



Harnessing the Power of Gamma-Delta T Cells

April 23, 2023



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Deep Experience Across Development and Biotechnology



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Co-Founder,
President and Chief
Executive Officer



**Lawrence
Lamb, PhD**
Co-Founder and
Chief Scientific
Officer



**Patrick
McCall, CPA**
Chief Financial
Officer



**Trishna
Goswami, MD**
Chief Medical Officer



**Kate Rochlin,
PhD**
Chief Operating
Officer

IN8bio's team has deep experience in cell therapy & oncology expertise:

- Diverse leadership team brings extensive background in oncology discovery, business insights, franchise creation, product development, regulatory affairs, and commercialization
- Business development and licensing expertise across biopharmaceutical and biotechnology companies. Founding of a private healthcare investment fund and management of public investments and cross-over portfolio at leading healthcare venture capital firm, New Leaf Venture Partners
- Specialization in transplantation immunology and recognized innovation in the field of $\gamma\delta$ T cells
- Leadership of Curadigm's spin-out from Nanobiotix and platform collaborations and partnerships
- Proven and measurable successes in bringing high profile candidates to market including Stemline, Immunomedics and Gilead Sciences

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BIOTAGENICS

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IMMUNOVENT

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 NEW LEAF VENTURE
PARTNERS

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UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Palmetto Health USC
MEDICAL GROUP

PiperJaffray.

 Stemline

TURNSTONE
BIOLOGICS

 UNIVERSITY OF
SOUTH CAROLINA

Our Mission – CANCER ZERO



We believe CANCER ZERO can be a reality

We challenge the status quo by designing gamma-delta ($\gamma\delta$) T cells that can both protect the immune system and target solid tumor cells

We are committed to durable outcomes to give people's lives back!

The Unmet Need in Oncology Trials is Significant

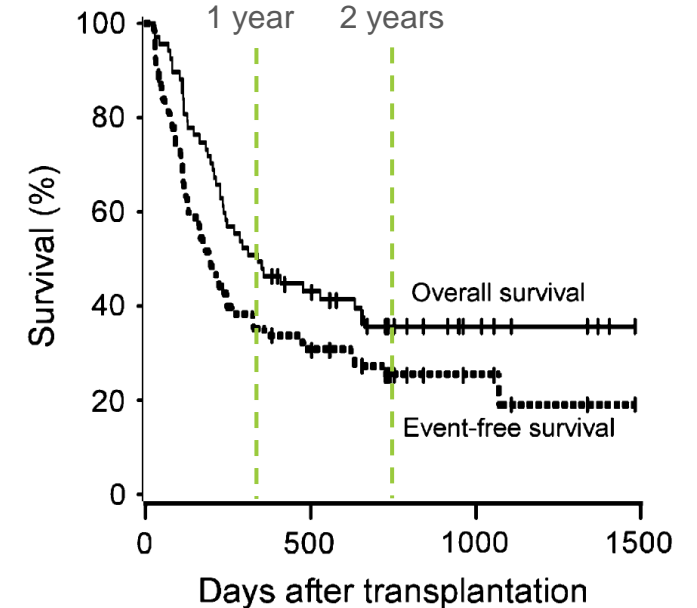
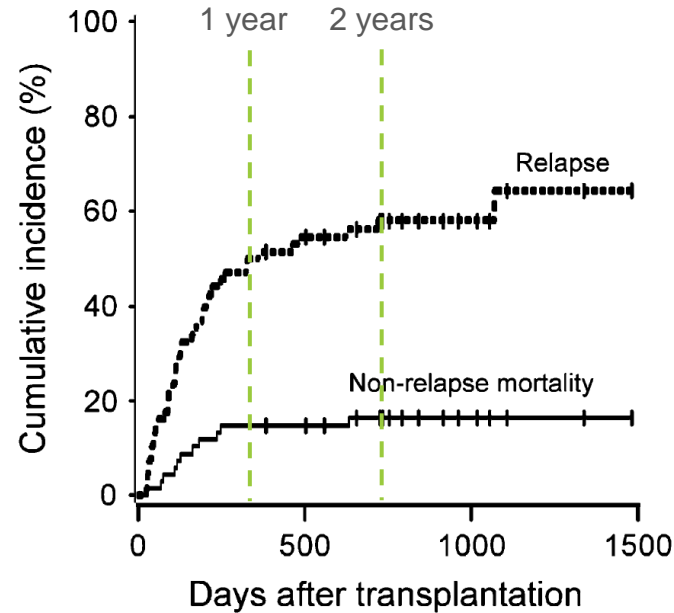
“When I was first diagnosed with AML, we (my wife and I) were updating the will and planning for the worst. Dr. McGuirk and his team discussed the gamma-delta clinical trial and asked if I wanted to participate. I was hoping for a cure, but I figured if I were not to make it, others might learn something from my participation in the trial. We were resigned for the worst but Dr. McGuirk and this trial gave us hope. Today we are living a pretty normal life with people in our community, the church and family. They prayed for us and for a successful treatment. Right now I am feeling good and we are so thankful.” – INB-100 patient

INB-100

Haploidentical Stem Cell Transplantation

The Hopkins Protocol

- Haploidentical transplants have increased the population eligible for stem cell transplantation but retain a ~51% risk of relapse at 1 year
- Gamma- delta ($\gamma\delta$) T cells are an inherent anti-cancer immune cell that may be able to preempt relapse and infections in the post-transplant setting



An Allogeneic Therapy to Reduce Leukemic Relapse

INB-100: Single-center, dose-escalation trial of DeltEx Allo gamma-delta T cells post-haploidentical HSCT

Treatment Arms

Single, ascending dose levels in a 3+3 design:

1. N = 3 (up to 6) patients, single dose of 1×10^6 cells/kg
2. N = 3 (up to 6) patients, single dose of 3×10^6 cells/kg
3. N = 3 (up to 6) patients, single dose of 1×10^7 cells/kg

Treatment Regimen & Timing

Fludarabine +
cyclophosphamide + TBI =
6 days



Haploidentical
HSCT*



INB-100 infusion within
7 days after
engraftment

*Neutrophil engraftment is ~15-20 days following HSCT

Primary Endpoints

- Safety
- Maximum tolerated dose (MTD) of DeltEx Allo gamma-delta T cell infusion
- Dose limiting toxicity (DLT)

