SENTI BIO™

SENTI-202
FLT3 OR CD33 NOT EMCN CAR-NK Cell Approach for Precise Targeting of AML

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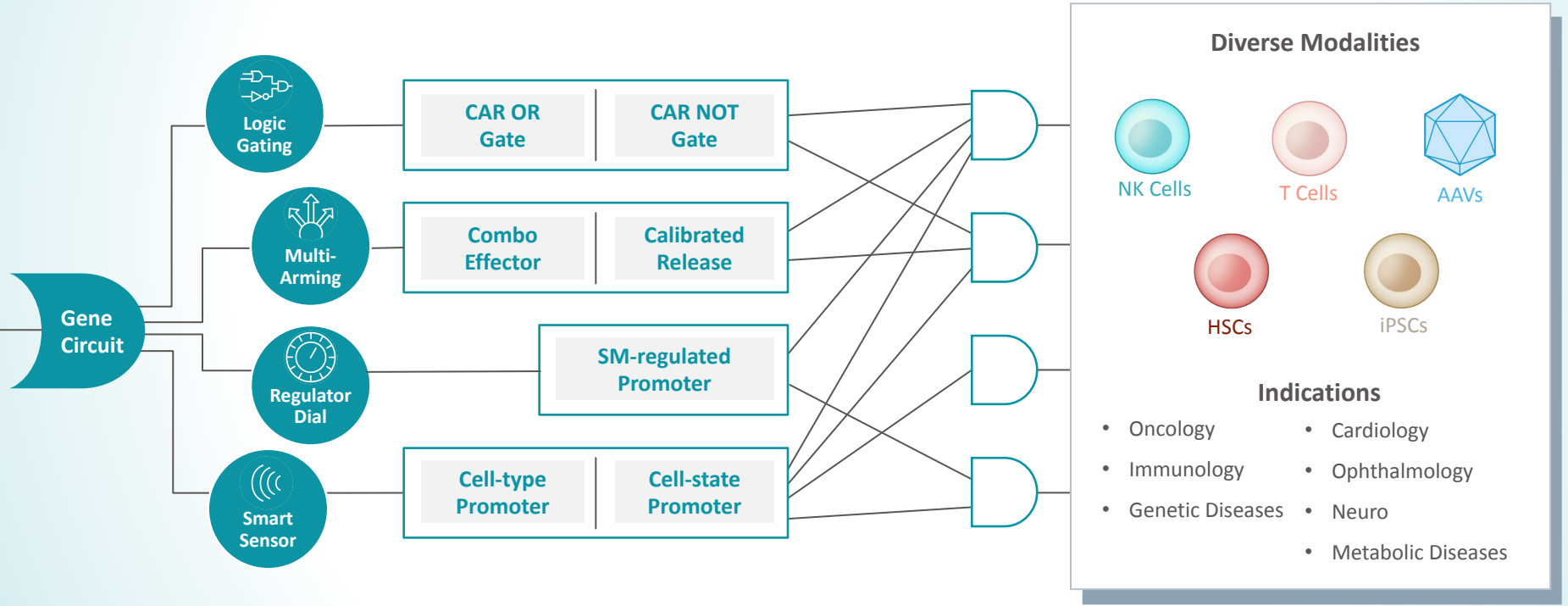
Senti Biosciences, Inc.

ASGCT 2022
Wed, May 18, 2022

Disclaimer

- Employee of Senti Biosciences, and receive salary and benefits from the company

Gene Circuits Could Potentially Power Multiple Cell and Gene Therapy Modalities for Broad Therapeutic Potential



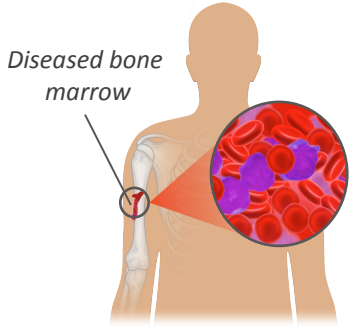
SENTI-202: Designed to Address Unmet Needs in the Treatment of Acute Myeloid Leukemia (AML)

SENTI'S LOGIC GATES SOLVE KEY DISEASE CHALLENGES IN AML

CHALLENGES	SENTI GENE CIRCUIT SOLUTIONS
Target heterogeneity Relapse due to incomplete targeting of leukemic stem cells (LSCs)	**OR Logic Gate** Targets multiple AML tumor associated antigens for improved clearance and lower relapse
Target heterogeneity Off-tumor toxicity and limited efficacy due to lack of AML-specific targets	**NOT Logic Gate** Enables broad targeting of AML while preserving healthy blood stem cells

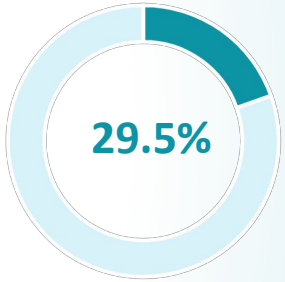
UNMET NEED IN AML

2020 US Incidence[1]



~20K
Patients diagnosed with AML this year

5-Year Survival[1]

