SENTI BIO

# Engineering the Future of Cell & Gene Therapies

August 2024

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# Investment Highlights and Upcoming Clinical Catalysts

## 2024 Accomplishments

**SENTI-202 for AML**

✓ First patient dosed in 2Q 2024

## Anticipated Clinical Catalysts

**SENTI-202 for AML**

- Initial clinical data by year-end 2024
- Durability data in 2025

**SENTI-301A for HCC (Liver Cancer)**

- First patient dosing in China 4Q 2024

**Central challenge in oncology:**

Current therapies cannot precisely distinguish cancer vs healthy cells

**Reduced therapeutic potential:**

Lack of specificity leads to limited efficacy, relapse and safety issues

**Senti's Approach:**

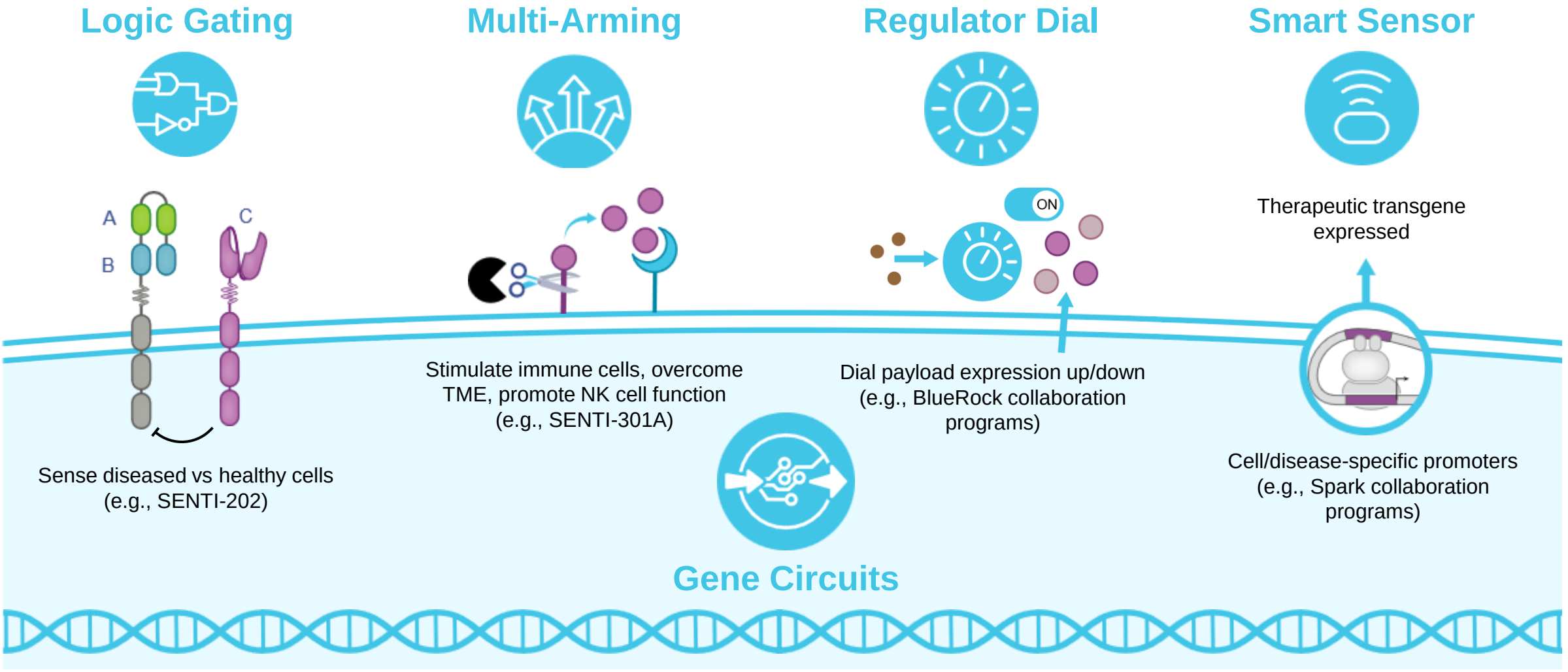
Senti's lead program, SENTI-202, utilizes proprietary Logic Gating technology designed to overcome AML disease heterogeneity by targeting LSCs while sparing healthy cells based on clinically validated CD33 and FLT3 targets