Secondary Endpoints

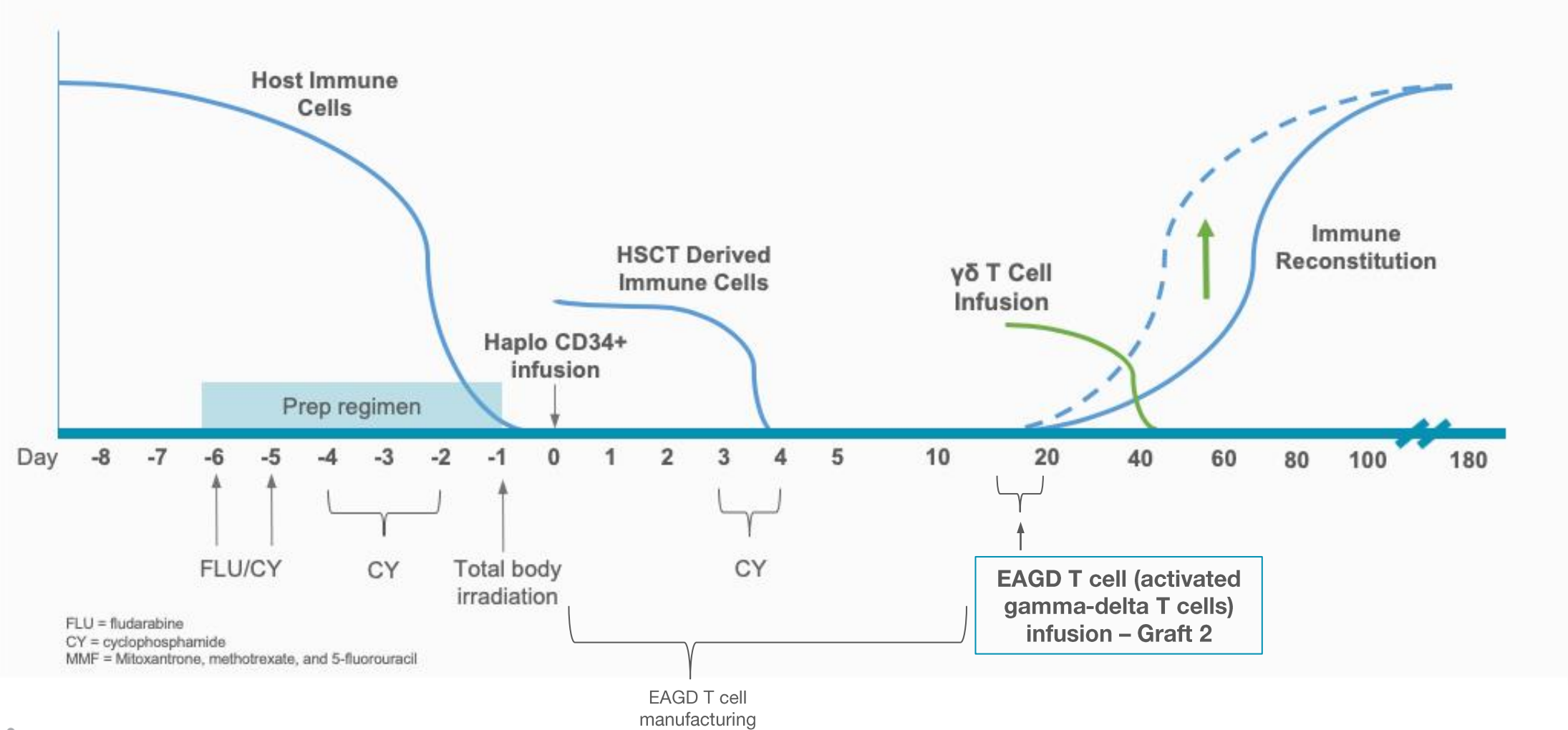
- Rate of acute and chronic graft versus host disease (aGVHD), relapse, and overall survival

Site

THE UNIVERSITY OF KANSAS
CANCER CENTER

Potential to Provide Protection During a Vulnerable Period

Gamma-Delta T Cell Expansion + Activation (EAGD) for Prophylaxis Against Leukemic Relapse



Source: IN8bio

Key Eligibility Criteria

- Adult patients with a haploidentical donor identified and successfully apheresed
- KPS ≥ 70
- Acute myeloid leukemia (AML) in morphologic complete remission (mCR) with intermediate/high-risk features or relapsed disease
- Chronic myelogenous leukemia (CML) in any chronic phase
- Myelodysplastic syndromes (MDS) with intermediate/high risk features
- Acute lymphocytic leukemia (ALL) in mCR with high-risk features or relapsed disease

Status of Patients Currently on Study

Patient	Dose Level	Age / Sex	Cytogenetics	Prior lines	Treatment Related Safety Events	Morphologic CR Duration (mos)
002	1	54 / female	High-risk AML trisomy 8+ and del7; FLT3 TKD, DNMT3A,	7+3+Idasanutlin	Gr.2 skin aGvHD- resolved	36.2+
003	1	45 / female	High-risk AML trisomy 8+ and del7: IDH2	7+3	Gr.2 GI aGvHD and Gr.2 skin rash Remains on Jakafi for skin GvHD	33.9+
006	1	66 / male	Relapsed AML s/p 7+3, ASXL1	7+3	Gr.2 skin aGvHD-resolved	22.2+
007	1	71 / male	Relapsed AML s/p 7+3, ASXL1	Pembrolizumab	Gr.2 skin aGvHD-resolved	7.8+
009	2	68 / male	Ph- ALL; p53 mutated, DNMT3A, GATA2	Induction E1910, blincyto, inotuzumab x2 cycles, CAR-T with Tecartus	Gr.1-2 skin GvHD within 2 weeks of $\gamma\delta$ infusion and Gr.2 diarrhea of unclear etiology	5.8+
010	2	62 / female	Relapsed AML	Hydrea; vidaza/venetoclax x7 cycles	Gr.2 skin GvHD within 30 days of $\gamma\delta$ infusion with undefined GI symptoms	5.6+
011	2	68 / male	ET, triple neg, with MDS/MPN overlap	Hydrea		2.6+
013						

Most Common (>3 pts.) or Critical Treatment Emergent AE's

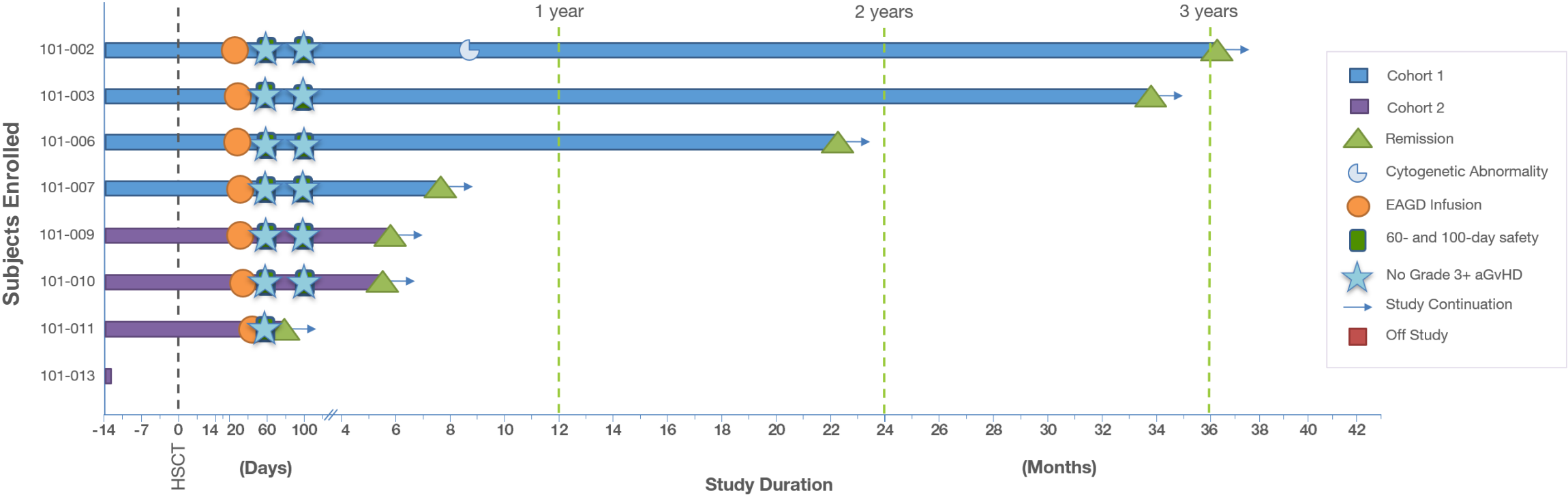
AE	Total (%)	Grade 1/2	Grade 3	Grade 4
WBC decreased	100			100
Anemia	100	14	86	
ALC decreased	29			29
ANC decreased	85	14	14	57
Platelet count decreased	100			100
Nausea	85	71	14	
Vomiting	57	57		
Diarrhea	57	57		
Acute GI GVHD	14	14		
Constipation	29	29		
Hypomagnesemia	71	71		
Hypokalemia	71	71		
Fatigue	29	29		
Noninfective cystitis	29	29		
Acute skin GVHD	71	71		
Rash	43	29	14	
Pruritus	29	29		
Creatinine increased	43	43		
Edema	43	43		

- 9 enrolled, N=7 evaluable for safety
- No DLT's as of Apr. 21, 2023
- 2 patients with CMV reactivation
- **Treatment Related SAE's:**
 - Gr.3 Acute Kidney Injury & Gr.2 acute skin GVHD in one patient
 - Gr.3 nausea in another patient
- **Other non-treatment related SAE's include:**
 - 001:Gr.5 multiorgan failure
 - 003: Gr.3 CMV reactivation
 - 004: Gr.5 sepsis and G4 MDS
 - 006: Gr.3 skin infection
 - 011: Gr.2 heart failure, a-fib and hemorrhagic cystitis
- **No treatment related deaths as of Apr. 21, 2023**
- **No SUSAR's or unexpected safety events reported as of Apr. 21, 2023**

