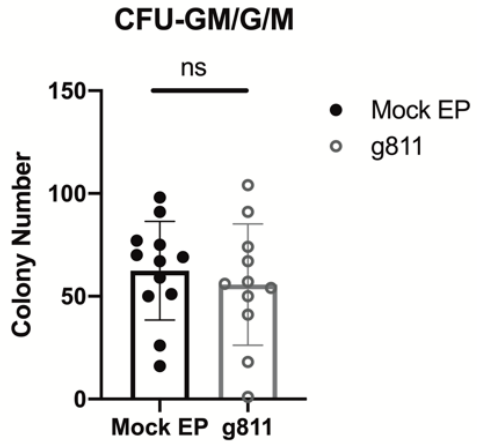
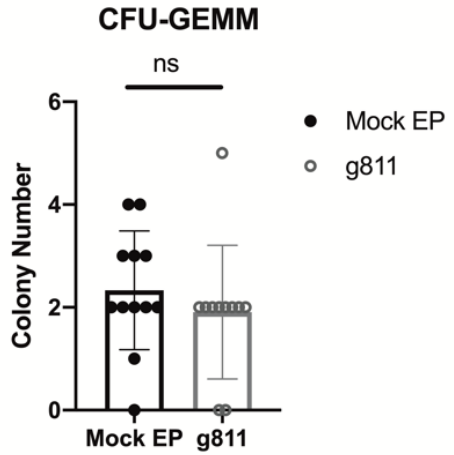
No impact of CD33 loss on Human Hematopoietic Progenitors (*in vitro*)

No impact of CD33 KO on HSPC Sub-pop Distribution

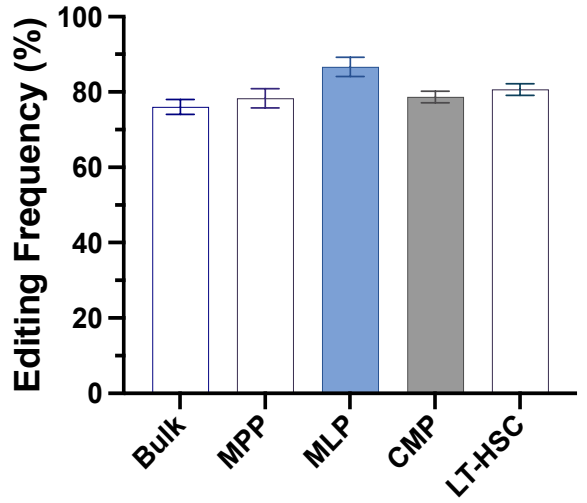








High Editing in all Sorted HSPC Sub-pops



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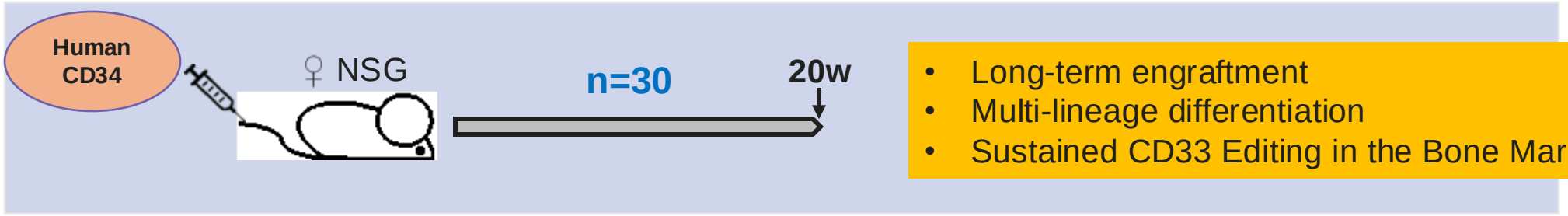
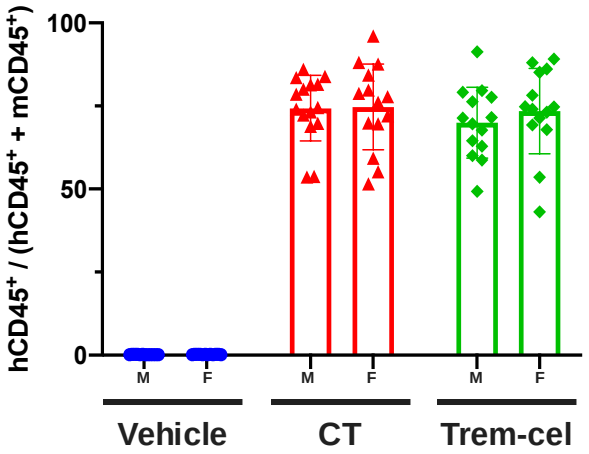
In vivo pre-clin Pharmacology and Safety Results of Trem-Cel: A xeno-transplant study:

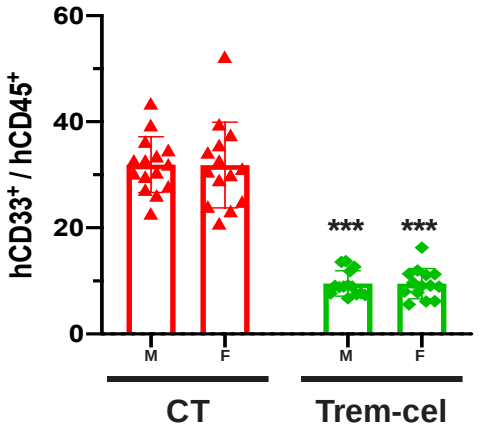


- Long-term engraftment
- Multi-lineage differentiation
- Sustained CD33 Editing in the Bone Marrow