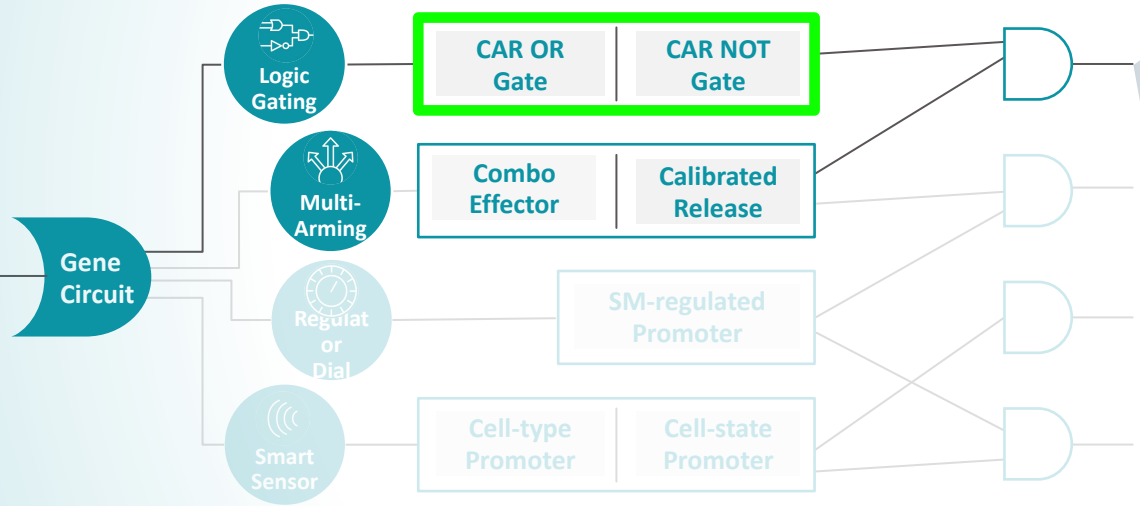


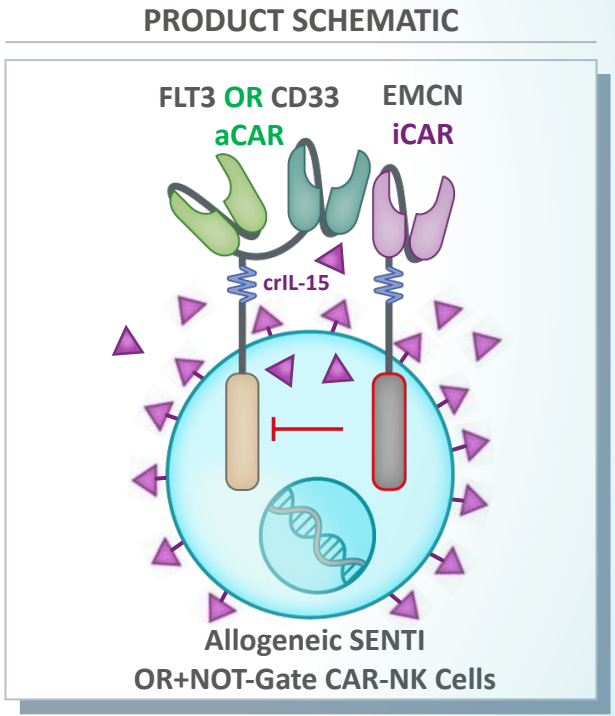
DUE TO DISEASE RELAPSE DRIVEN BY LEUKEMIC STEM CELLS (LSCs)

SENTI'S LOGIC-GATED CAR-NK PROGRAM OFFERS POTENTIAL TO DEVELOP A CURE FOR AML PATIENTS IN THE ABSENCE OF A BONE MARROW TRANSPLANT

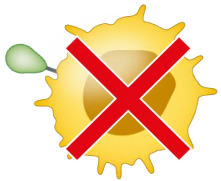
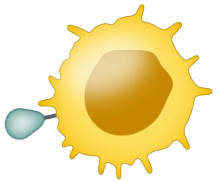
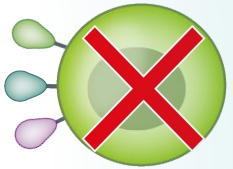
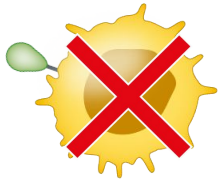
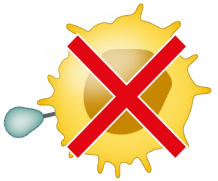
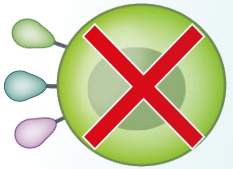
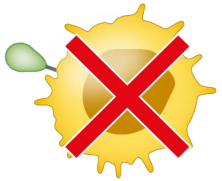
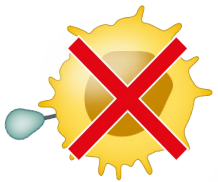
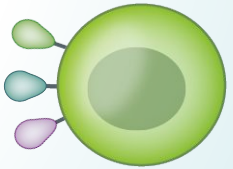
[1] SEER Cancer Stat Facts: Acute Myeloid Leukemia

SENTI-202: Potential to Develop a Cure Without a Bone Marrow Transplant





SENTI-202: Logic Gated Gene Circuit May Enable Clearance of AML Blasts & LSCs While Sparing Healthy HSCs

	SENSE INPUTS	COMPUTE LOGIC	RESPOND WITH OUTPUTS: AML Blasts	AML Stem Cells	Healthy HSCs/PCs
	Antigen: CD33, FLT3, EMCN				
	CD33	NO LOGIC			
	FLT3, CD33	OR GATE ONLY (FLT3 OR CD33)			
SENTI-202	FLT3, CD33, EMCN	OR/NOT GATE (FLT3 OR CD33) NOT EMCN			

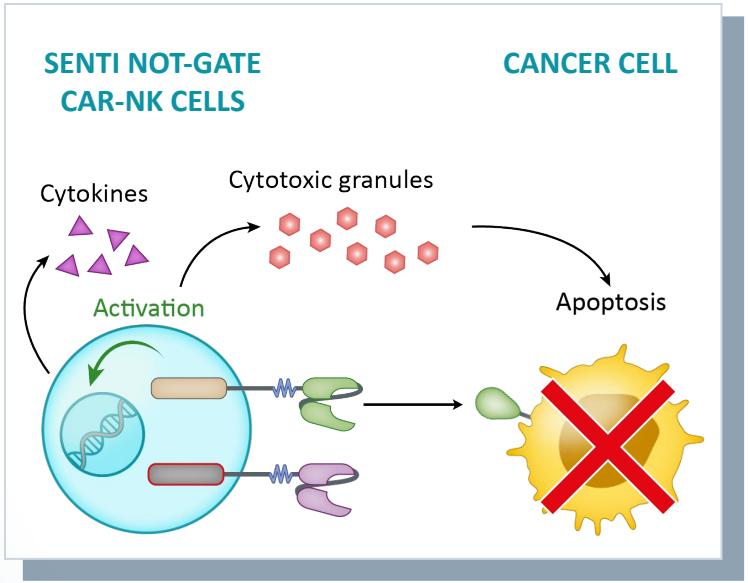
CD33 is over-represented on AML blast cells; FLT3 is a marker for AML LSCs; HSCs=hematopoietic stem cells; PCs = progenitor cells

Fast Logic Gating Enables Highly Specific Therapies by Recognizing Multiple Antigens

Toolbox of Gene Circuits

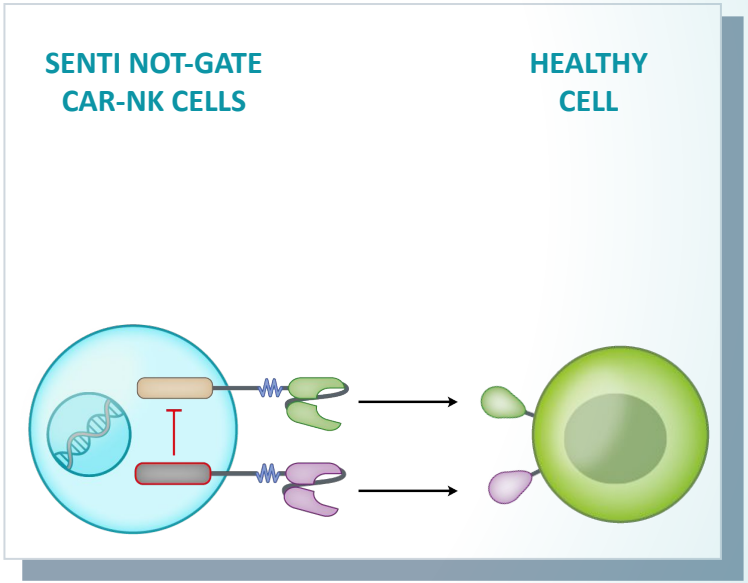
- Logic Gating
- Multi-Arming
- Regulator Dial
- Smart Sensor

