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

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

**SENI’S LOGIC GATES SOLVE KEY DISEASE CHALLENGES IN AML**

<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>SENTI GENE CIRCUIT SOLUTIONS</th>
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<tbody>
<tr>
<td>Target heterogeneity</td>
<td><strong>OR Logic Gate</strong></td>
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<tr>
<td>Relapse due to incomplete</td>
<td>Targets multiple AML tumor associated antigens for</td>
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<tr>
<td>targeting of leukemic stem</td>
<td>improved clearance and lower relapse</td>
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<td>cells (LSCs)</td>
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<tr>
<td></td>
<td><strong>NOT Logic Gate</strong></td>
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<tr>
<td>Target heterogeneity</td>
<td>Enables broad targeting of AML</td>
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<tr>
<td>Off-tumor toxicity and limited</td>
<td>while preserving healthy blood stem cells</td>
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<tr>
<td>efficacy due to lack of</td>
<td></td>
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<tr>
<td>AML-specific targets</td>
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**UNMET NEED IN AML**

- **2020 US Incidence**
- **5-Year Survival**

- **DISEASED BONE MARROW**
- **~20K** Patients diagnosed with AML this year

**SENI’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

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

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

- SENTI NOT-GATE CAR-NK CELLS
- CANCER CELL

  - Activation
  - Cytotoxic granules
  - Apoptosis

  - Activating CAR (aCAR)
  - Tumor-Associated Antigens

SAFETY ANTIGEN ENGAGEMENT ENABLES PROTECTION OF HEALTHY CELLS

- SENTI NOT-GATE CAR-NK CELLS
- HEALTHY CELL

  - 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**

**NOT-Logic Gated CAR-NK Cells**

Healthy Cells + 50:50 Cancer Cells

**NOT-GATED CAR-NK CELLS REDUCE KILLING OF HEALTHY CELLS**

<table>
<thead>
<tr>
<th>NOT-GATED CAR-NK CELLS</th>
<th>RESULTING IN ENRICHMENT OF HEALTHY CELLS</th>
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</thead>
<tbody>
<tr>
<td>Control CAR-NK Cells</td>
<td>0% Healthy Cells of All Target Cells</td>
</tr>
<tr>
<td>NOT GATED CAR-NK Cells</td>
<td>100% Healthy Cells of All Target Cells</td>
</tr>
</tbody>
</table>

**Source:** Internal data

**I.V. injection**

**Blood collection**

Healthy Cells Spared

Cancer Cells Killed

**50:50**

**Logic Gating**

**Multi-Arming**

**Regulator Dial**

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

SENTI’S DESIGN-BUILD-TEST-LEARN ENGINE

- **Central Knowledge Database**
  - Biological Data

- **DESIGN**
  - Centralized Gene Circuit Design Team
    - ML / computational algorithms
    - Patient disease bioinformatics
  - Alternative Designs

- **BUILD**
  - Vector Core, Cell Manufacturing Core, Disease Indication Teams
    - DNA, vector and cell engineering with GMP-relevant processes
  - Production Efficiency

- **TEST**
  - Disease Indication Teams, in vivo Core, Analytical Core
    - Automated high throughput screening
    - Analytical testing on process efficiencies and robustness
  - Hit Selection

- **LEARN**

**SENTI’S DESIGN-BUILD-TEST-LEARN (DBTL) PROCESS**
Systematic Gene Circuit Optimization for FLT3 OR CD33 NOT EMCN CAR-NK Cell Development

>500 SENTI-202 total constructs tested
1. NK Cell Engineering Platform Optimization Yielded >80% CAR Expression

Flow cytometry-based CAR expression assay

Source: Internal data
2. Gene Circuit Promoter Design Optimization Enabled >70% CAR expression

Flow cytometry-based CAR expression assay

Allogeneic SENTI OR+NOT Gate CAR-NK Cells

Source: Internal data
3. Bivalent Activating CAR (aCAR) Binder Optimization Significantly Improves In Vivo Tumor Suppression and Mouse Survival

In Vitro Cytotoxicity activity

- AML Killing Assay
  - No Virus
  - Bivalent design A
  - Bivalent design B

In Vivo AML (MV4-11) Tumor Suppression

- Treatment
  - (1.) PBS
  - (2.) Bivalent design A CAR-NK
  - (3.) Bivalent design B CAR-NK

AML (MV4-11) imaging: Day 87

Mouse Survival Curve

- Probability of Survival
  - P-value
    - (3.) vs. (1.) = 0.0034
    - (3.) vs. (2.) = 0.0064

Source: Internal data
4. **Inhibitory CAR (iCAR) Binder Humanization Process** Increased NOT GATE function

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

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

Tumor-associate antigen+
Tumor-associate antigen+ and safety antigen+

Source: Internal data
6. Calibrated Release (cr) IL-15 Enabled Optimization for 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

Tumor cell abundance (relative)

IL-15 secreted concentration (pg/mL)

Source: Internal data
Robust Single Gene Circuit Expression of all SENTI-202 Components

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

>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

**PRIMARY AML SAMPLES WITH EXPANDED BLAST POPULATIONS**

- Healthy BMMC
- AML #857 (M2)
- AML #847 (M3)

**FLT3 OR CD33 CAR-NK CELLS KILL PRIMARY AML CELLS**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Percent Killing</th>
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<tbody>
<tr>
<td>AML #770 (M2)</td>
<td>**</td>
</tr>
<tr>
<td>AML #857 (M2)</td>
<td>***</td>
</tr>
<tr>
<td>AML #847 (M3)</td>
<td>**</td>
</tr>
<tr>
<td>AML #837 (M5)</td>
<td>*</td>
</tr>
<tr>
<td>AML #846 (M5)</td>
<td>***</td>
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</tbody>
</table>

* 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

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 ($p < 0.05$).
Protection of Primary Healthy HSCs: Senti-202 Protects Primary Healthy HSCs While Maintaining On-Target Killing of Cancer Cells

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

- >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
Together, We Can Outsmart Complex Diseases With Intelligent Medicines.

Brian.garrison@sentibio.com
We’re hiring…

Are you ready to create a new generation of smarter medicines?

https://careers.sentibio.com/