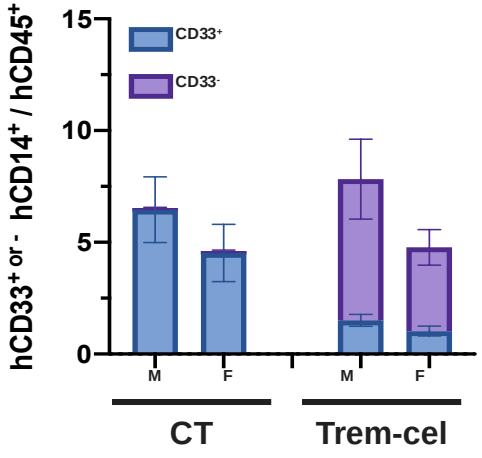
No change in Total Human Chimerism (% hCD45)



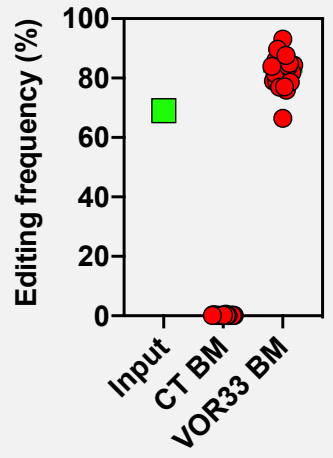
Reduction of CD33+ Myeloid Cells



Loss of CD33 from CD14+ Monocytes



Long-term (20W) persistence of Bulk Editing in all mice



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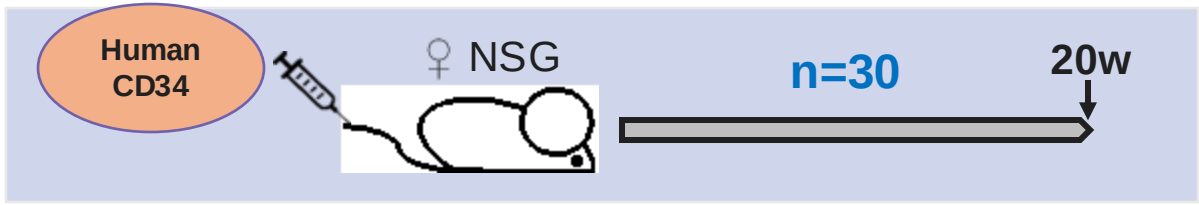
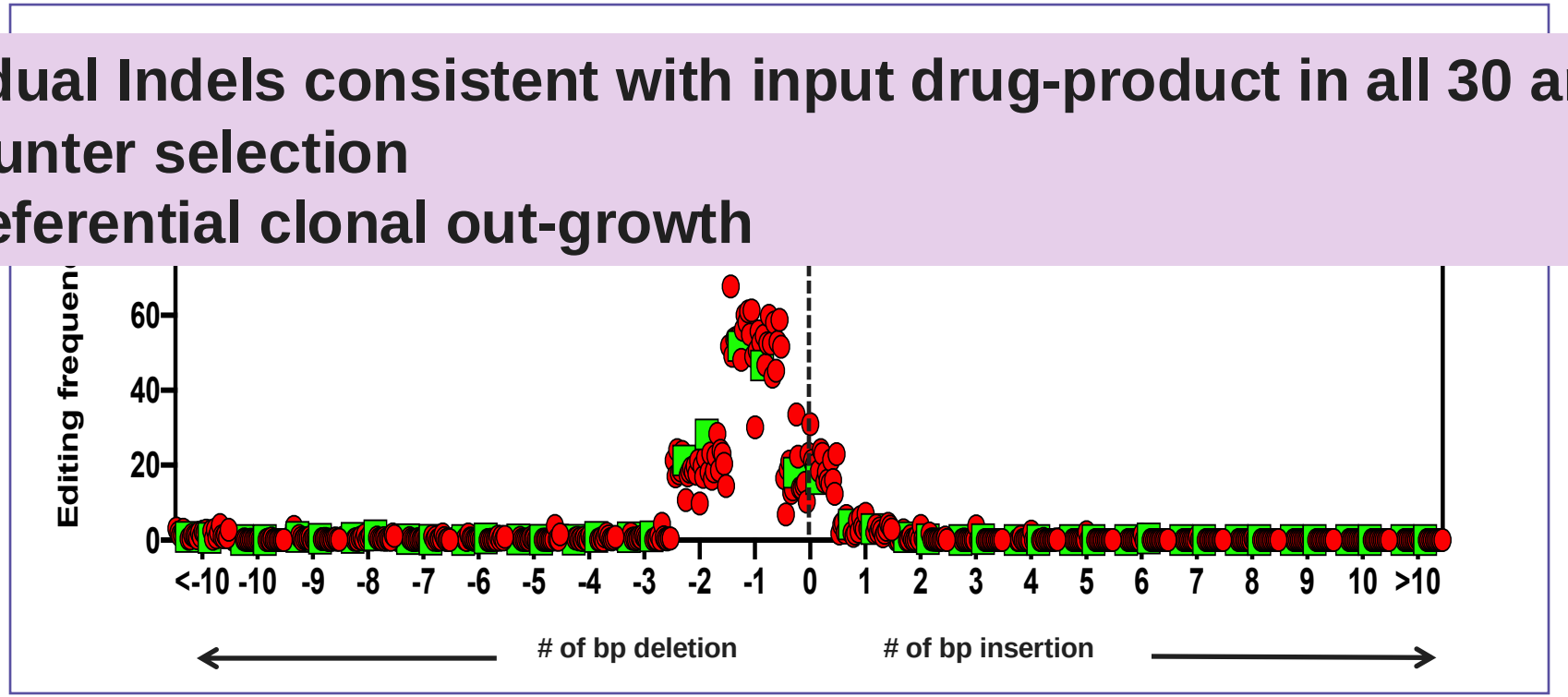
Pre-clin Pharmacology and Genetic Safety Results of Trem-Cel: The InDel spectra:



- Individual Indels consistent with input drug-product in all 30 animals
- No counter selection
- No preferential clonal out-growth