INB-100: Long-term Durability of Responses

Clinical Results to Date

- 7 patients treated
- no DLTs, no CRS, ICANs or GvHD of grade 3 or greater
- Two of three patients surpassing 2 years and one patient nearing 2 years remaining in morphological complete remission



First patient surpassing 3 years without leukemic relapse

Immune Reconstitution



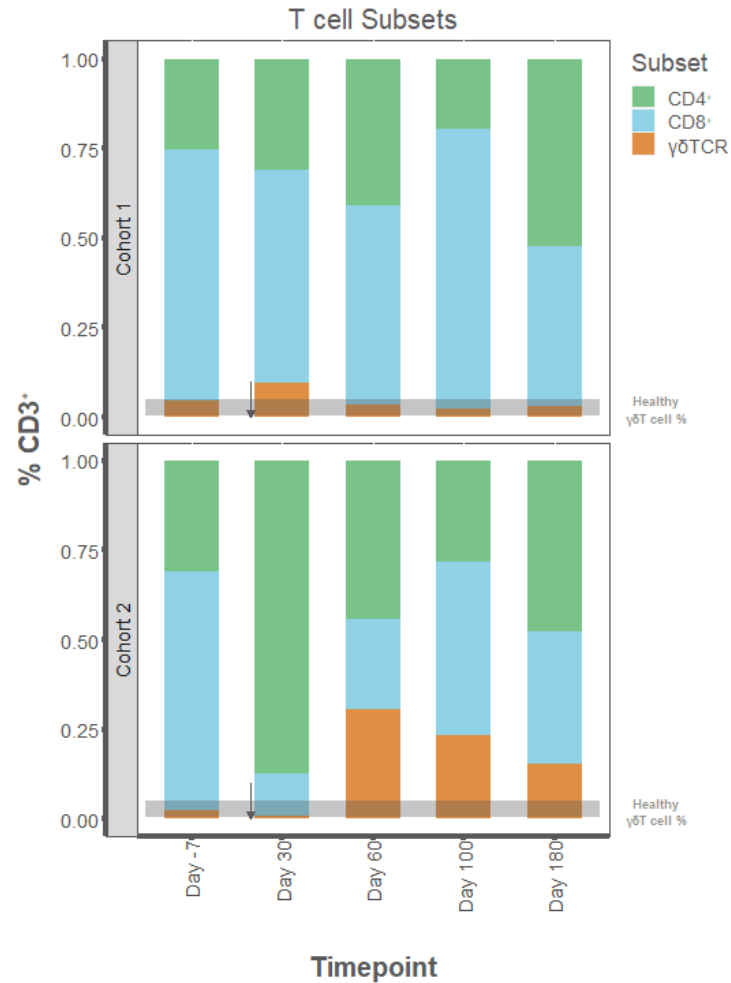
Lymphocyte subset absolute count (a)

- Significant T cell depletion through the first 100 days post-BMT followed by slow recovery of abCD3+CD4+ and abCD4+CD8+ T cells.
- In both Cohort 1 and 2 patients, $\gamma\delta$ T cells (primarily V δ 2+ subtype) slowly recovered and increased toward normal levels.
- B cell counts recovered in the first 30 days and NK cells remained within the low normal range throughout.

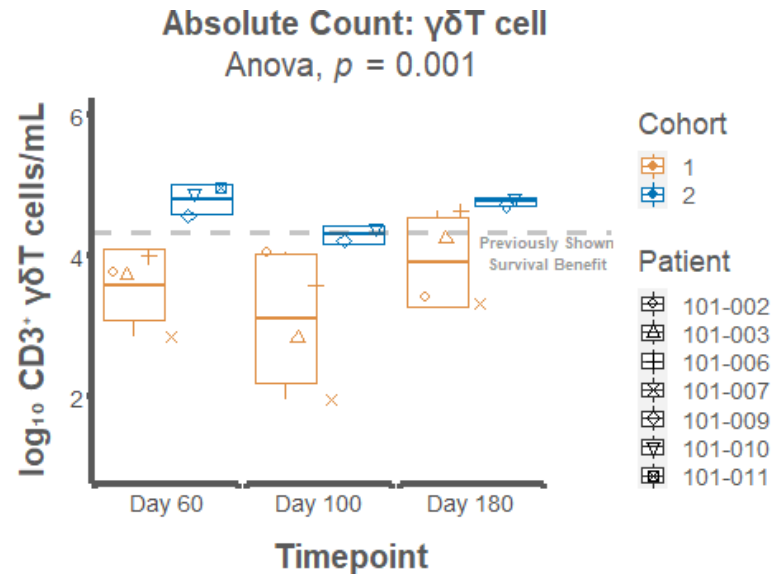
NK cells known to be the first to recover in the haploidentical setting, remain generally within normal ranges throughout treatment and are therefore proportionately higher.

Importantly, a significant ($p = 0.001$) increase in $\gamma\delta$ T cells count (b) was noted at the Day +60, +100 and +180 timepoints for Cohort 2 over Cohort 1, demonstrating greater continuing expansion and persistence of $\gamma\delta$ T cells at the higher dose level.