TUMOR-ASSOCIATED ANTIGENS (TAA) ENGAGEMENT TRIGGERS CANCER CELL KILLING



Activating CAR (aCAR) — Tumor-Associated Antigens

SAFETY ANTIGEN ENGAGEMENT ENABLES PROTECTION OF HEALTHY CELLS

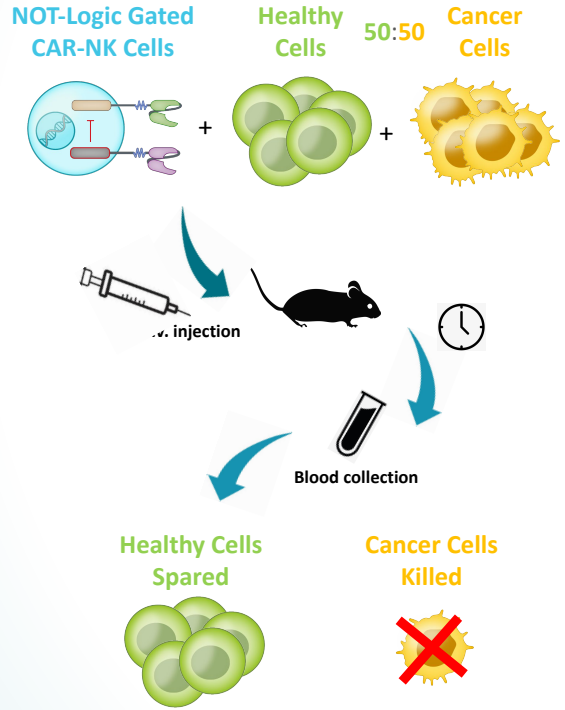


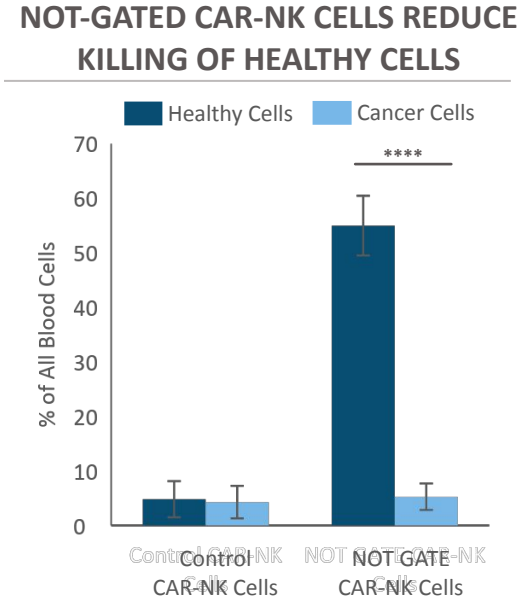
Inhibitory CAR (iCAR) — Safety Antigen

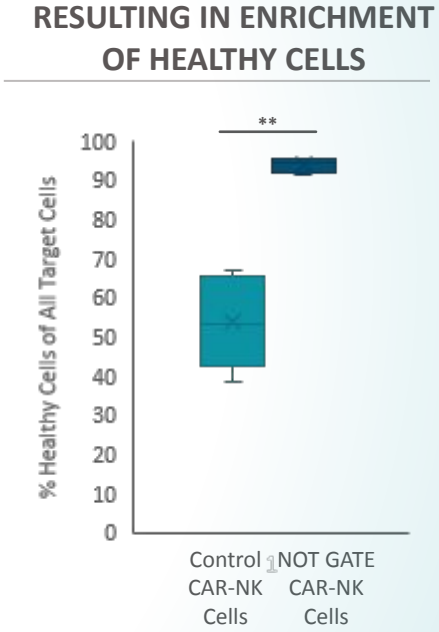
NOT Logic Gate Functions *In Vivo* to Specifically Kill Cancer Cells and Spare Healthy Cells