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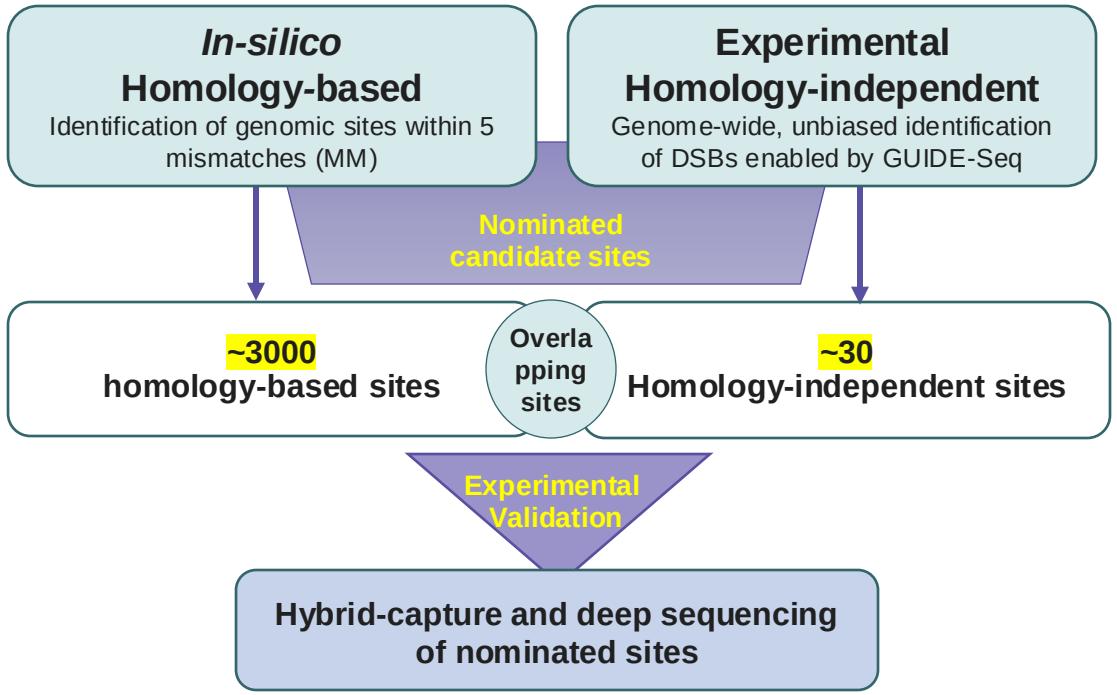
Pre-clin Pharmacology and Safety Results of Trem-Cel:

No adverse events observed in the GLP-Safety study

No off-target concerns



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Trem-cel:

a CD33 KO Hematopoietic Transplant

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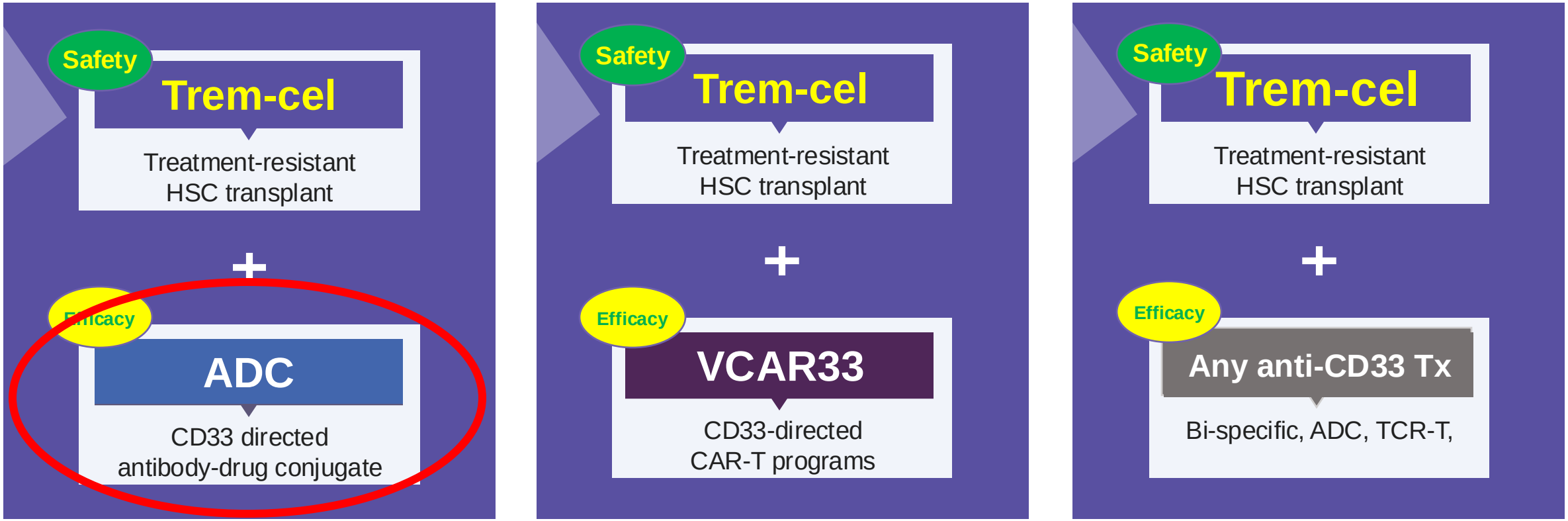
The Vision: Trem-cel Can improve Tx index in Multiple Combinations



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Shielding of trem-cel from CD33 directed Antibody Drug Conjugate Mylotarg (GO)

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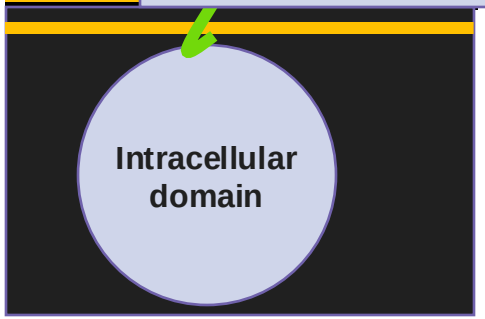
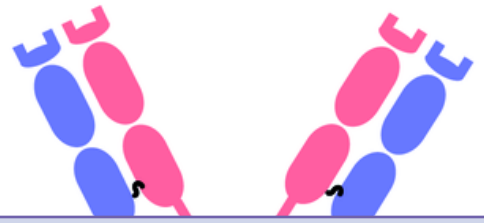
CD33 directed ADC: Gemtuzumab Ozogomycin (GO) or Mylotarg