$\gamma\delta$ T Cell Reconstitution

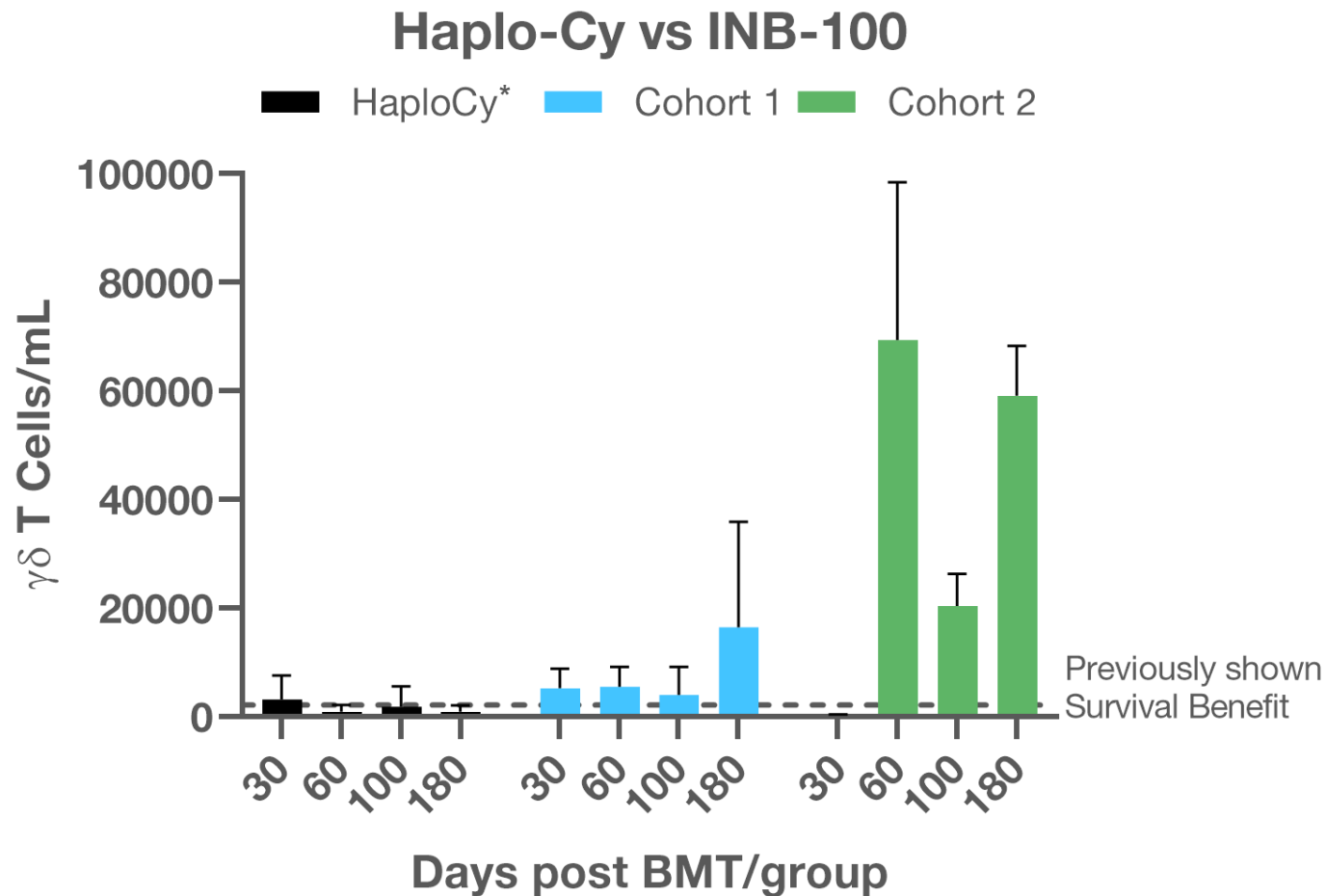


Durability Between Cohorts



- Significant ($p = 0.001$) increase in absolute $\gamma\delta$ T cell count noted at the Day+60, Day +100 and Day +180 timepoint for Cohort 2 patients over those in Cohort 1
- Cohort 2 patients received 3x the $\gamma\delta$ T cell dose, thereby increasing the potential for homeostatic reconstitution and durability consistent with numbers previously reported in clinical studies for haploidentical transplant to improve survival

Absolute $\gamma\delta$ T Cell Counts

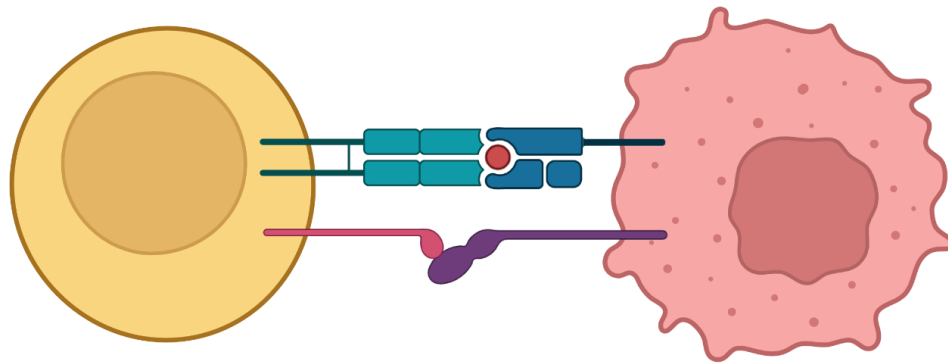


- Comparison of $\gamma\delta$ T cell count recovery between patients who received haploidentical BMT + post-BMT Cy without $\gamma\delta$ T cell infusion and INB-100 patients from Cohort 1 and Cohort 2
- Cohort 2 patients receive 3x the $\gamma\delta$ T cell dose as Cohort 1
- Dose dependent increase of circulating $\gamma\delta$ T cells at Days +60, +100 and +180 for INB-100 treated patients

INB-300

Current CAR-Ts Target both Malignant and Normal Cells

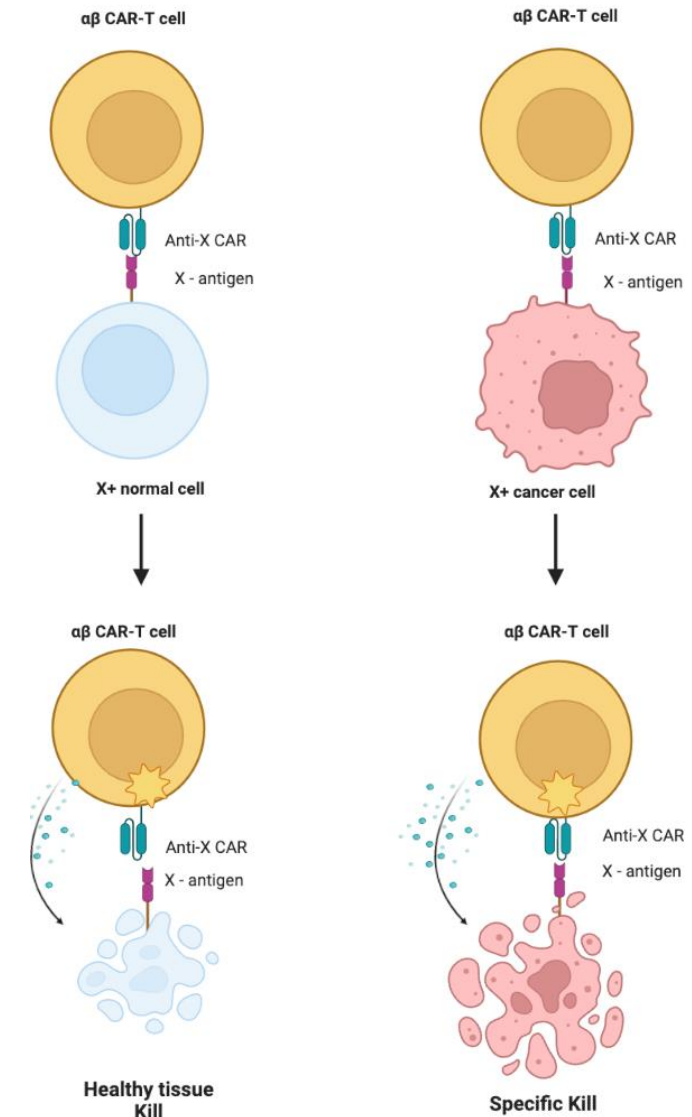
Targeting tumor associated antigens (TAAs) drive tissue aplasia



$\alpha\beta$ CTL

Cancer cell

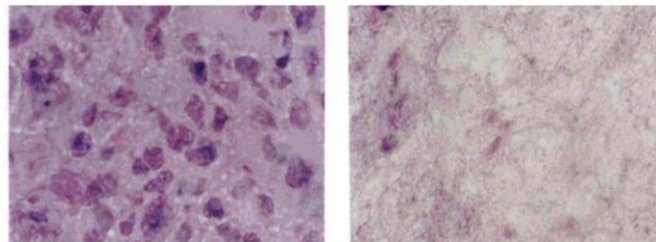
- Alpha-beta ($\alpha\beta$) cytotoxic T Lymphocytes (CTL) are narrowly specific for TAA peptides, but CAR-T constructs will bind to any cell expressing the target antigen



A Unique CAR-T Platform that Spares Healthy Tissue

Novel Non-Signaling $\gamma\delta$ CAR-T Platform (ns-CAR)

- ns-CAR platform lacks CD3 ζ signaling domain
- IL-15 included to increase cell persistence
- Multiple recognition domains can be utilized:
 - Peptides such as chlorotoxin (CLTX) that bind glioma and numerous other solid tumor cancers with limited binding to healthy tissues⁽¹⁾