Toolbox of Gene Circuits

- Logic Gating
- Multi-Arming
- Regulator Dial
- Smart Sensor



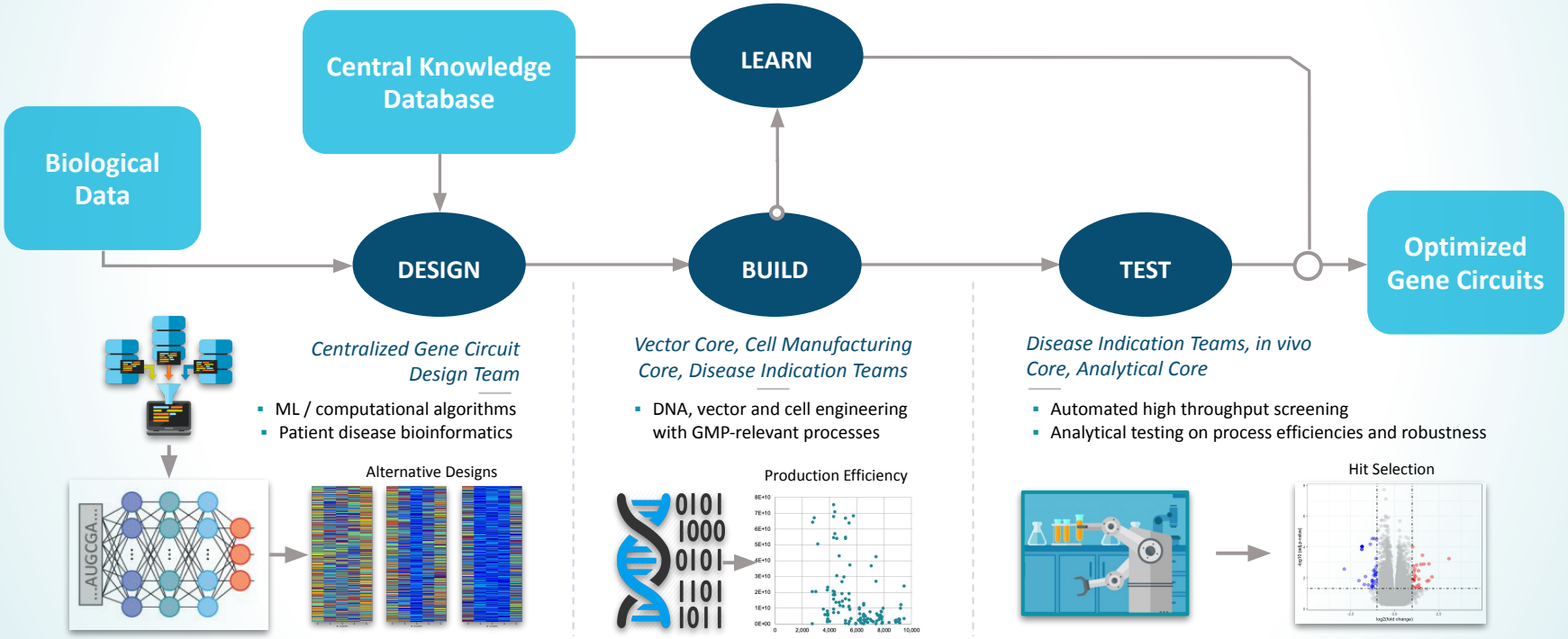




Source: Internal data

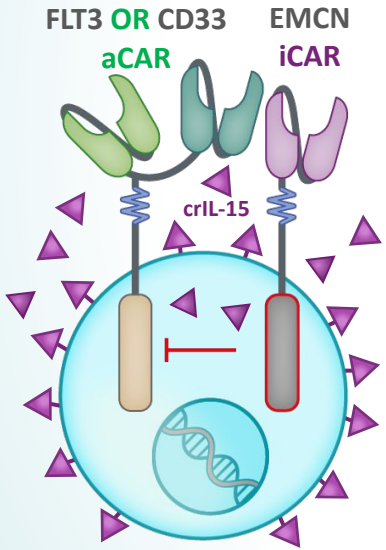
Powerful and Scalable Engine Optimizes Gene Circuits to Enable Creation of Intelligent Medicines

SENTI'S DESIGN-BUILD-TEST-LEARN ENGINE



Systematic Gene Circuit Optimization for FLT3 OR CD33 NOT EMCN CAR-NK Cell Development

1. NK Cell Engineering Platform
2. Gene Circuit Promoter Design
3. Bivalent Activating CAR (aCAR) Binder Design
4. Inhibitory CAR (iCAR) Binder Design
5. Inhibitory CAR (iCAR) Intracellular Domain
6. Calibrated release IL-15
7. Complete circuit
8. POC Data



Allogeneic SENTI OR+NOT Gate CAR-NK Cells

>500 SENTI-202 total constructs tested

1. NK Cell Engineering Platform Optimization Yielded >80% CAR Expression

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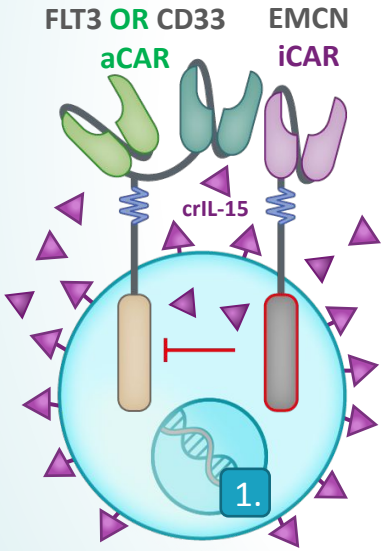
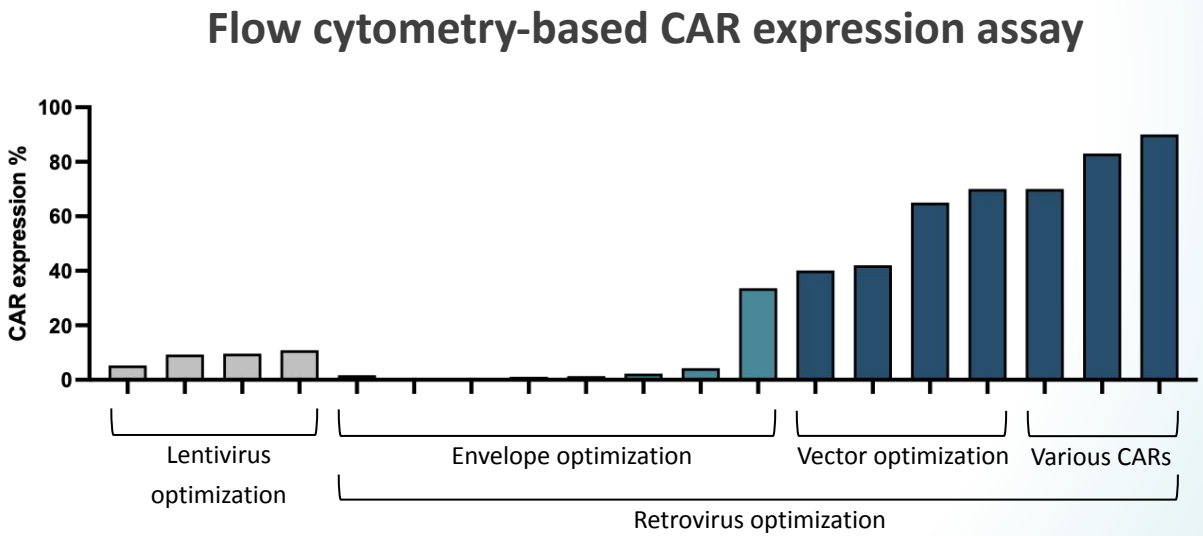


