SENTI BIO

Precise Targeting of AML With OR/NOT Logic-Gated Gene Circuits in CAR-NK Cells

Brian S. Garrison, Han Deng, Gozde Yucel, Nicholas W. Frankel, Marcela Ayala Guzman, Russell M. Gordley, Michelle Hung, Derrick Lee, Marcus Gainer, Kathryn Loving, Jenny Chien, Tiffany Pan, Wesley Gorman, Nelia Leemans, Alice Lam, Travis Wood, Wilson Wong, Philip Lee, Tim Lu, Gary Lee

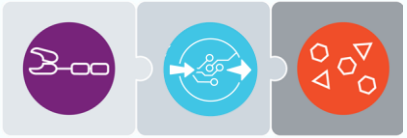
ASGCT – Abstract #77
6:00pm ET, May 12, 2021

Disclosure

- Employee of Senti Biosciences, and receive salary and benefit from the company
- This presentation included verbal remarks by the presenter that are not included here

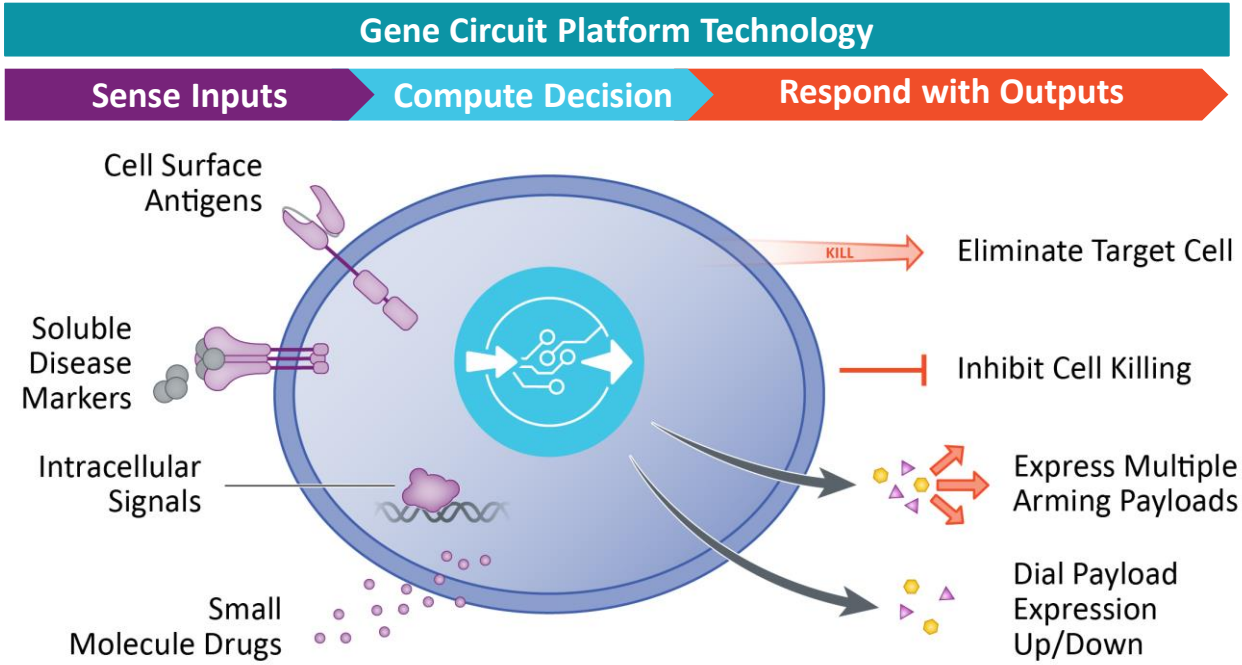
Senti's Gene Circuit "Software" Platform Technologies Embed Logic Into Cell & Gene Therapies, Which May Address Certain Challenges Facing Existing Medicines

About Gene Circuits



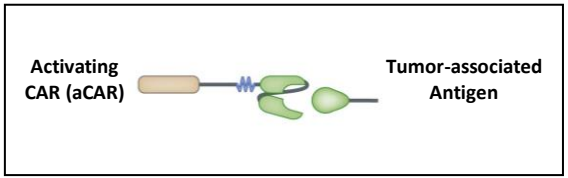
Senti creates novel and proprietary combinations of DNA sequences as ***gene circuits*** that implement ***biological logic***.

Senti's gene circuits may power "***smart***" cell and gene therapies with enhanced therapeutic properties.

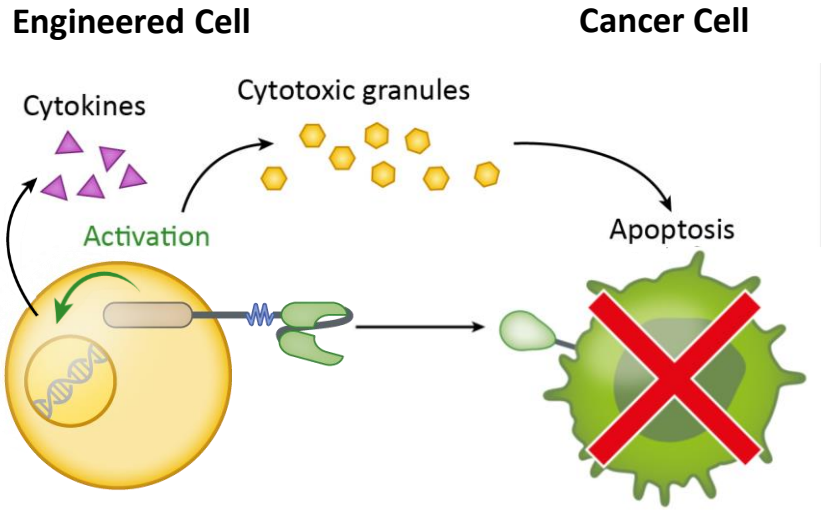


Source: Adapted from Science, 359:6376 (2018)

Senti's NOT GATE Technology is Intended to Solve a Fundamental Problem in Cancer Therapy



Tumor Antigen Engagement Triggers Cancer Cell Killing

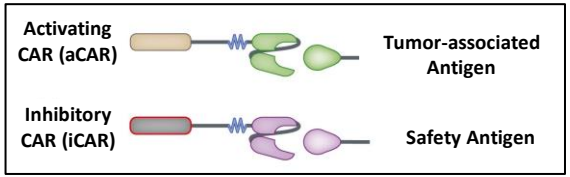


Question: How do we prevent on-target/off-tumor toxicity?

Answer: NOT Logic Gate

How Does the NOT GATE Work?