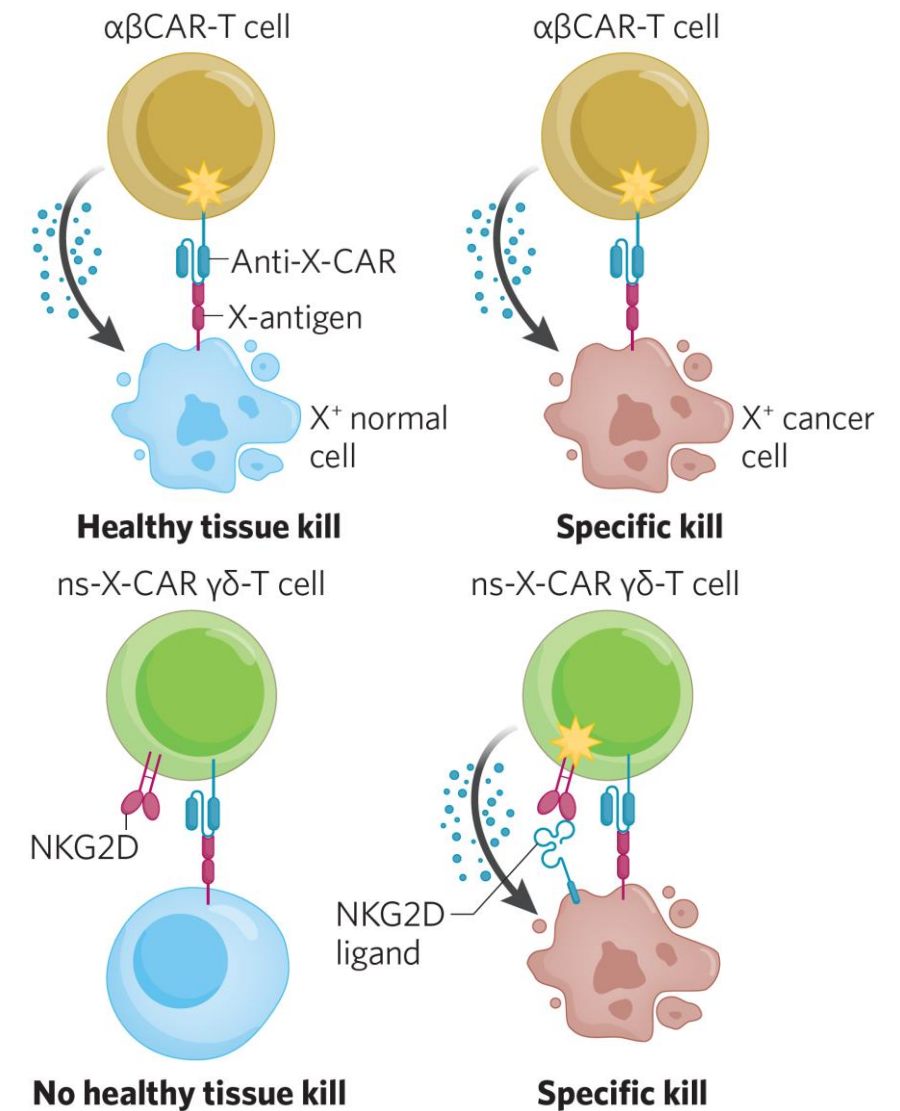


GBM+CLTX

Normal+CLTX

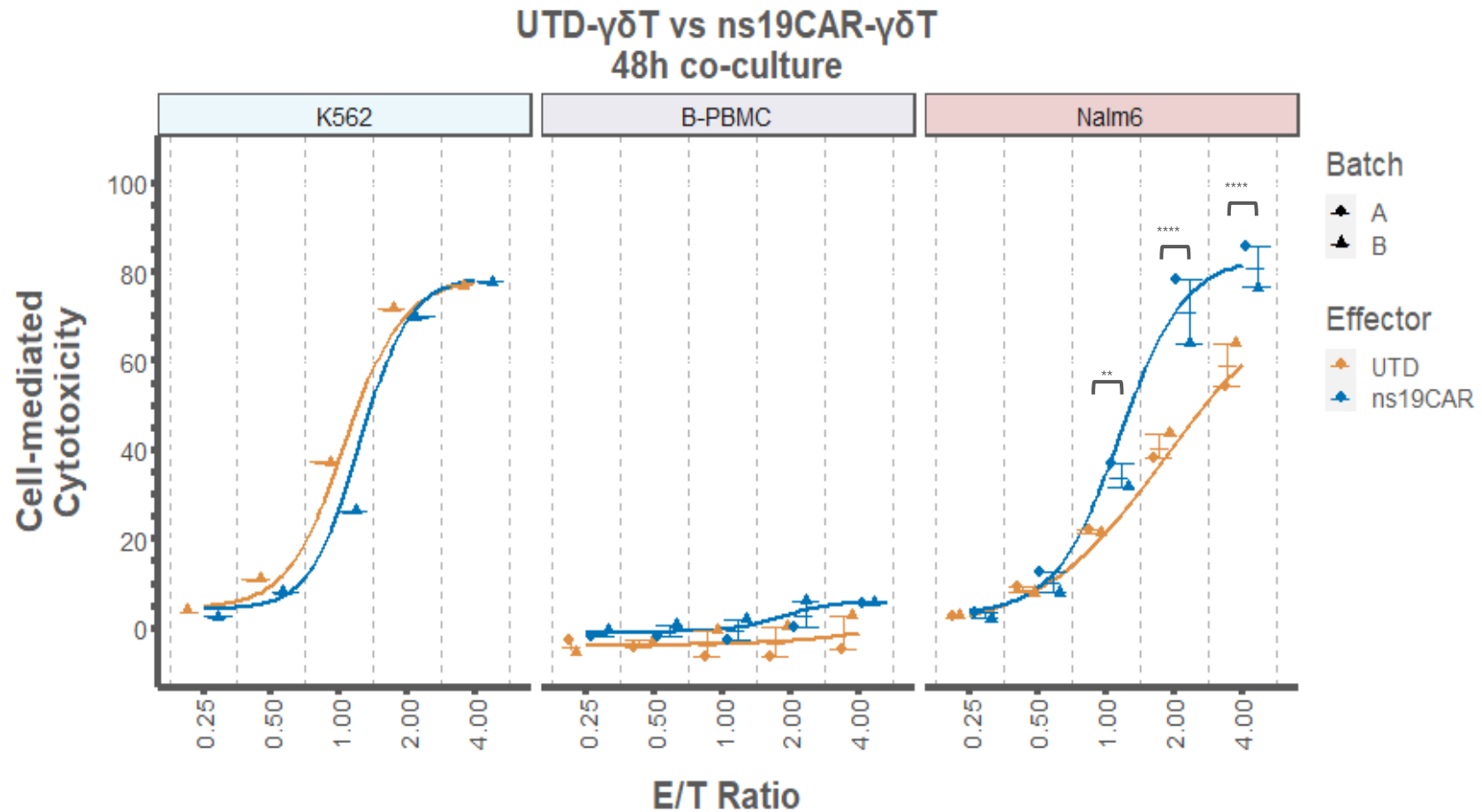
CLTX stains tumors but not healthy tissue

- Preclinical CD19 proof-of-concept demonstrates a >15x difference in the ability to spare healthy B cells from PBMCs while having high cytotoxicity against Nalm6 CD19+ leukemia cells
- INB-330 - Advancing a novel CD33 construct for AML