Allogeneic SENTI OR+NOT Gate CAR-NK Cells



Source: Internal data

2. Gene Circuit Promoter Design Optimization Enabled >70% CAR expression

1. NK Cell Engineering Platform
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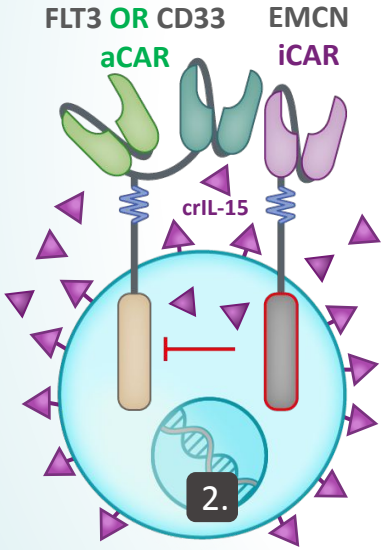
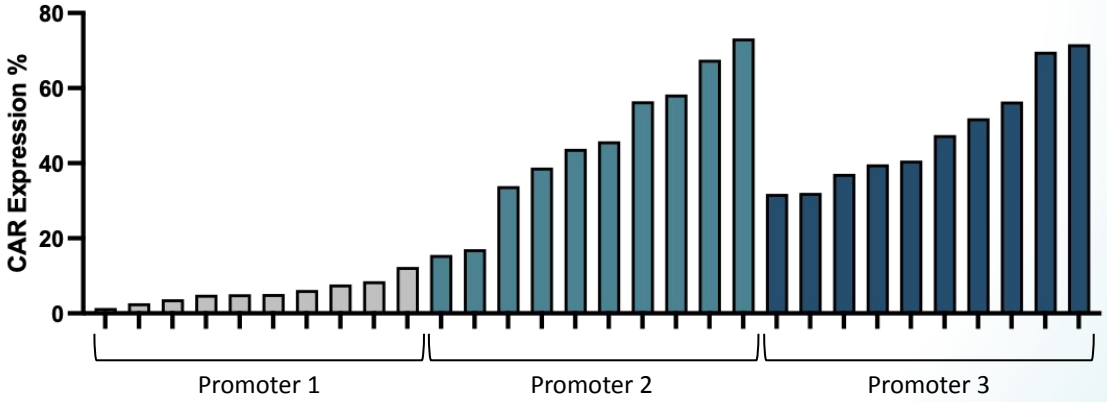


Allogeneic SENTI OR+NOT Gate CAR-NK Cells

Flow cytometry-based CAR expression assay



Source: Internal data

3. Bivalent Activating CAR (aCAR) Binder Optimization Significantly Improves *In Vivo* Tumor Suppression and Mouse Survival

1. NK Cell Engineering Platform
2. Gene Circuit Promoter Design
3. **Bivalent Activating CAR (aCAR) Binder Design**
4. Inhibitory CAR (iCAR) Binder Design
5. Inhibitory CAR (iCAR) Intracellular Domain
6. Calibrated release IL-15
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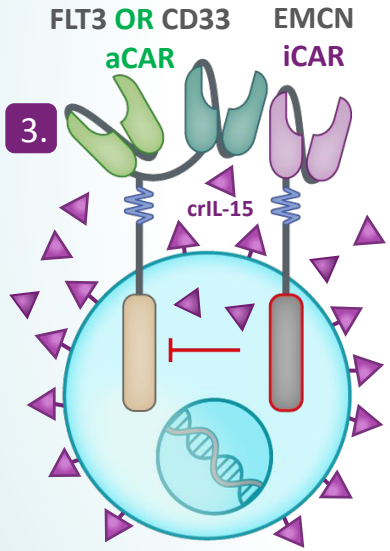
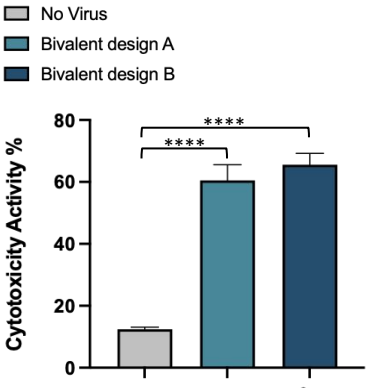
8. POC Data



Allogeneic SENTI OR+NOT Gate CAR-NK Cells

In Vitro Cytotoxicity activity

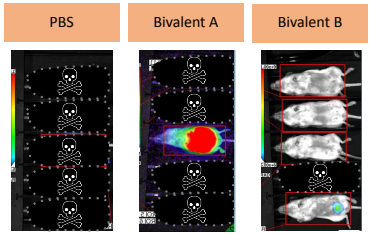
AML Killing Assay



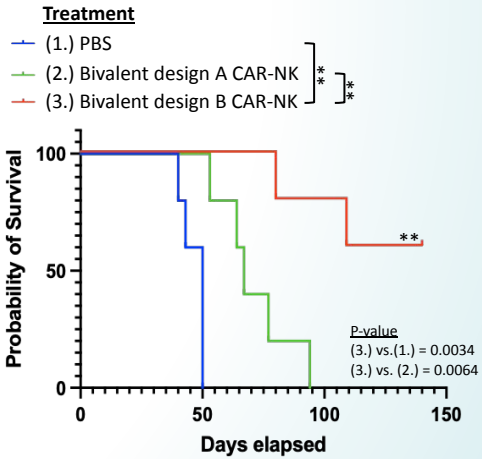
In Vivo AML (MV4-11) Tumor Suppression

Tumor bioluminescence

AML (MV4-11) imagining: Day 87

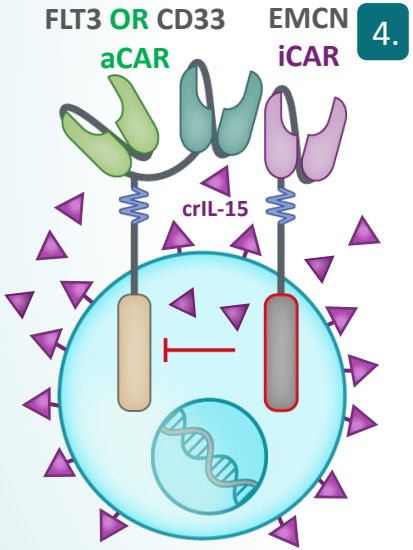


Mouse Survival Curve



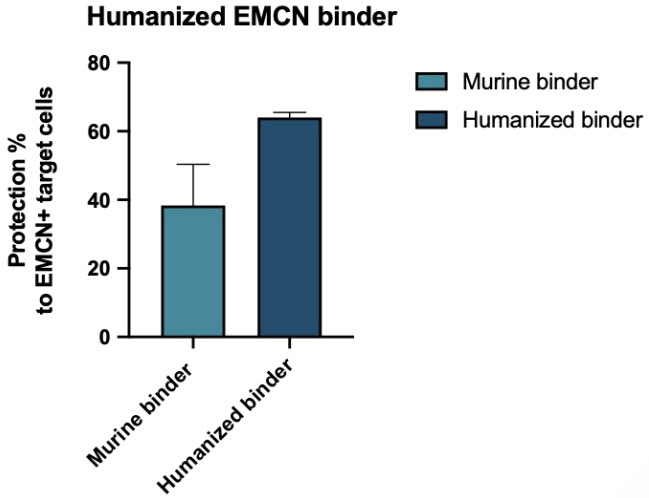
Source: Internal data

4. *Inhibitory* CAR (iCAR) Binder Humanization Process Increased NOT GATE function



Allogeneic SENTI OR+NOT Gate CAR-NK Cells

NOT GATE cell protection assay



Source: Internal data

5. *Inhibitory* CAR (iCAR) Intracellular Domain Screen Identified Architectures Most Compatible with SENTI-202 Target Antigens