Senti's NOT GATE Technology is Intended to Solve a Fundamental Problem in Cancer Therapy



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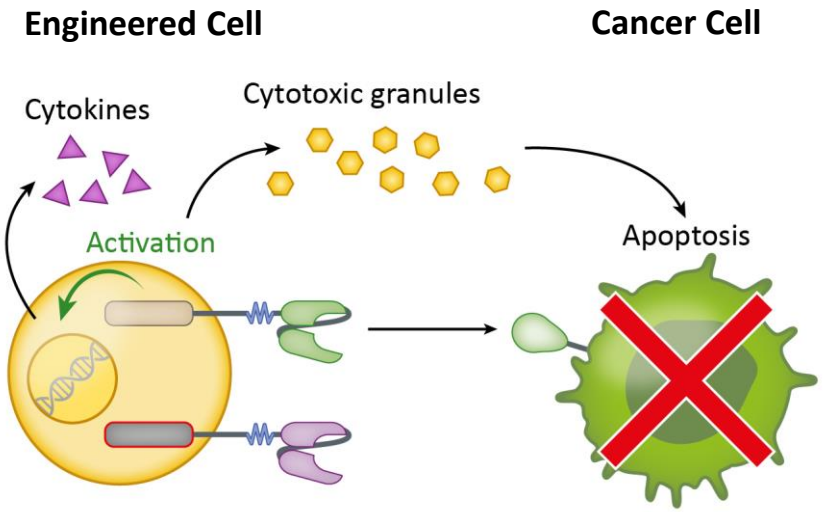
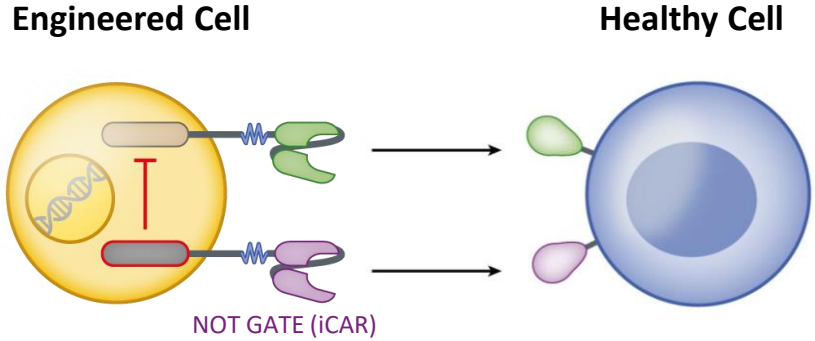
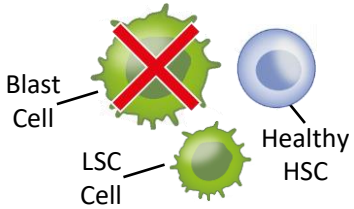


Safety Antigen Engagement Enables Protection of Healthy HSCs

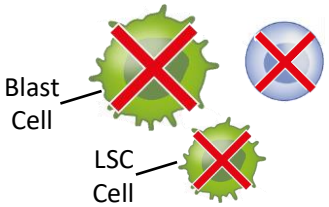


For Acute Myeloid Leukemia (AML), We Believe that Different Therapies Designed to Target Multiple Antigens are Needed

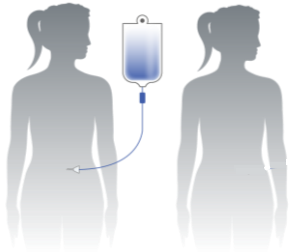
Challenges for Current Acute Myeloid Leukemia (AML) Therapies



Single-target Toxicity: Challenging to comprehensively target all AML subsets, including blasts and AML leukemic stem cells (LSCs), with single antigens → decreased efficacy and increased relapses



Indiscriminate Toxicity: Challenging to target AML cells without also killing healthy hematopoietic stem cells (HSCs) with single antigens → toxicity/safety issues



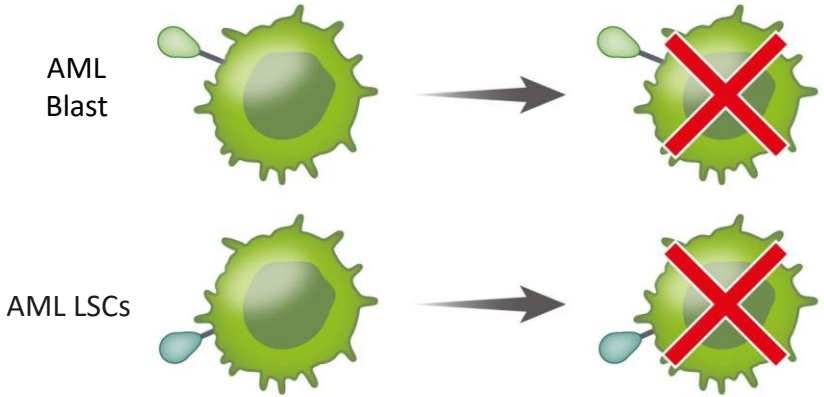
Bone marrow transplant carries morbidity/mortality risks and limitations due to donor availability

Source: https://www.cancer.org/cancer/acute-myeloid-leukemia/treating/targeted-therapy.html

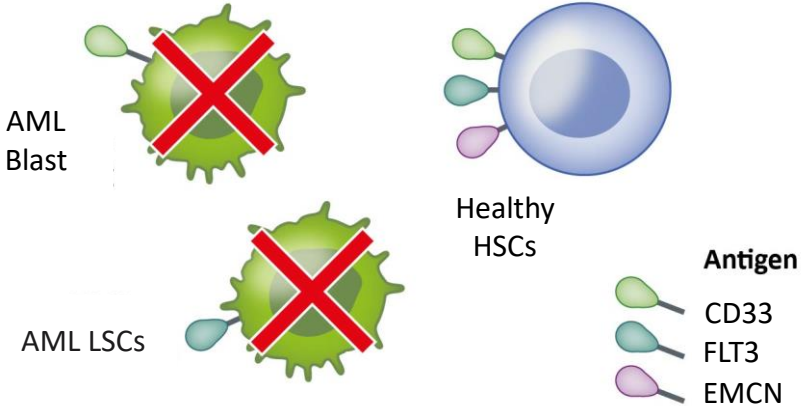
Senti's Approach to the Challenges of AML

Senti's CAR-NK Cells Are Programmed To Recognize Multiple Targets and Spare Healthy HSCs

Target and Kill Both Leukemic Cell Types…



…While Preserving Healthy HSCs



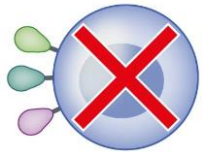
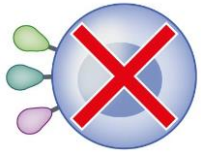
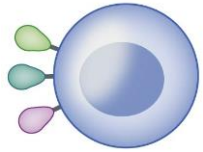
Key Takeaways

We believe that protection of 10-20% of healthy HSCs would be sufficient to enable hematopoietic recovery and provide clinical benefit to patients