CD33





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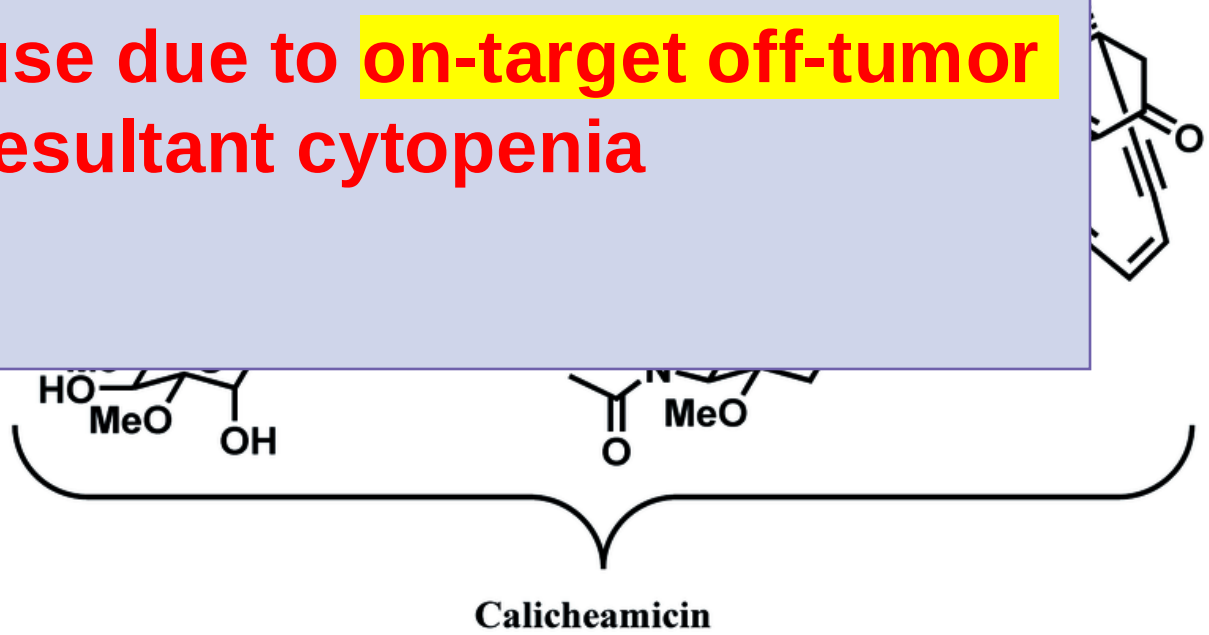

Calicheamicin

No post-transplant use due to on-target off-tumor tox and resultant cytopenia

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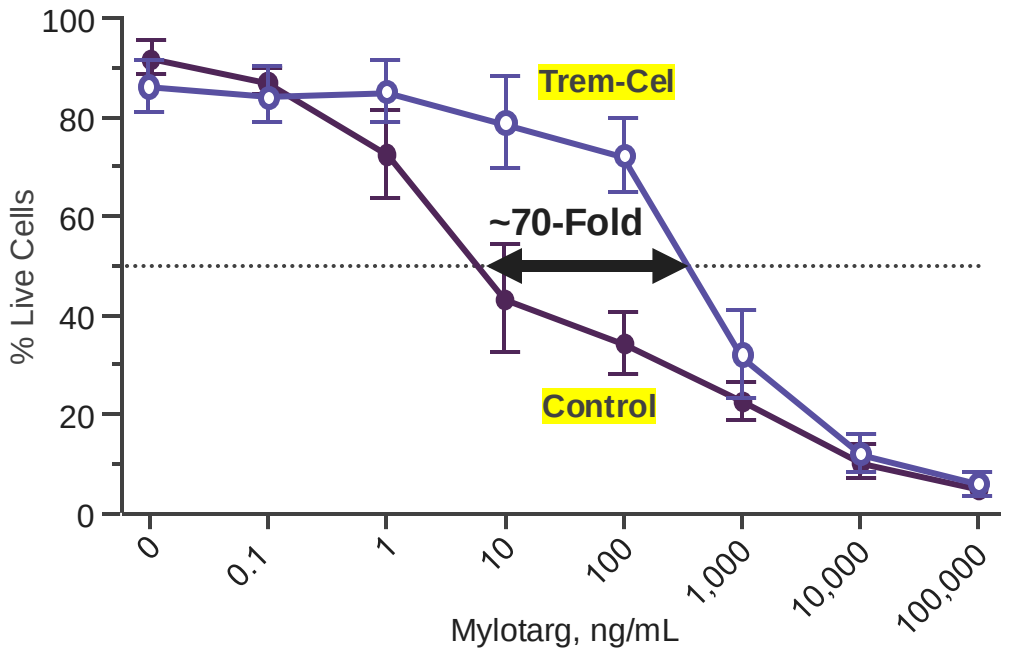
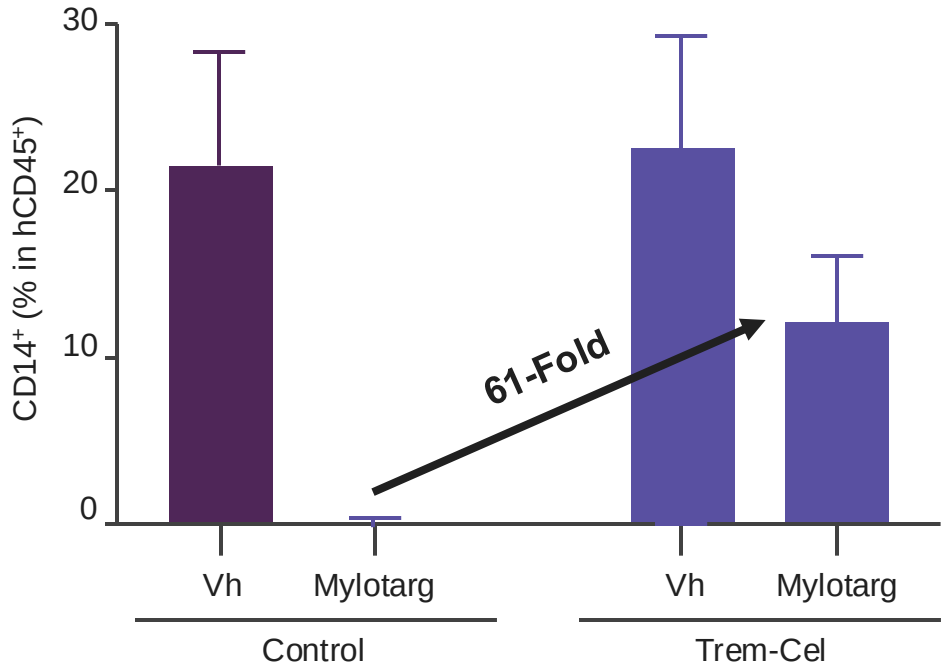
Pre-clinical: Trem-cel is Resistant to Mylotarg