1. NK Cell Engineering Platform
2. Gene Circuit Promoter Design
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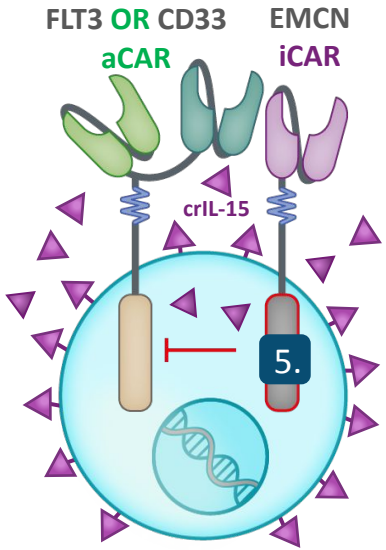
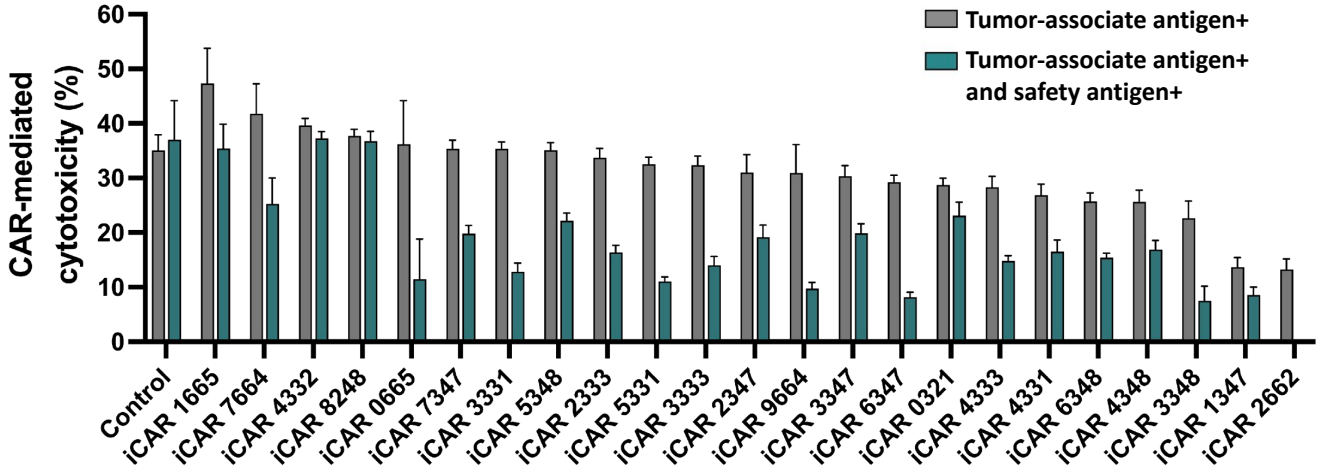
5. **Inhibitory CAR (iCAR) Intracellular Domain**
6. Calibrated release IL-15
7. Complete circuit
8. POC Data



Allogeneic SENTI OR+NOT Gate CAR-NK Cells

In vitro aCAR-mediated killing (gray) and iCAR-mediated protection (teal) assay



Source: Internal data

6. Calibrated Release (cr) IL-15 Enabled Optimization for CAR-NK Cells

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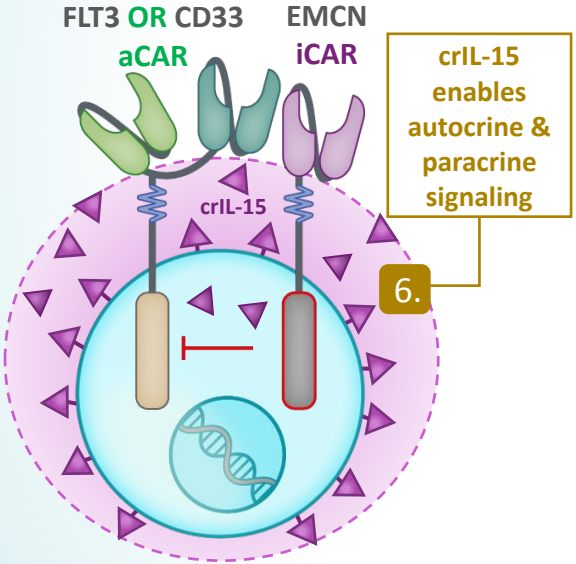
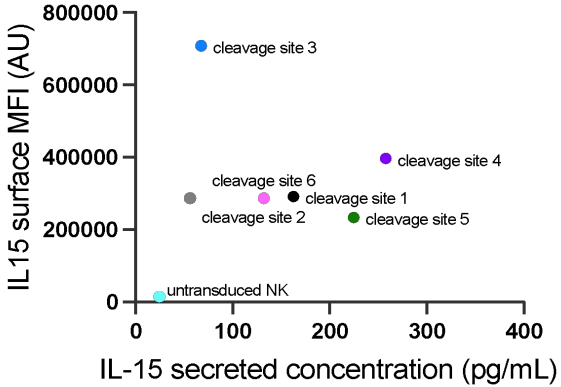
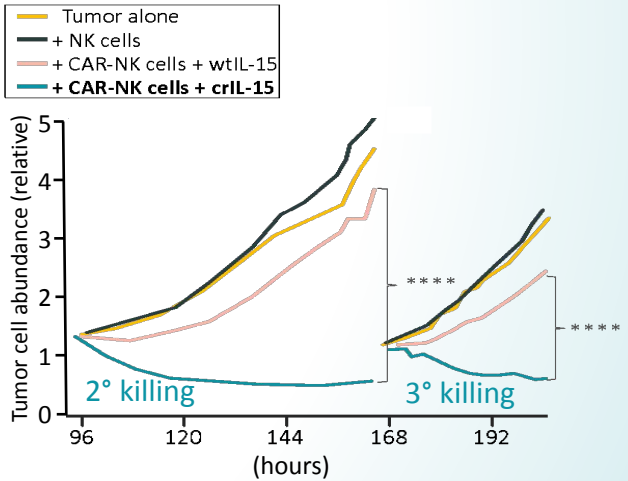