**Broad Applicability:**

Logic Gating technology has the potential to address a wide range of opportunities in oncology

AML: Acute Myeloid Leukemia; LSCs: Leukemic Stem Cells

# Gene Circuits Could Enhance Precision, Control, and Activity of Cell & Gene Therapies




TME: tumor microenvironment

# Internal Focus on Oncology, Partnering to Support Non-Oncology Indications

| Programs | Target | Application | Preclinical | Early Stage Clinical | Late Stage Clinical | Collaborator |
|---|---|---|---|---|---|---|
| **SENTI-202** | CD33 and/or FLT3 | AML, MDS and other blood cancers | | | | |
| **SENTI-301A**[1] | GPC3 | HCC and other solid tumors | | | | CELEST 晟临生物 |
| **Multiple Gene Therapy Programs** | Undisclosed | Eye, CNS and liver diseases | | | | Roche Spark THERAPEUTICS |
| **Multiple iPSC Cell Therapy Programs** | Undisclosed | Regenerative medicine | | | | BAYER BlueRock THERAPEUTICS |

CNS: Central nervous system; HCC: Hepatocellular carcinoma; MDS: Myelodysplastic Syndrome

[1] Collaboration with Celest for clinical development to treat solid tumors in China, with an option to expand to Hong Kong, Macau, and Taiwan

# Industry-Leading Management With Top-Tier Board and Scientific Advisors

## Tim Lu, MD, PhD
CEO and Co-founder

## Yvonne Li
Interim CFO and Treasurer

## Kanya Rajangam, MD, PhD
President, Head of R&D and CMO

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Scientific Co-Founder, MIT

Wilson Wong, PhD
Scientific Co-Founder, Boston University

Michael Andreeff, MD, PhD
MD Anderson Cancer Center

Martin Fussenegger, PhD
ETH Zurich

Lawrence Fong, PhD
UCSF

Michael Kalos, PhD
Arsenal, Janssen, Lilly

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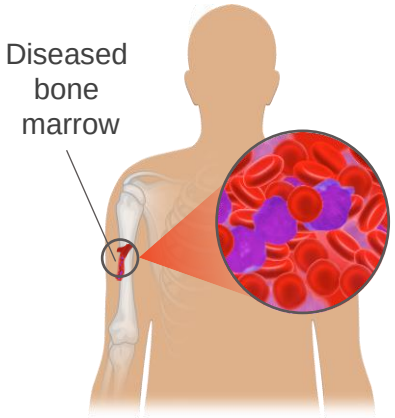
# SENTI-202

# Limited Standard of Care Options for R/R AML

## R/R AML patient outcome




**Median survival of 5.3 months[1]**

5-year survival rate is 12.6%[1]