In vitro (HL-60 cell line)



In vivo (xeno-transplant mouse model)



- Engineered cells were not enriched for CD33 deletion and some cell death was expected based on residual CD33 expression
- Free calicheamicin dissociated from Mylotarg may have led to non-specific cell death

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Results from VBP101

An ongoing Phase I/II trial

trem-cel transplanted AML patients treated with Mylotarg in maintenance setting

Engraftment, hematologic protection and Relapse-Free Survival

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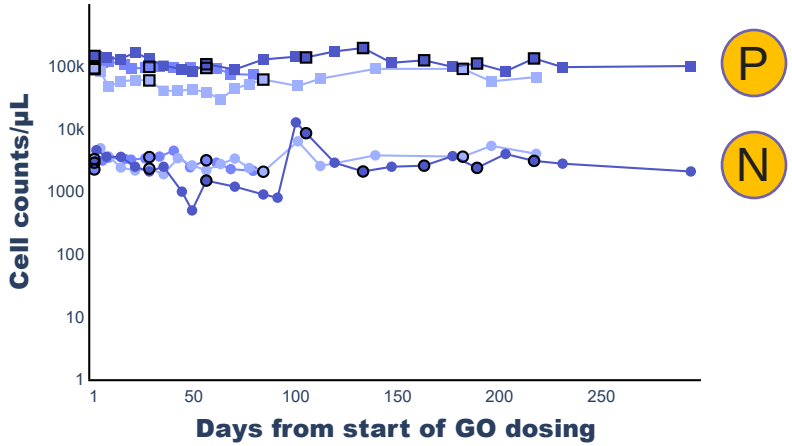
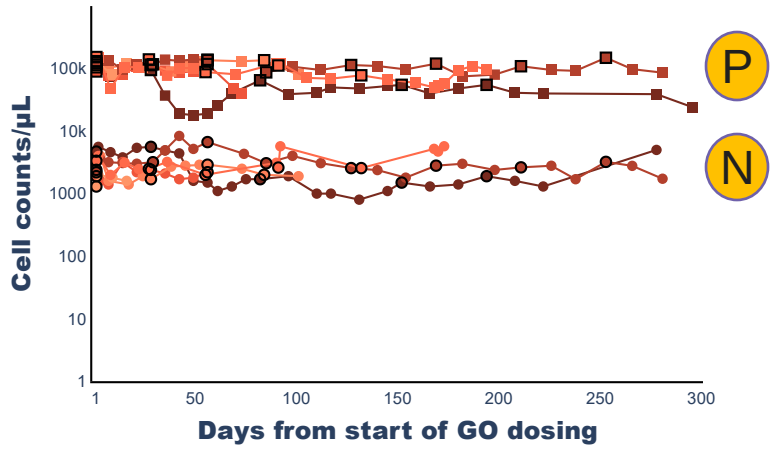
Trem-cel Provides Hematologic Protection upon Mylotarg Dosing