Allogeneic SENTI OR+NOT Gate CAR-NK Cells

Use of tunable cleavage site enables regulated IL-15 presentation & secretion



crIL-15 outperforms soluble IL-15 in 2° and 3° serial killing assay



Source: Internal data

Robust Single Gene Circuit Expression of all SENTI-202 Components

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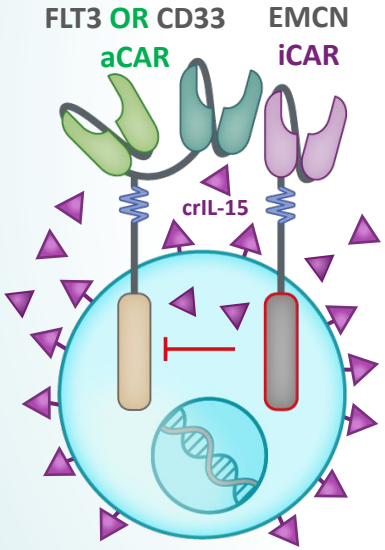
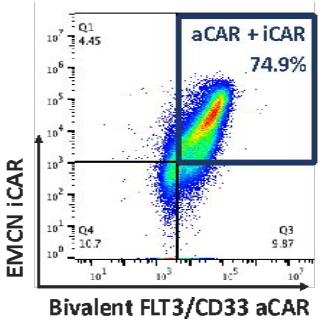
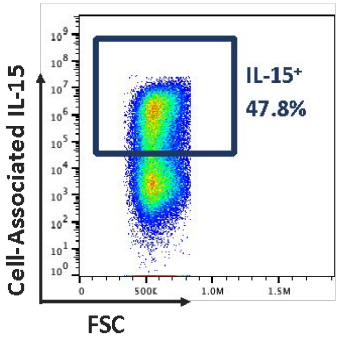


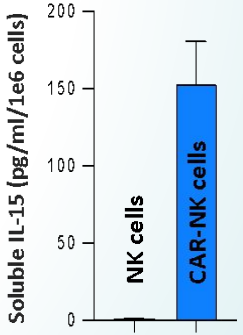
Allogeneic SENTI OR+NOT Gate CAR-NK Cells

>70% aCAR + iCAR Co-Expression



Robust Cell-Associated and Secreted IL-15





Source: Internal data

***In Vitro* Activity:** FLT3 OR CD33 CAR-NK Cells Demonstrate Significant *In Vitro* Activity Against AML

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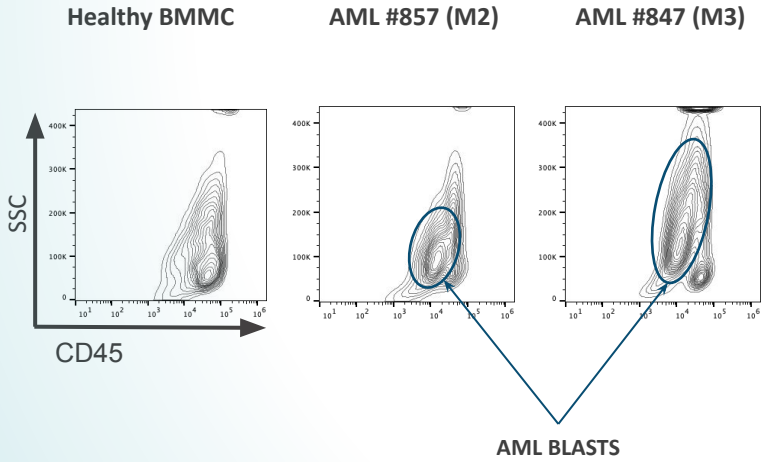
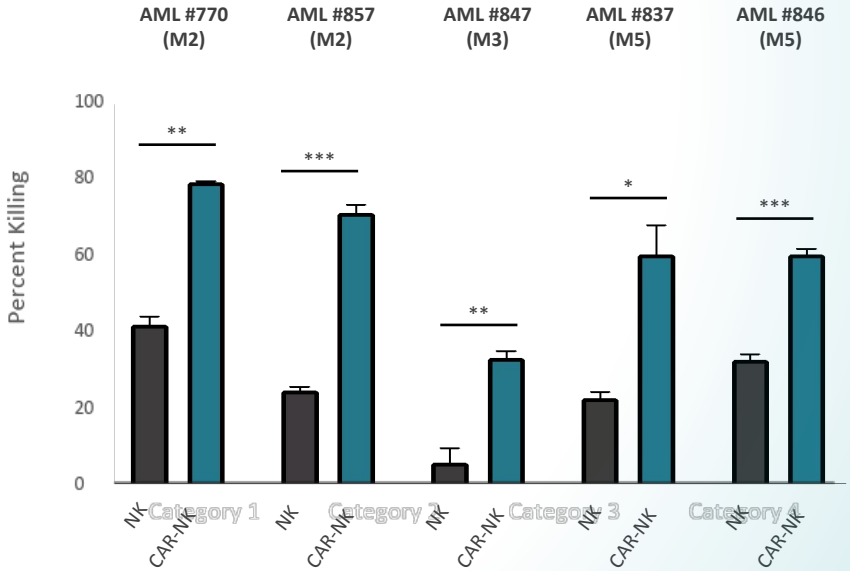
PRIMARY AML SAMPLES WITH EXPANDED BLAST POPULATIONS



FLT3 OR CD33 CAR-NK CELLS KILL PRIMARY AML CELLS



* p < 0.05; ** P ≤ 0.01; *** P ≤ 0.001

Source: Internal data

In Vivo Activity: FLT3 OR CD33 CAR-NK Cells Significantly Suppressed Tumor Growth, Reduced Tumor Burden and Improved Survival

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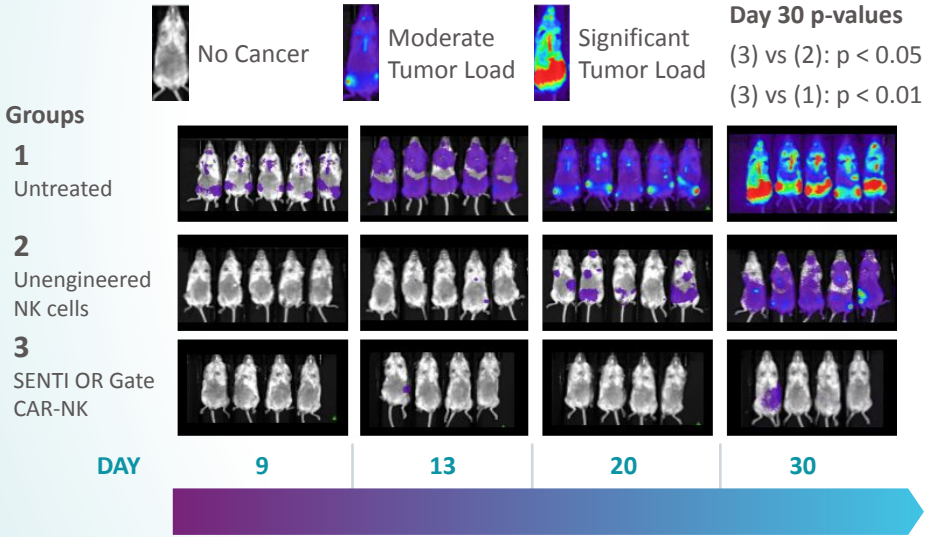
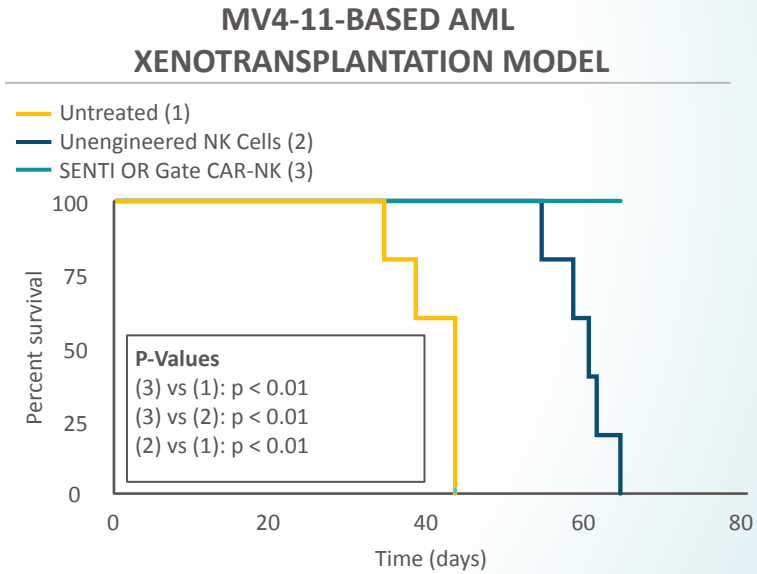