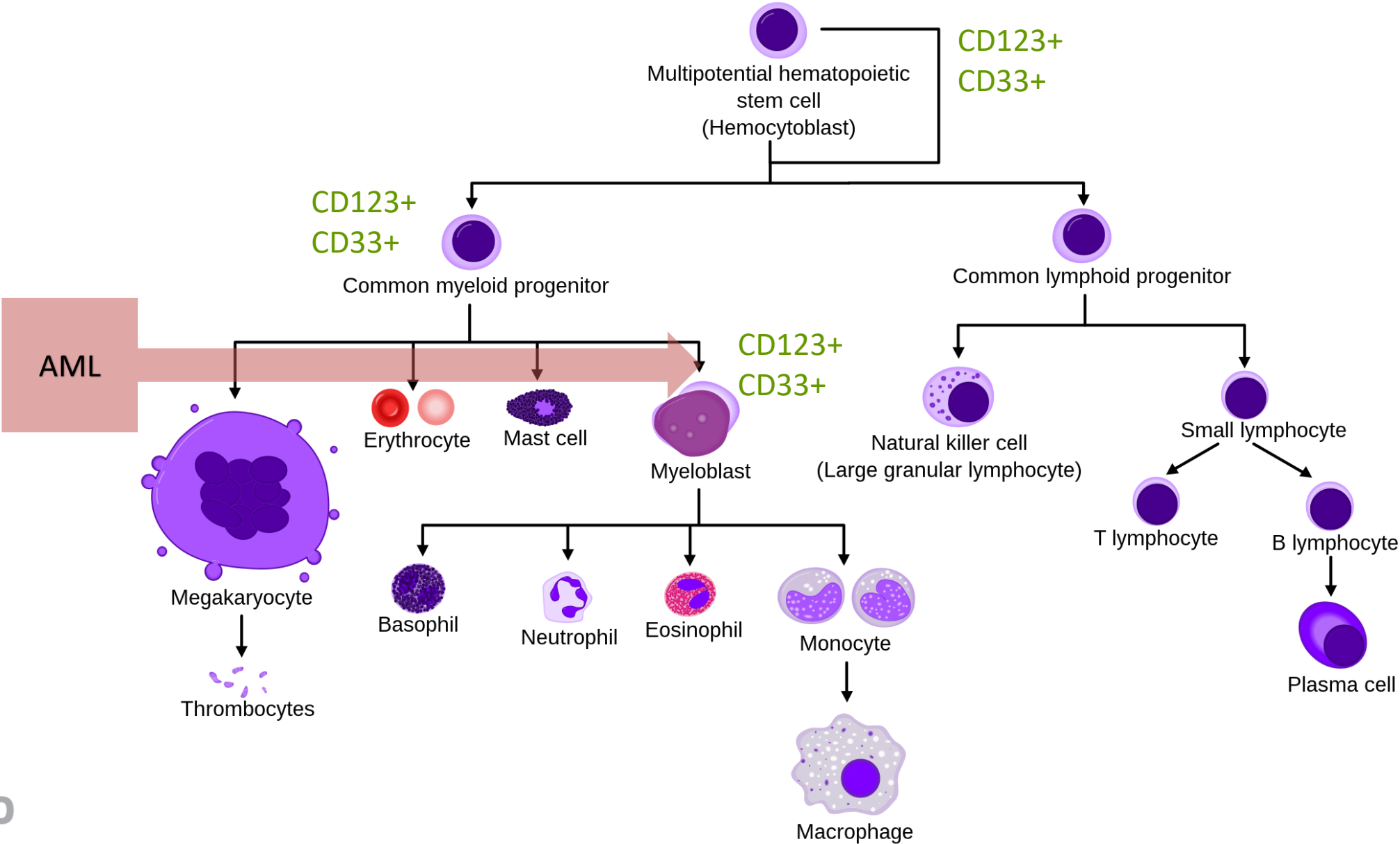


ns19CAR $\gamma\delta$ T Cytotoxicity: 48hr. Co-culture

K562 (CD19+), Nalm6 (CD19+) and B-PBMC (CD19+) cells; 2 experiments, normalized



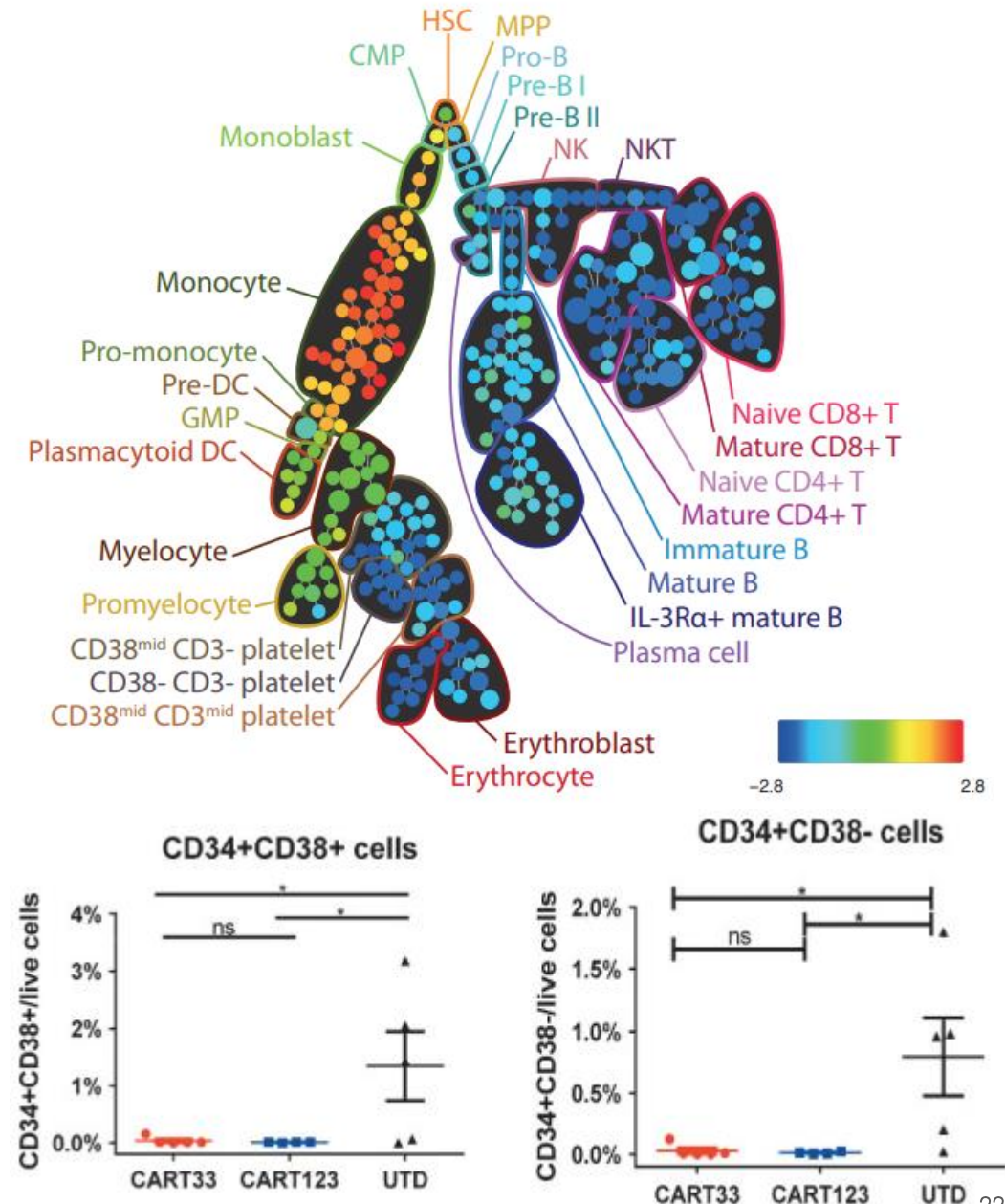
Overview: Hematopoiesis and AML



AML and CAR targeted therapies:

Current state and challenges

- AML is the most common acute leukemia in adults
- No specific and optimal target antigen for AML
- CD33 is expressed in majority (>90%) of the AML cells, high expression indicates poor outcomes
- CD33 is also expressed in normal myeloblasts and HSPCs
- Unclear biological function, maybe redundant?
- Drug delivery: Internalize drug cargo upon monoclonal antibody binding
- Current CAR (signaling CAR-T/NK) therapy : targeting CLL-1, CD33, or CD123
 - Challenges:
 - Limited efficacy
 - Lacking specific AML TAA
 - On-target off-tumor cytotoxicity to HSCs and HPCs lead to impaired hematopoiesis
 - CRISPR/Cas KO of CD33 in HSCs before CD33CAR-T infusion
 - Transient expression of CAR(mRNA electroporation)