**Major treatment challenges:**

1. Disease heterogeneity
2. Durability of response
3. Healthy cell toxicity
4. Treatment tolerability

## AML has the worst relapse rate of any blood cancer

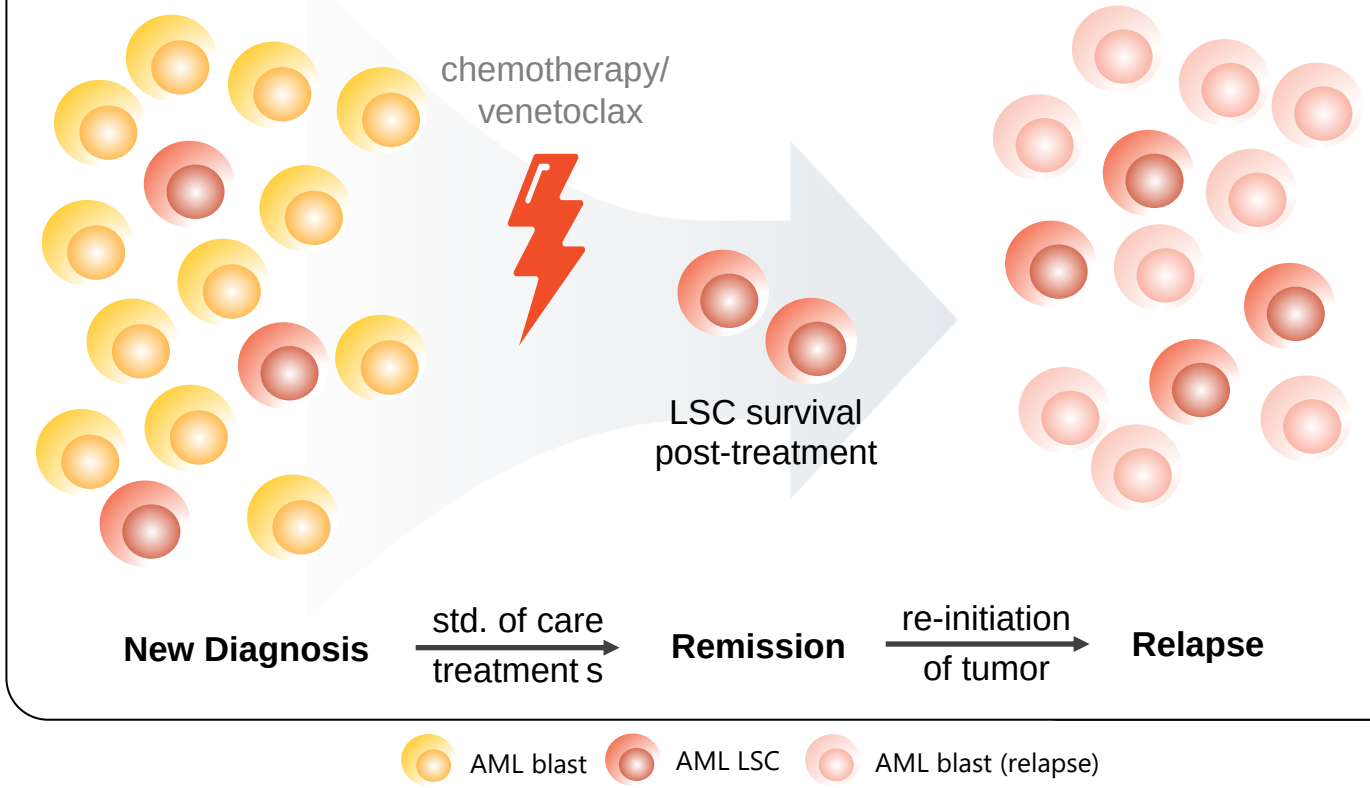
- 50%–70% of patients who obtain complete response (CR) eventually relapse[2]
- 21-32% CR/CRh rate with approved treatments for CD33+ AML, FLT3 and IDH1/2 mutated AML
  - No SOC after progression on mutationally targeted disease
- Allogeneic Hematopoietic Stem Cell Transplant (HSCT) is the only curative option but is limited to younger/ fit patients
- Presence of residual LSCs after treatment correlates with poorer prognosis and increased likelihood of relapse[3]
  - Residual LSCs contribute to worse prognosis and higher likelihood of relapse after treatment
  - Rare population that have markers similar to HSC; built in off-tumor on-target protection is key to effectively targeting LSCs