SENTI FLT3 OR CD33 CAR-NK cells achieved statistically significantly greater anti-tumor activity compared to untreated control mice ($p < 0.01$) and mice treated with unengineered NK cells ($p < 0.05$)



FLT3 OR CD33 CAR-NK cells significantly suppressed tumor growth and increased survival

Source: Internal data

Protection of Primary Healthy HSCs: SENTI-202 Protects Primary Healthy HSCs While Maintaining On-Target Killing of Cancer Cells

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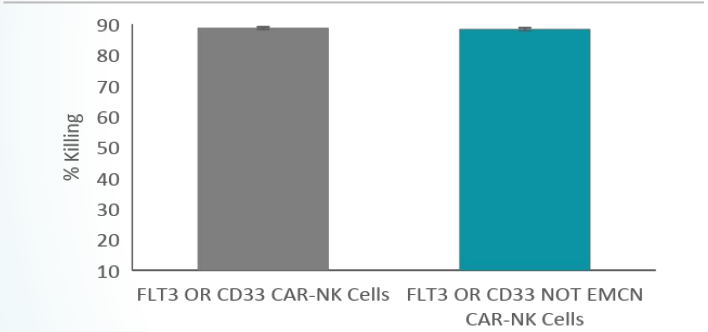
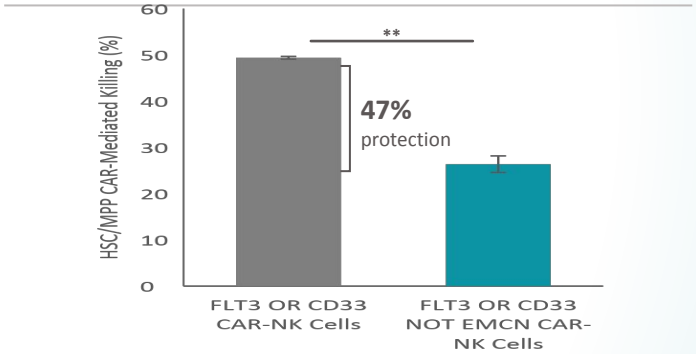
8. POC Data

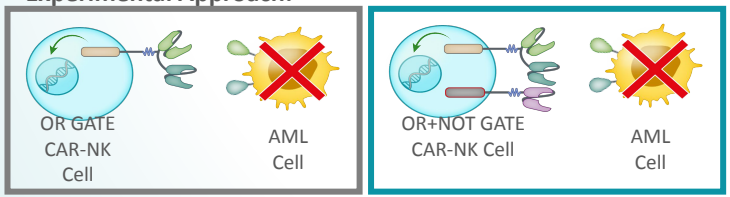
EMCN NOT-GATE CAR-NK CELLS EFFECTIVELY KILL AML CANCER CELLS

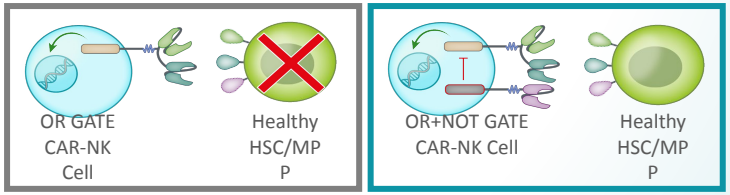


EMCN NOT-GATE CAR-NK CELLS PROTECT HEALTHY HSCs/MPPs



Experimental Approach:



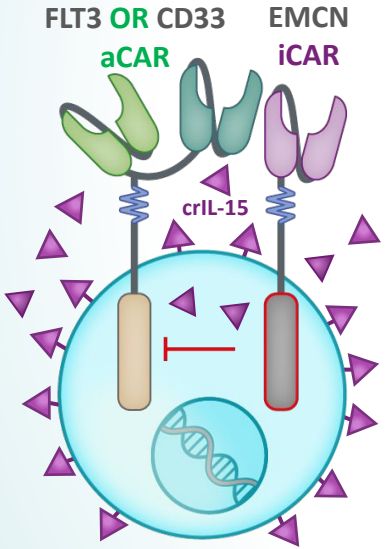


Source: Internal data

We believe that **protecting 10-20%** of Healthy HSCs is clinically meaningful.

Summary: Progress to Date Paves the Way for SENTI-202 IND Filing in 2023

1. NK Cell Engineering Platform
2. Gene Circuit Promoter Design
3. Bivalent Activating CAR (aCAR) Binder Design
4. Inhibitory CAR (iCAR) Binder Design
5. Inhibitory CAR (iCAR) Intracellular Domain
6. Calibrated release IL-15
7. Complete circuit
8. POC Data



Allogeneic SENTI OR+NOT Gate CAR-NK Cells

- >500 total constructs generated and tested
- Extensive systematic gene circuit optimization resulted in high CAR expression
- SENTI-202 exhibited significant killing activity *in vitro* against primary AML cells in patient samples
- SENTI-202 demonstrated significant AML tumor growth suppression and improved mouse survival *in vivo*
- SENTI-202 NOT GATE protects primary donor HSCs while maintaining on-target killing of cancer cells

SENTI BIO

Together, We Can Outsmart Complex Diseases With Intelligent Medicines.

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SENTI BIO

We’re hiring…

https://careers.sentibio.com/