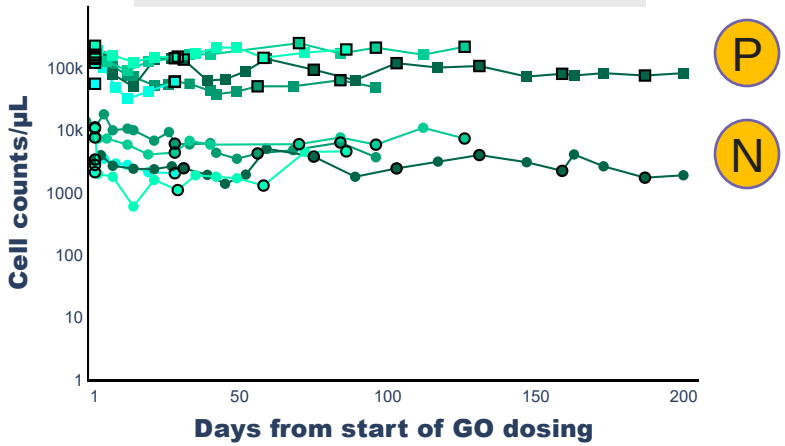
Cohort 1 (0.5 mg/m^2) n=3



Cohort 2 (1 mg/m^2) n=6



Cohort 3 (2 mg/m^2) n=6



P Platelet

N Neutrophil

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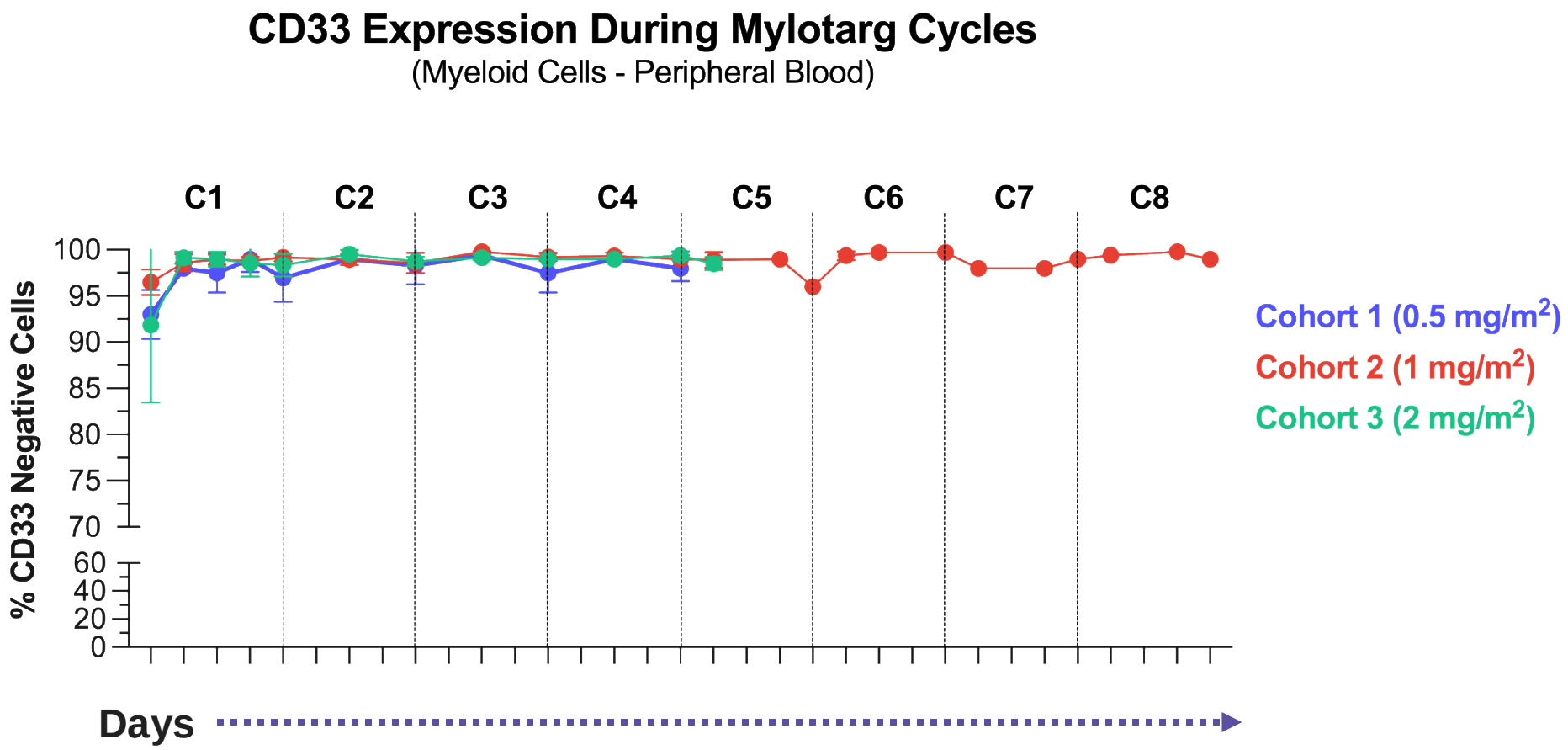
Trem-cel treatment leads to Enrichment and maintenance of CD33-negative Myeloid Cells upon GO Dosing



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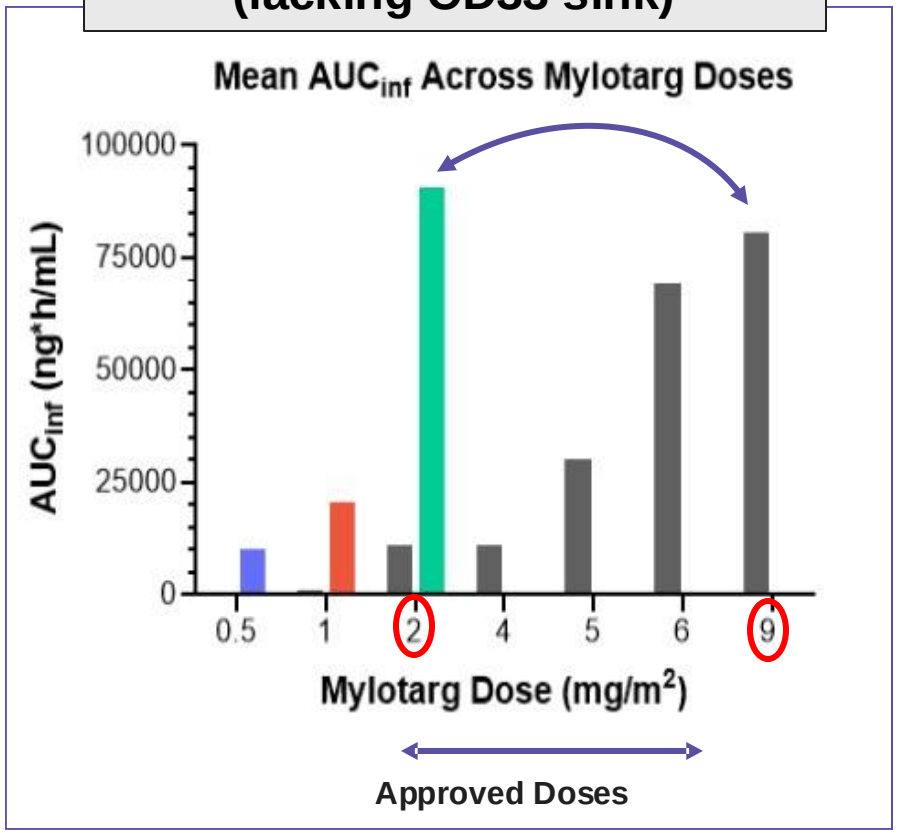
Mylotarg is efficacious (AUC) and safe (C_{max}) in CD33-null trem-cel Setting even at the highest dose used in VBP101

Efficacy: High Mylotarg AUC (lacking CD33 sink)



First dose Mylotarg (GO) exposure (AUC_{inf}) (Left panel) and C_{max} (right panel) compared to first dose Mylotarg PK values in R/R AML patients (FDA ODAC 2017)

Note: some AUC_{inf} values may fall outside 20 percent extrapolation.