EMCN is Endomucin

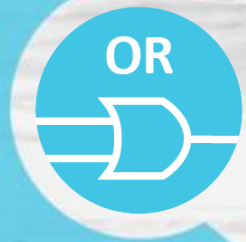
Deep Clearance of AML Blasts and LSCs While Sparing Healthy HSCs

Antigen: CD33 FLT3 EMCN

Sense Inputs	Compute Decision	Respond with Outputs: AML Blasts	AML LSCs	Healthy HSCs/PCs
CD33	**No Logic**			
FLT3, CD33	**OR GATE Only** (FLT3 OR CD33)			
FLT3, CD33, EMCN	**OR/NOT GATE** (FLT3 OR CD33) NOT EMCN			

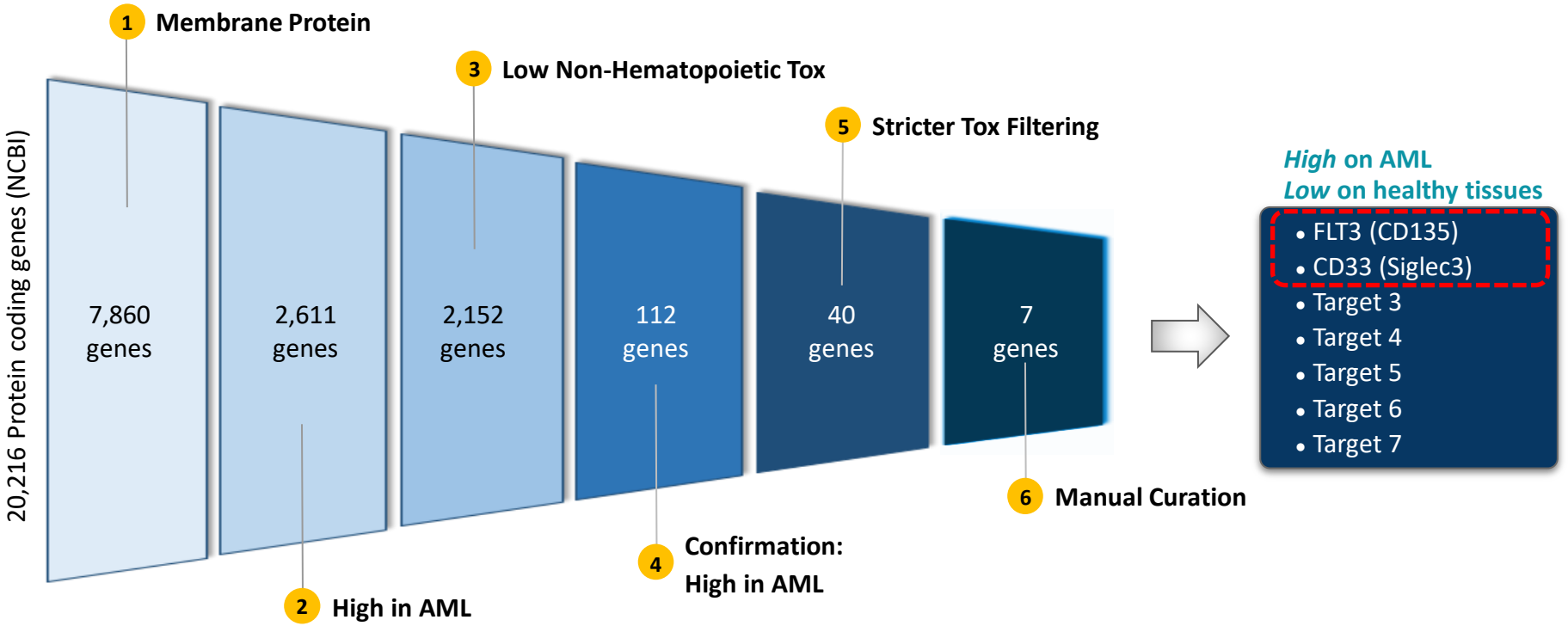
CD33 is over-represented on AML blast cells; FLT3 is a marker for AML LSCs; HSCs=hematopoietic stem cells; PCs = progenitor cells

OR Logic Gating



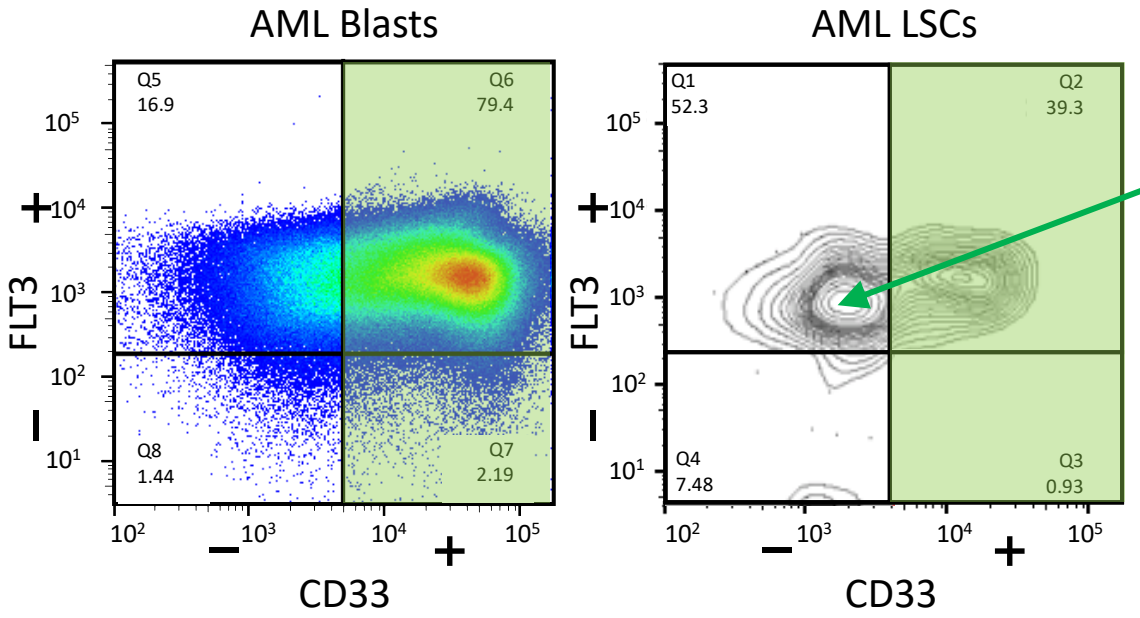
Targeting the Tumor-Associated Antigens FLT3 and CD33