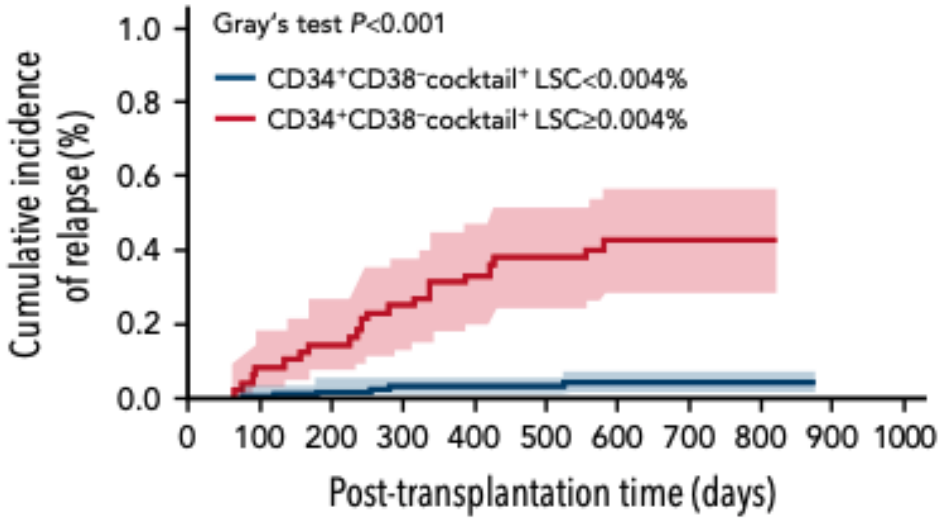
R/R: relapsed or refractory; CRh: complete remission with partial hematologic recovery; SOC: standard of care

[1] Brandwein AJBR 2020; [2] Heuser Annals of Oncology 2020; [3] Zeijlemaker Leukemia 2019