Validation of CD33-nsCAR with CD69 activation in Jurkats

To validate the function of the sCAR and nsCAR constructs, transduced Jurkat cells are cocultured with KG-1 AML cells that are CD33+(nTPM:37.9*), CD123+(nTPM:21.7*) and PD-L1_low (nTPM:0.5*)

signaling-CAR

Non signaling-CAR

UTD

CD33-Z-EGFP

Tonic
signaling

CD33-noZ-EGFP

CD33-noZ-mCherry

w/o KG-1

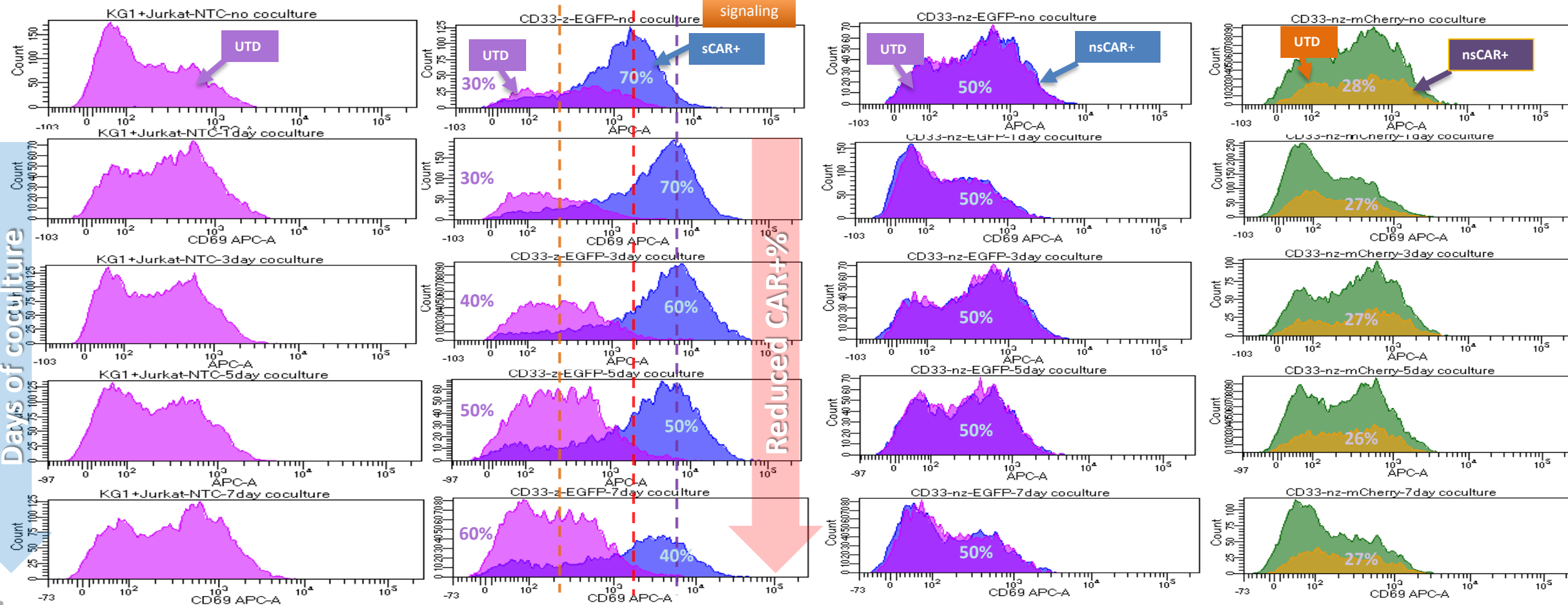
w/ KG-1
1-Day

w/ KG-1
3-Day

w/ KG-1
5-Day

w/ KG-1
7-Day

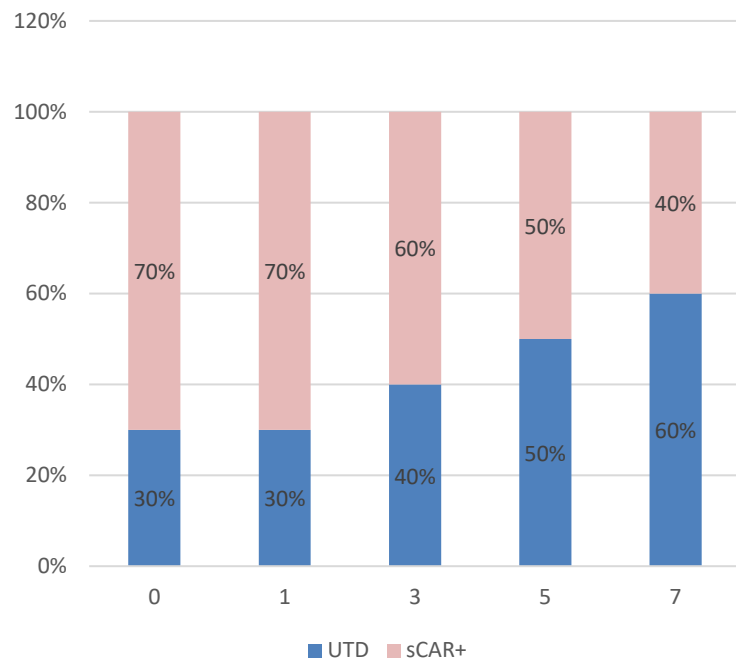
Days of coculture



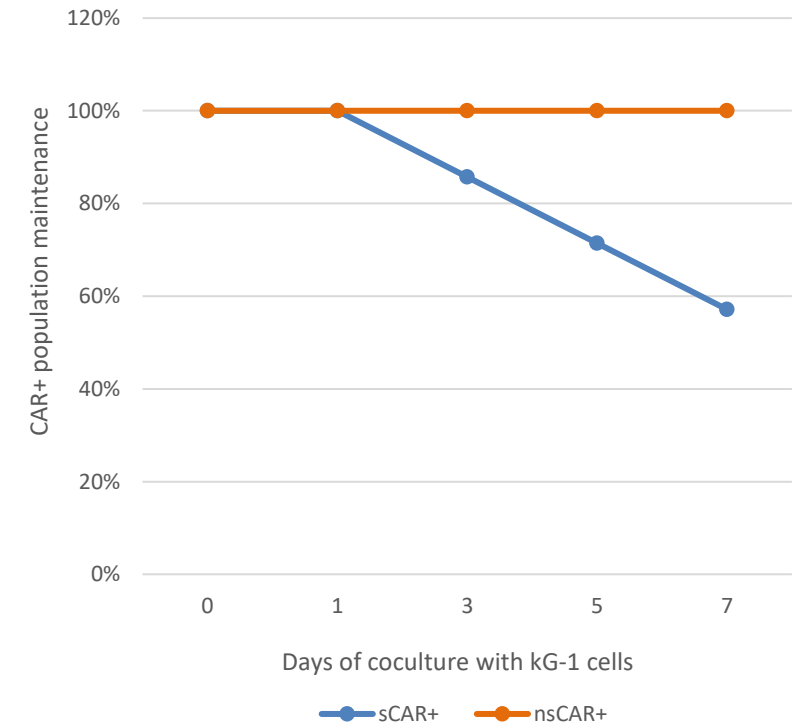
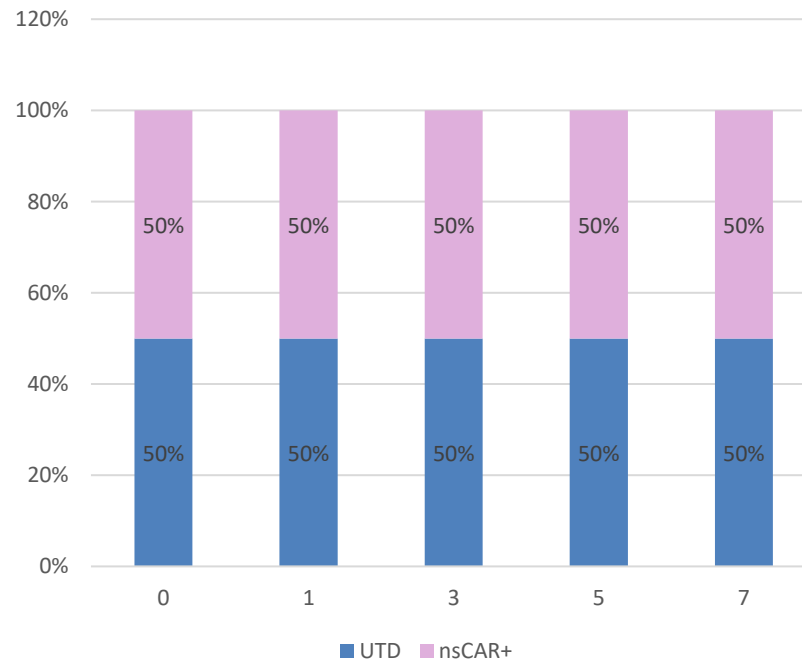
nsCAR Platform Prevents AICD and Loss of CAR

s33CAR Jurkat cells show AICD when cocultured with target cells for extended time