Senti Identified FLT3/CD33 as an Ideal OR GATE Target Antigen Pair for AML



Source: Internal data

Focusing Only on CD33 Addresses AML Blasts but Largely Misses AML LSCs

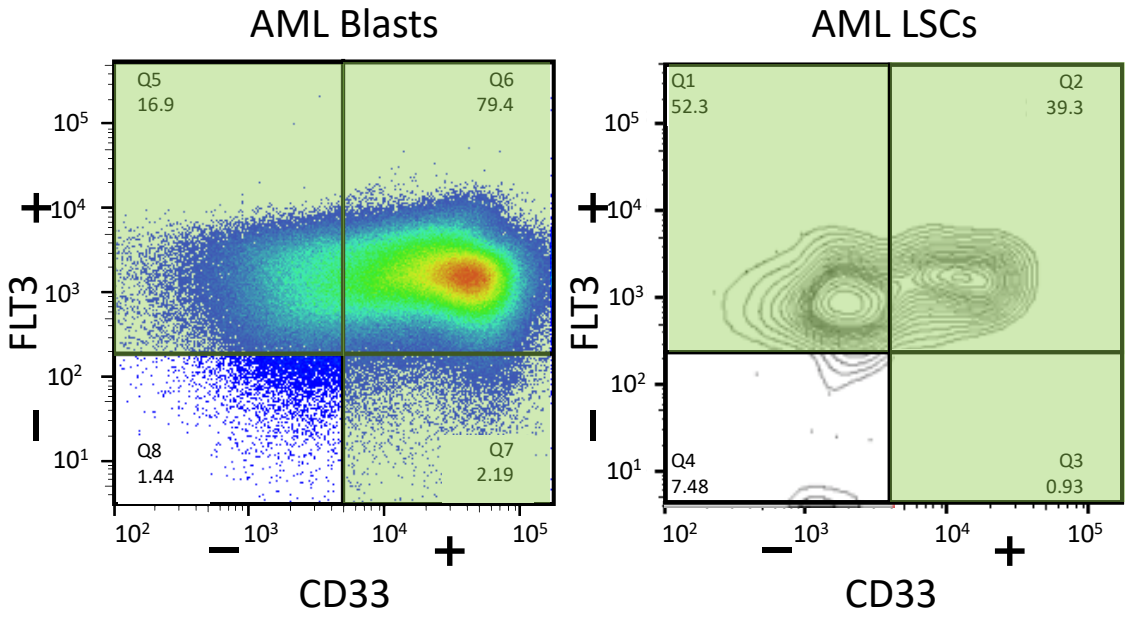


Key Takeaways

- Based on our preclinical study, **when only CD33+ cells are targeted, a substantial number of AML LSCs may not be targeted**
- We believe this may lead to suboptimal efficacy and relapses

Source: Internal data

By Targeting either FLT3 or CD33 Antigens With an OR GATE, We Believe that Comprehensive Killing of Cancer Cells Is Possible

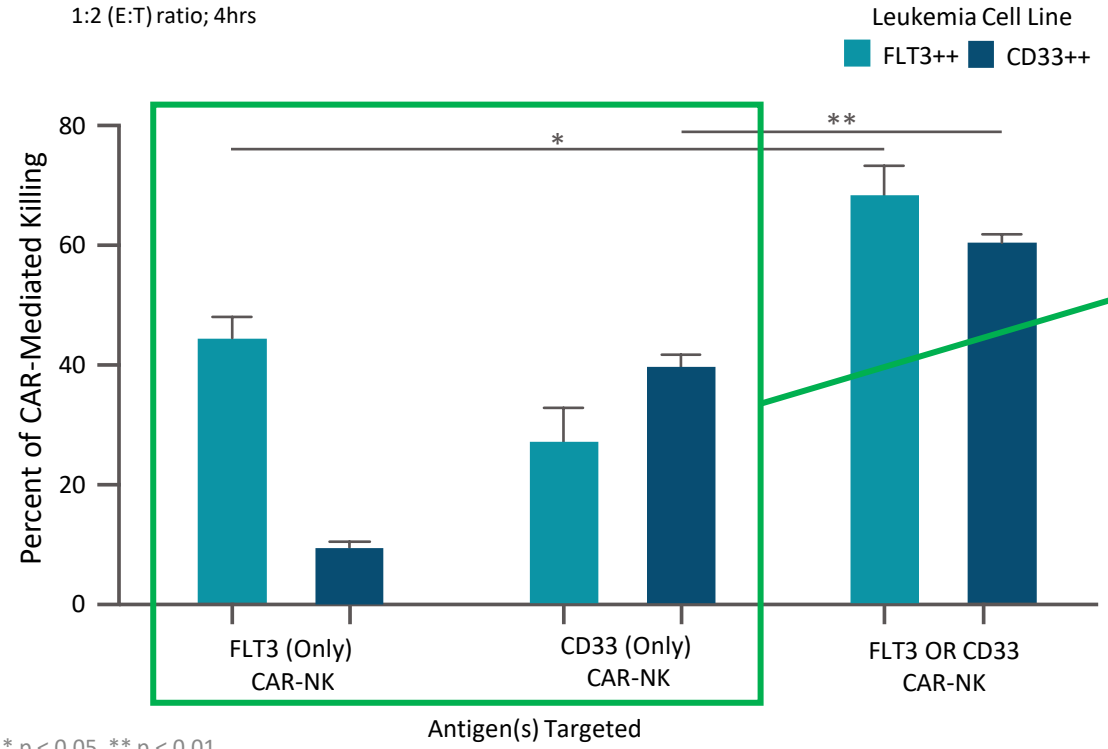


Key Takeaways

- **Based on our preclinical studies, targeting either FLT3 or CD33 antigens enables more comprehensive targeting of cancer cells**
- We believe improved efficacy may be achieved if both major populations of AML Blasts and AML LSCs are comprehensively targeted

Source: Internal data

OR GATE Facilitated Improved Killing of Cancer Cells Expressing Either Antigen Target Based on Preclinical Data