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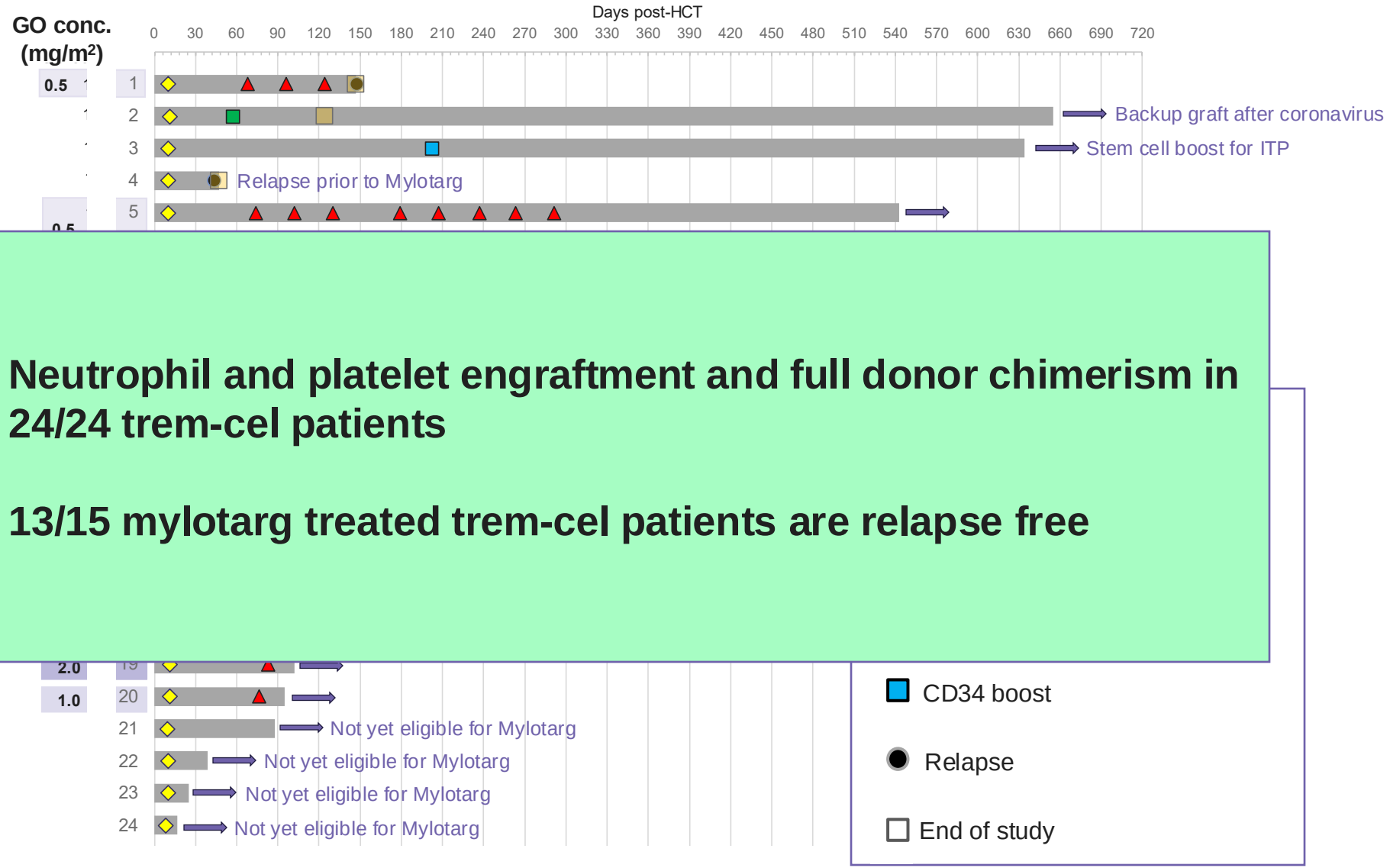
Trem-cel transplanted patient courses:



- **Neutrophil and platelet engraftment and full donor chimerism in 24/24 trem-cel patients**
- **13/15 mylotarg treated trem-cel patients are relapse free**