sCAR+% vs days of KG-1 coculture

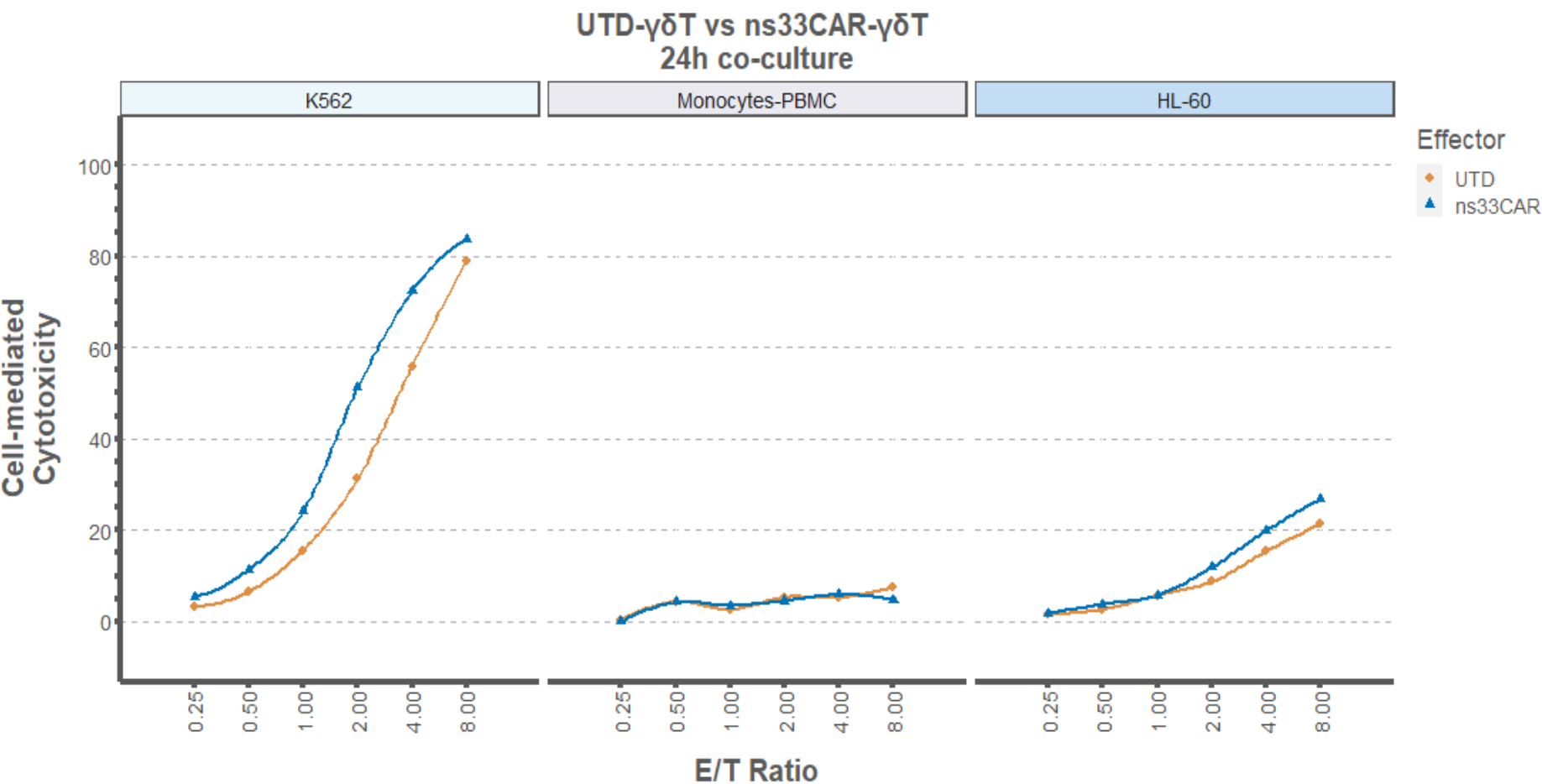


nsCAR+% vs days of KG-1 coculture

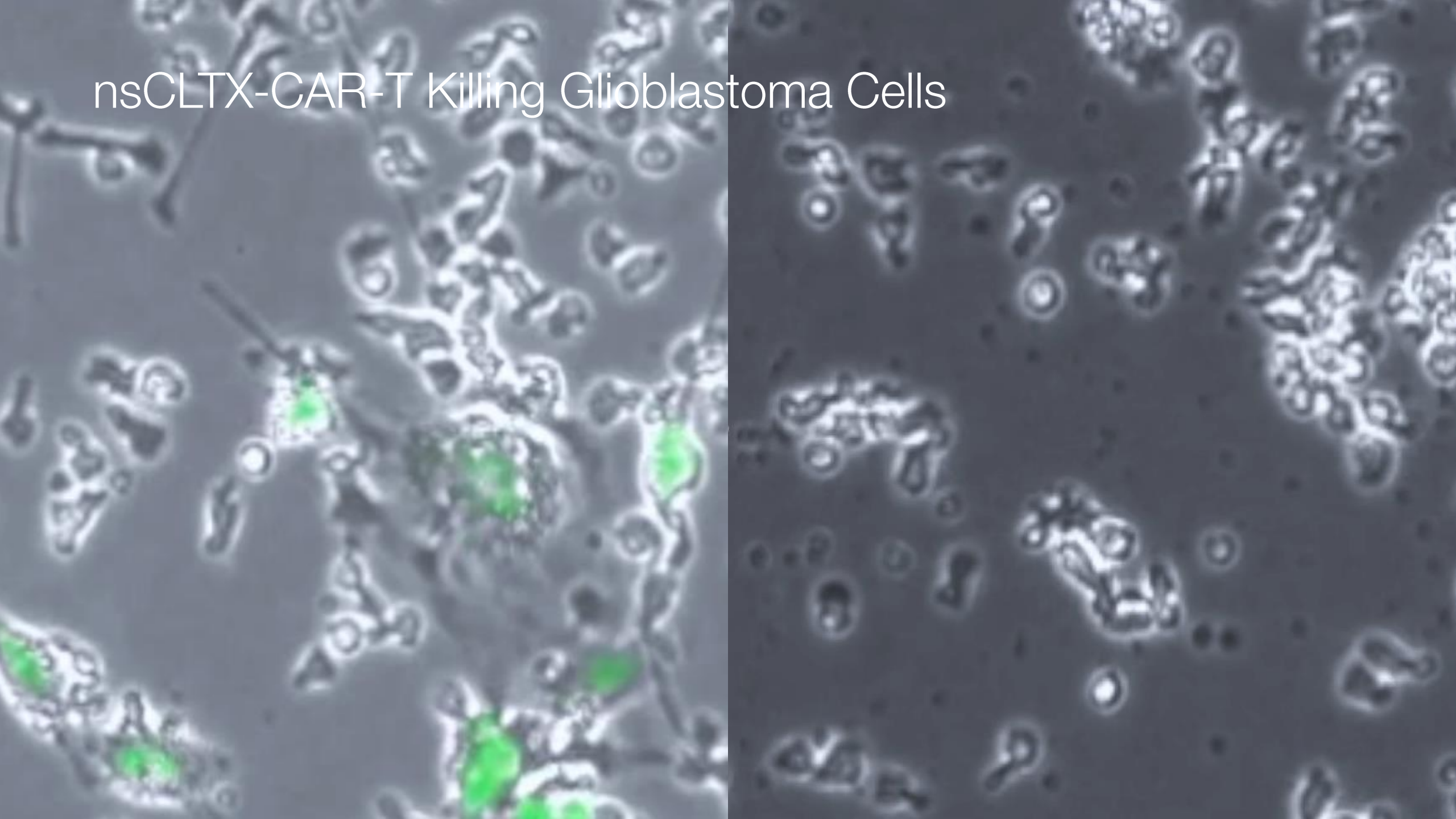


ns33CAR $\gamma\delta$ T Cytotoxicity: 24hr. Co-culture

K562 (CD33+), HL-60 (CD33+) and Monocytes-PBMC (CD33+) cells; 1 experiments



nsCLTX-CAR-T Killing Glioblastoma Cells





Harnessing the Power of Gamma-Delta T Cells

April 2023