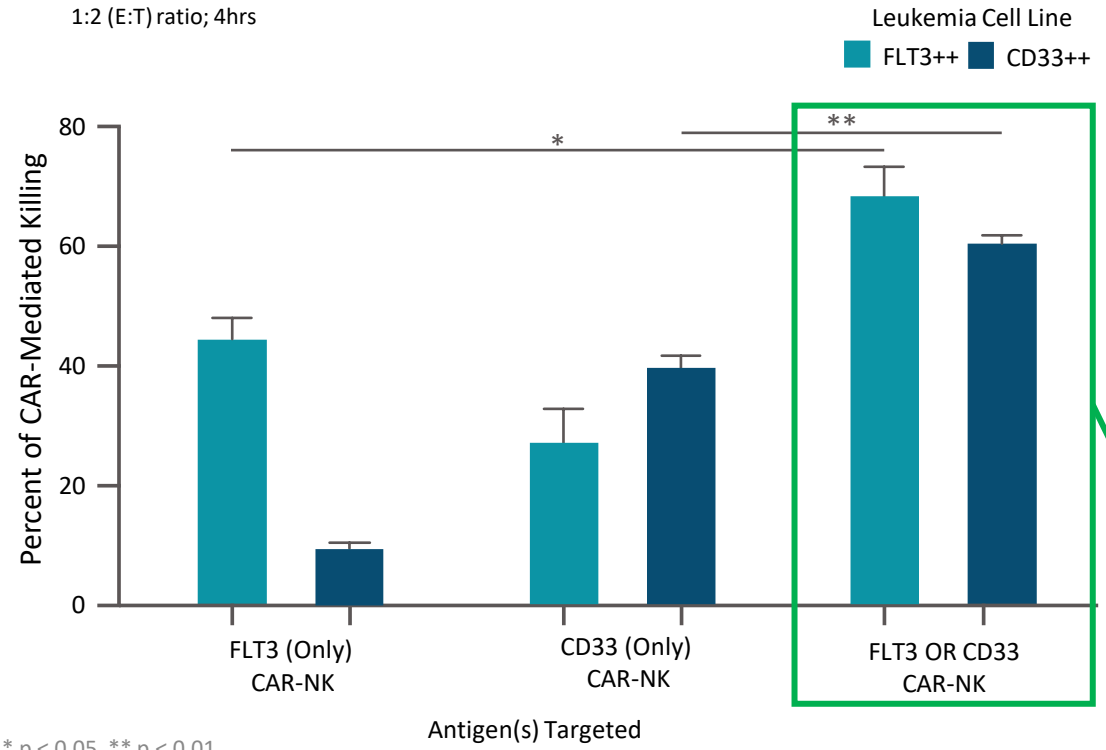
* $p < 0.05$, ** $p < 0.01$

Source: Internal data

Key Takeaways

- **Only targeting the FLT3 antigen had modest FLT3++ cell killing but little CD33++ cell killing**
- **Only targeting the CD33++ antigen poorly addressed FLT3++ cells**
- Being able to target either antigen may result in more robust CAR-mediated cell killing

OR GATE Facilitated Improved Killing of Cancer Cells Expressing Either Antigen Target Based on Preclinical Data



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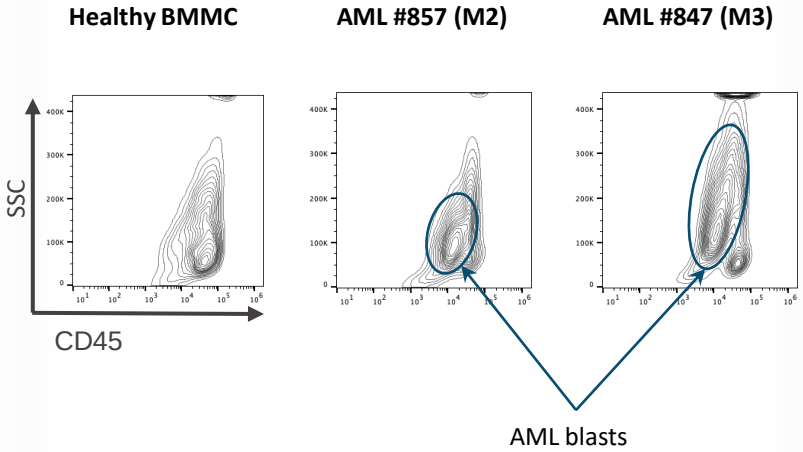
- Only targeting the CD33++ antigen poorly addressed FLT3++ cells
- **Being able to target either antigen may result in more robust CAR-mediated cell killing**

* $p < 0.05$, ** $p < 0.01$

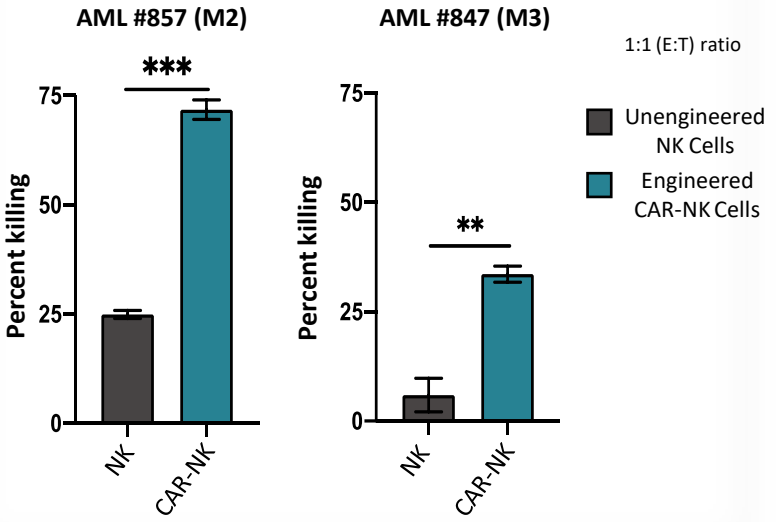
Source: Internal data

OR Gated CAR-NK Cells Demonstrated Significant Cytotoxicity Against Primary AML Samples

Primary AML Samples With Expanded Blast Populations



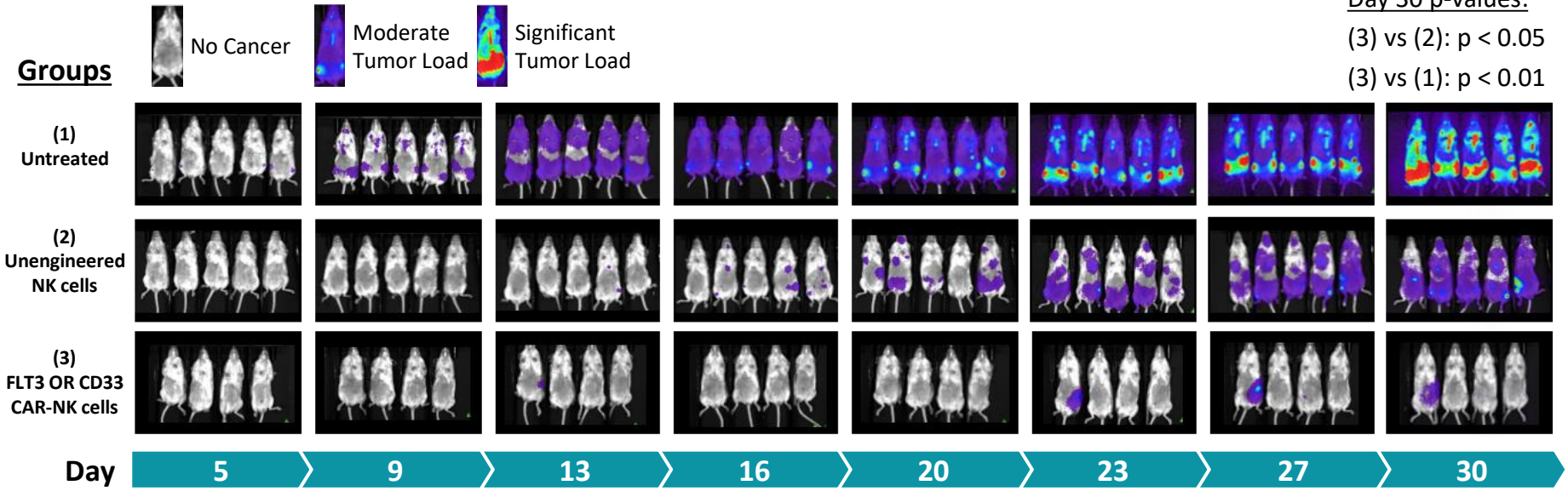
FLT3 or CD33 CAR-NK Cells Killed Primary AML Cells