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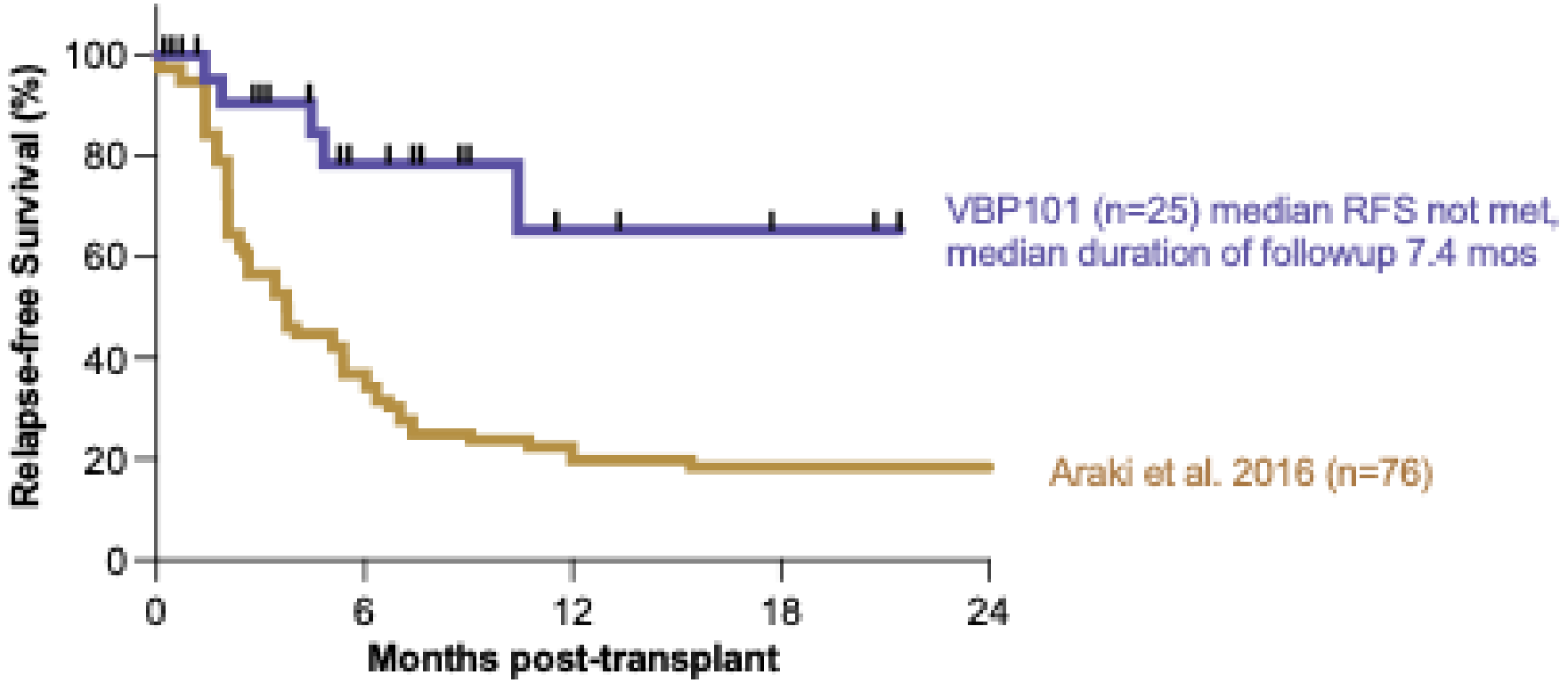
Relapse-free Survival of VBP101 patients compared to SoC Allo transplant



*Data not from head-to-head trial.

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VOR
Transforming the lives of cancer patients by p ring
engineered hematopoietic stem cell (eHSC) ies
Passion
Enthusiastically driving our science toward innovative medicines
Fellowship
Fostering genuine bonds of collaboration and
Humility
Transforming the lives of cancer patients by pioneering
engineered hematopoietic stem cell (eHSC) therapies

#2033

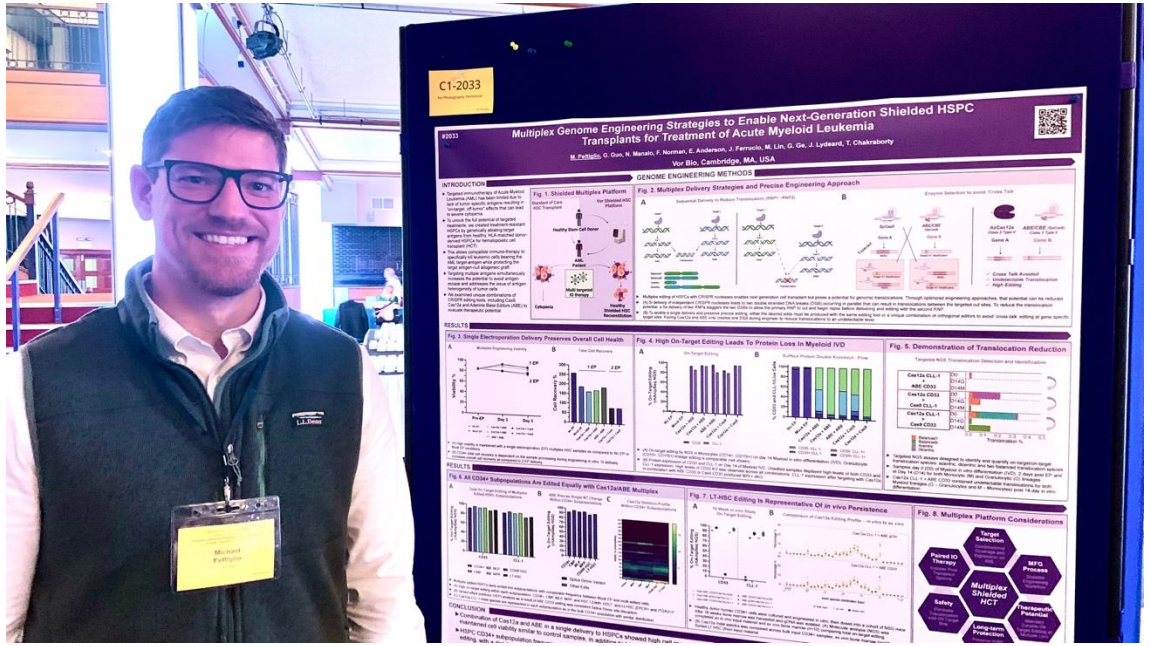
Multiplex Genome Engineering Strategies to Enable Next-Generation Shielded HSPC Transplants for Treatment of Acute Myeloid Leukemia

M. Pettiglio, G. Guo, N. Manalo, F. Norman, E. Anderson, J. Ferrucio, M. Lin, G. Ge, J. Lydeard, T. Chakraborty

Vor Bio, Cambridge, MA, USA

Poster 2033

Michael Pettiglio



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