** P ≤ 0.01; *** P ≤ 0.001

Source: Internal data

FLT3 OR CD33 CAR-NK Cells Significantly Suppressed Tumor Growth in Preclinical AML Xenotransplantation Study

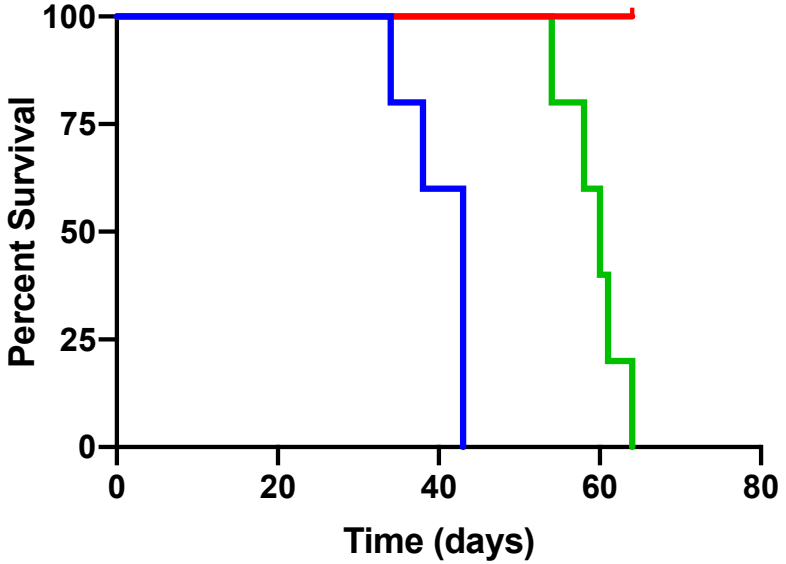


Key Takeaways

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 ($p < 0.05$)

Source: Internal data

FLT3 OR CD33 CAR-NK Cells Significantly Increased Mouse Survival in Preclinical AML Xenotransplantation Study



FLT3 OR CD33 CAR-NK Cells (3)

Unengineered NK Cells (2)

Untreated (1)

P-Values:

(3) vs (1): $p < 0.01$

(3) vs (2): $p < 0.01$

(2) vs (1): $p < 0.01$

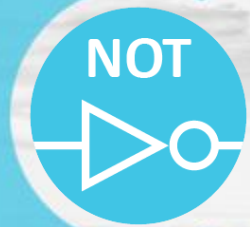
Key Takeaways

FLT3 OR CD33 CAR-NK cells significantly suppressed tumor growth and increased animal survival in an MV4-11-based AML xenotransplantation model

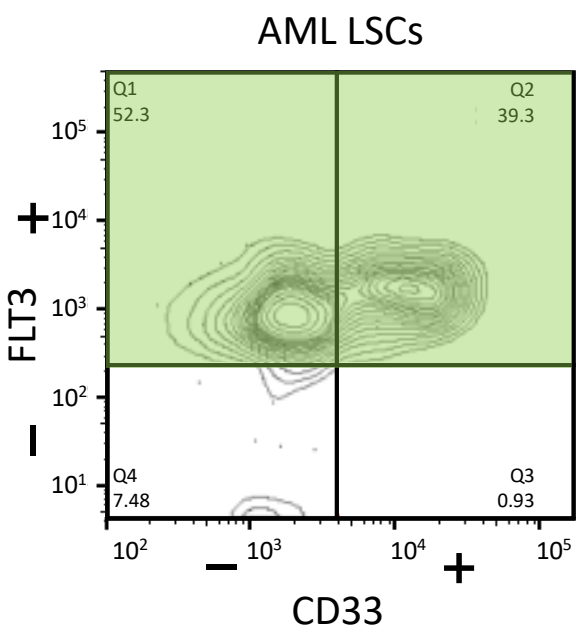
Source: Internal data

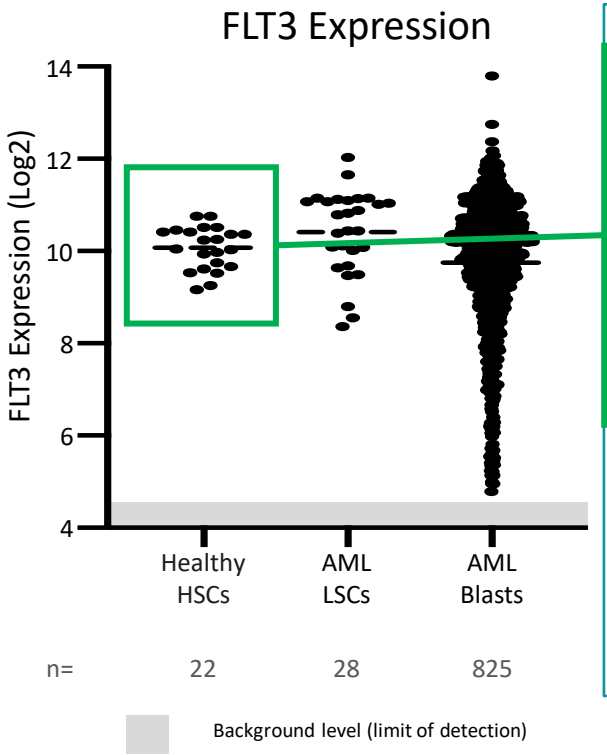
NOT Logic Gating

NOT GATE for
protection of healthy cells



Based on Preclinical Data, Targeting Only FLT3 Addresses AML LSCs But May Kill Healthy HSCs as Well



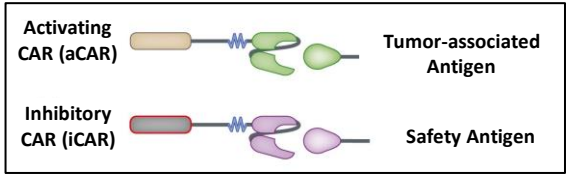


Key Takeaways

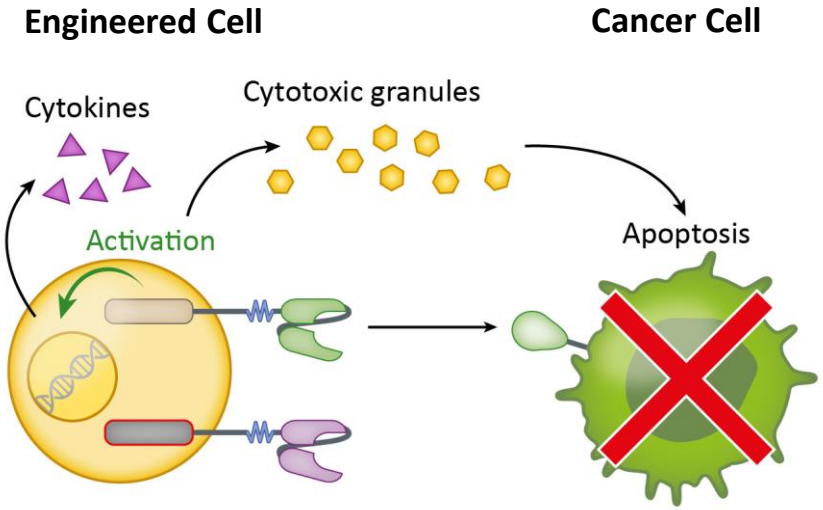
- AML LSCs can be effectively killed by targeting FLT3+ cells
- **However, FLT3 expression on AML cells has a large overlap with Healthy HSCs, leading to toxicity challenges**

Source: Internal data

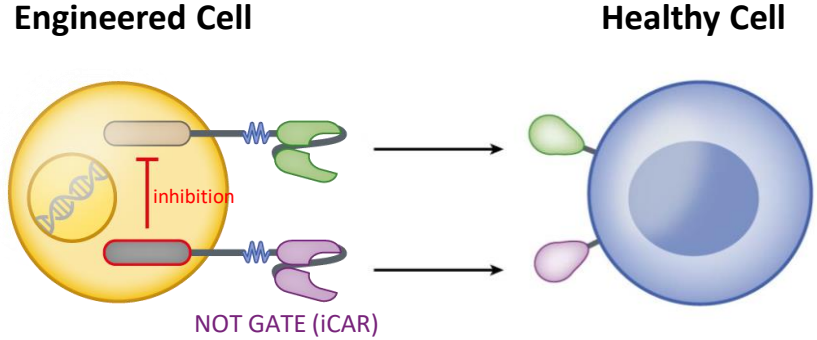
Senti's NOT GATE Technology is Intended to Solve a Fundamental Problem in Cancer Therapy



Tumor Antigen Engagement Triggers Cancer Cell Killing



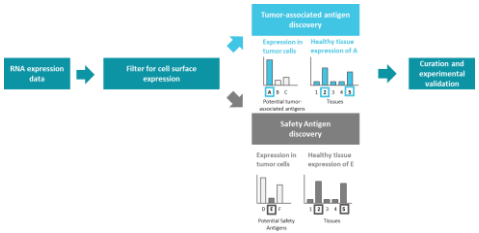
Safety Antigen Engagement Enables Protection of Healthy HSCs



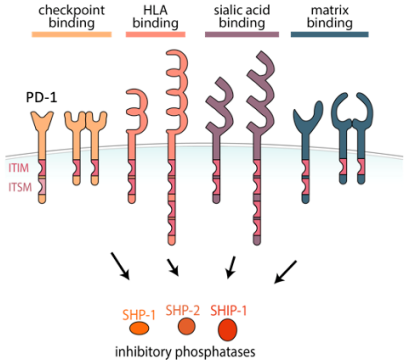
Senti Leverages Bioinformatics Approaches To Identify Suitable Safety Antigens and Screen NOT GATE Architectures To Build Next-Gen Precision Cell Therapies

Senti NOT GATE Platform

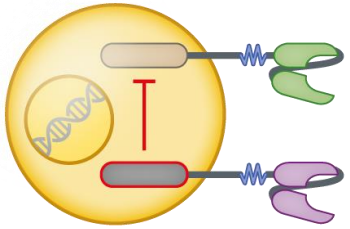
Bioinformatics Platform for Safety Antigen Identification



NOT GATE Architecture Screening & Discovery



Precision-Guided Immune Cell Therapies



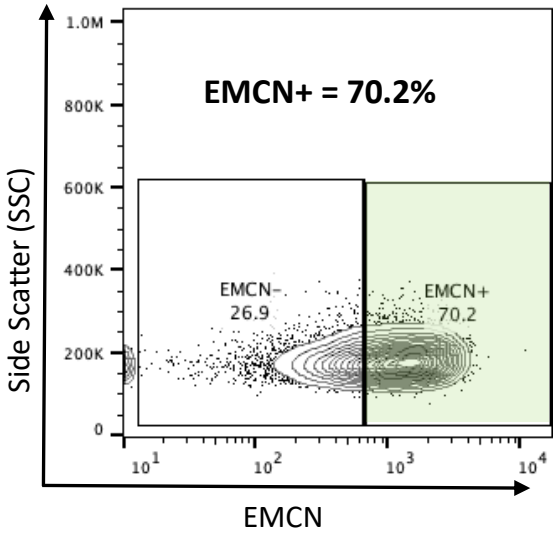
Digital Presentation:

Precise Tumor Targeting with NOT GATE Chimeric Antigen Receptor Gene Circuits

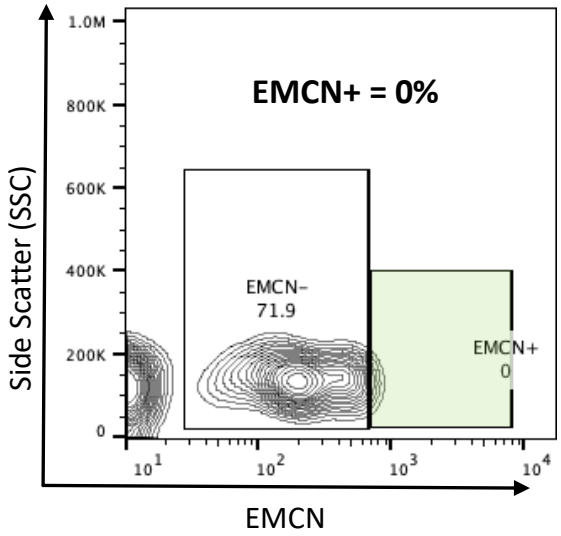
Tuesday May 11 from 8:00–10:00am ET (abstract #960)

Senti Identified a NOT GATE Safety Antigen Called EMCN That Distinguishes AML LSCs From Healthy HSCs

Healthy HSCs
(from healthy donor)



AML LSCs
(from AML patient)

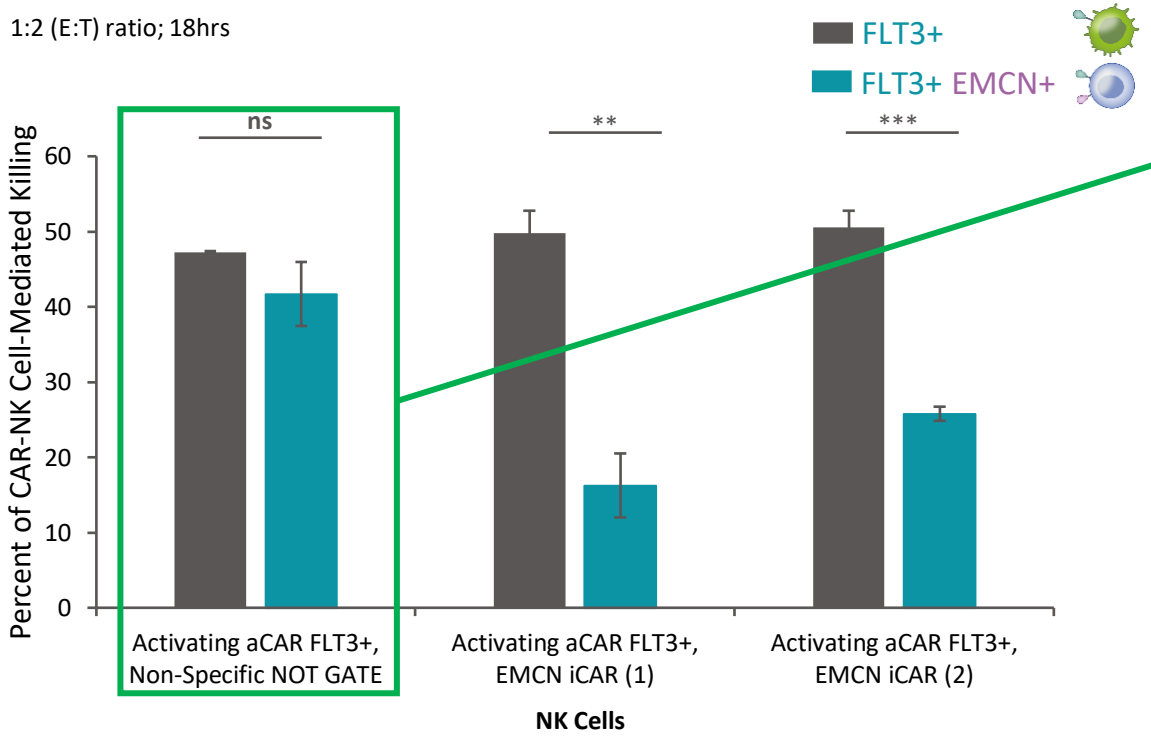


Key Takeaways

- The ‘NOT GATE’ uses EMCN as a Safety Antigen input to differentiate between healthy HSCs and AML cells
- This enables targeted killing of cancer cells while sparing Healthy HSCs, thereby improving the therapeutic window

Source: Internal data

NOT GATE Enabled Protection of Cells Expressing EMCN While Maintaining On-Target Killing of FLT3+ Cancer Cells



ns = not significant; ** p < 0.01, *** p < 0.001

Source: Internal data

Key Takeaways

- **Without an EMCN-specific NOT GATE, FLT3+ cells undergo NK cell-mediated killing**
- With EMCN-specific NOT GATE, presence of EMCN on target cells reduce cytotoxicity by 67% while preserving NK cell-mediated killing of FLT3+ cancer cells
- We believe that protecting 10-20% of Healthy HSCs is clinically meaningful

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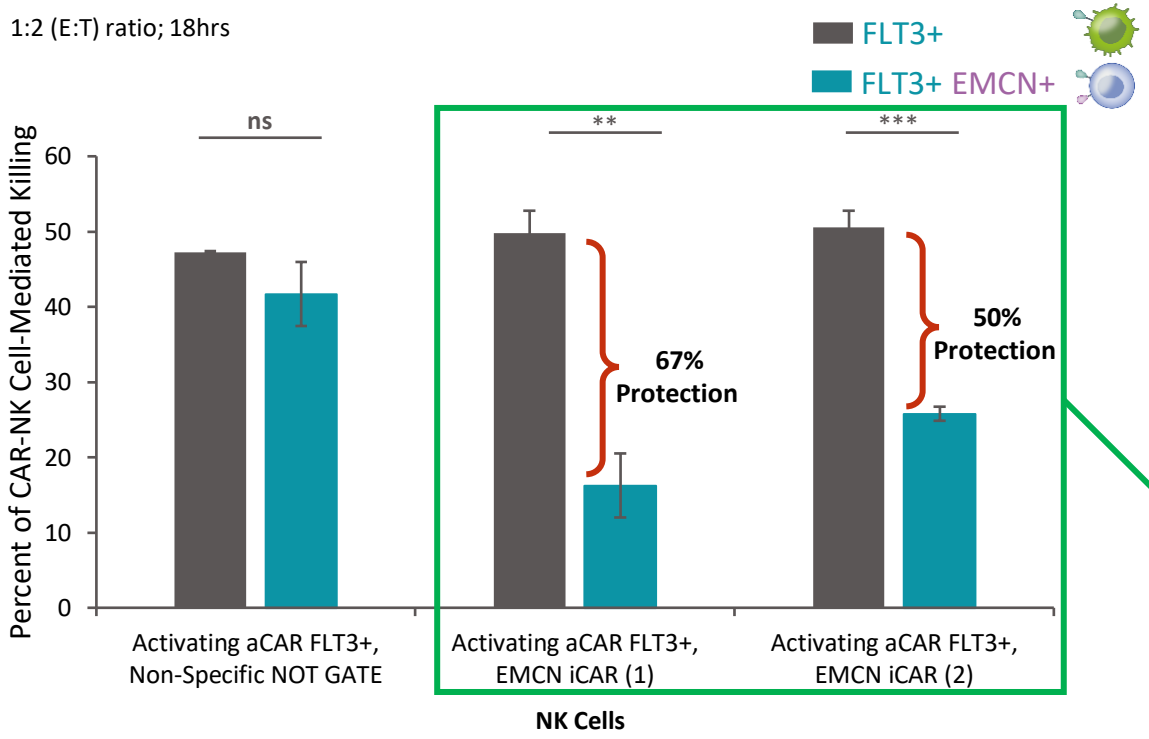

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Senti's R&D Headquarters (South San Francisco, CA, USA)

HQ and R&D Center

- Senti's multi-modal preclinical research labs – South San Francisco, CA
- SSF is a major Biotech hub with high density of facilities and R&D talent in over 150 companies
- Proximity to major biopharma sites, institutions, and SFO

SENTI BIO

Together, We Can Outsmart Complex Diseases With Intelligent Medicines.

Oral Presentation:

Small Molecule-Regulated Gene Circuit for Controlling Cytokine Expression in Cell Therapies

Friday May 14 from 1:45–2:00pm ET (abstract #214)

Digital Presentation:

Precise Tumor Targeting with NOT GATE Chimeric Antigen Receptor Gene Circuits

Tuesday May 11 from 8:00–10:00am ET (abstract #960)

Brian.garrison@sentibio.com