# Targeting AML LSCs May Be Essential for Increased Durability and Longer Remissions

## Etiopathology



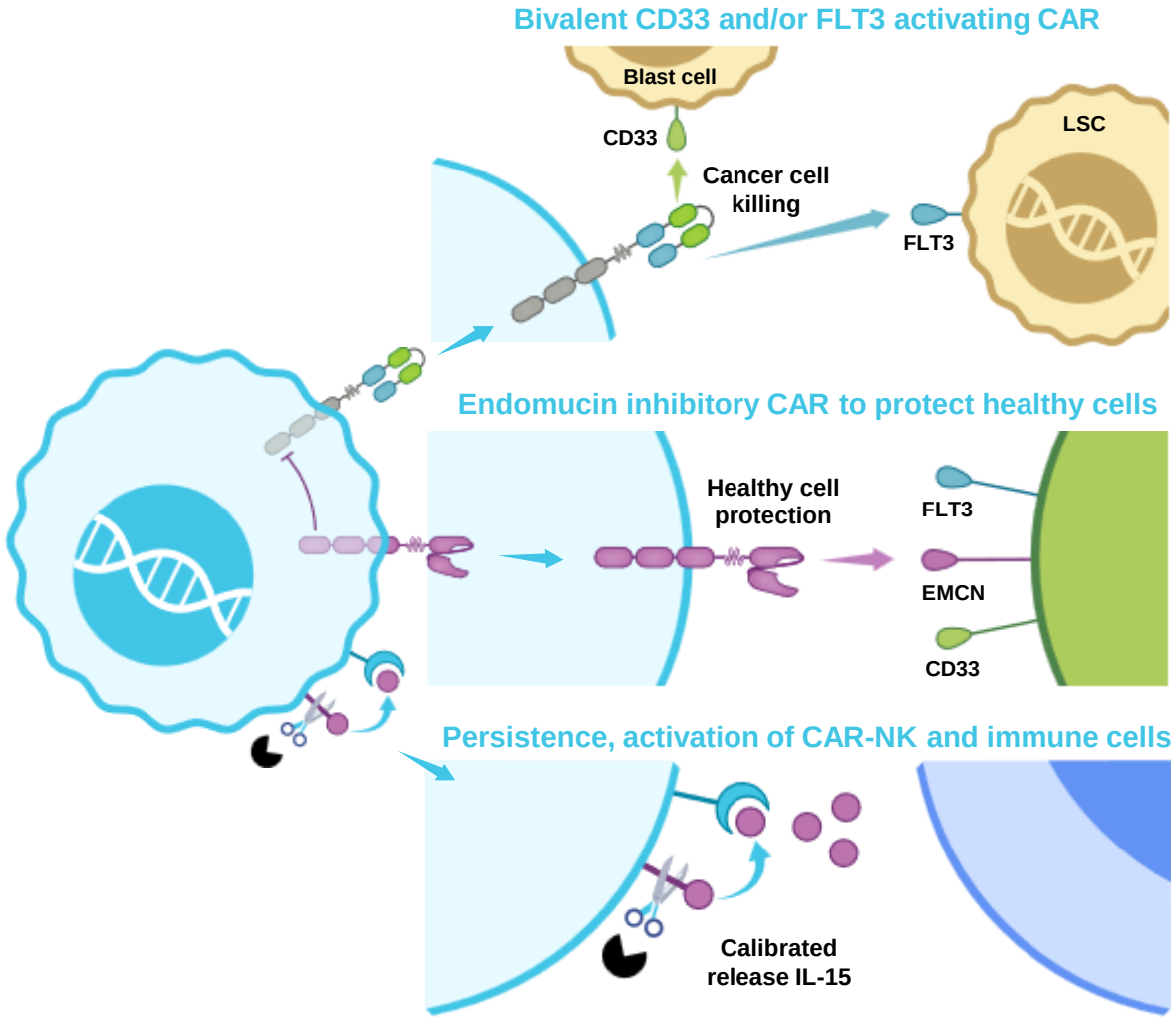




**Relapses after initial successful treatment are thought to originate from the outgrowth of persistent LSCs[1]**

- **Relapse correlates with LSC frequency[2]**
- **No available therapies specifically target LSCs**

[1] Zeijlemaker Leukemia 2019; Arnone Cancers 2020; van Gils Frontiers in Oncology 2021; Li Blood 2022; Hanekamp BJH 2020; Stelmach Haematologica 2023; [2] Li Blood 2022

# SENTI-202 Is a First-In-Class Selective Off-the-Shelf Investigational Cell Therapy for Blood Cancers




## Activating CAR "kill" signal

- Bivalent CD33 and/or FLT3 CAR targets validated AML targets
- Potential for deep and durable responses in AML and other blood cancers

## Inhibitory CAR "protect" signal

- Inhibition by endomucin (EMCN) protective antigen
- EMCN selectively expressed on healthy hematopoietic stem cells (HSCs) for potentially improved safety and increased therapeutic window

## Calibrated release IL-15

- Cell expansion, persistence, and tumor killing

**Initial clinical data expected by year-end 2024**

**Durability data expected in 2025**

# SENTI-202 is Designed to Address AML Heterogeneity Which Contributes to Disease Relapse/Refractoriness

## Treatment Challenges

### 1 Disease heterogeneity

AML cells have many antigen targets that are not uniformly expressed on all cancer cells

### 2 Durability of response

Limited durability from tumor escape, incomplete clearance of both leukemic blasts and LSCs

**Other CAR-based therapies target a single AML antigen leading to tumor escape and eventual relapse[1]**

**CD33 allogeneic CAR-NK cell therapy**: 60% CR rate as of 11/2022 (previously 80% on 6/2022)[2]

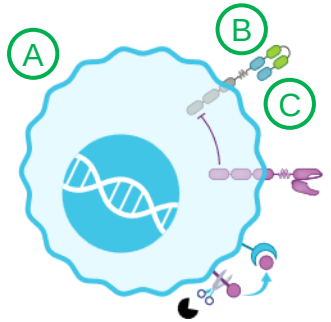
**Targeting CD33 largely addresses blast cells and misses LSCs, leading to disease evasion and relapse**

**NKG2D allogeneic CAR-NK cell therapy**: 22-67% CR/CRi rate and a short durability of <4 mo[3]

**Leukemic stem cells downregulate NKG2D ligands leading to poor response durability[1]**

## Senti's Solution

**SENTI-202 incorporates three key killing mechanisms to overcome AML heterogeneity with potential for deeper and longer remissions**



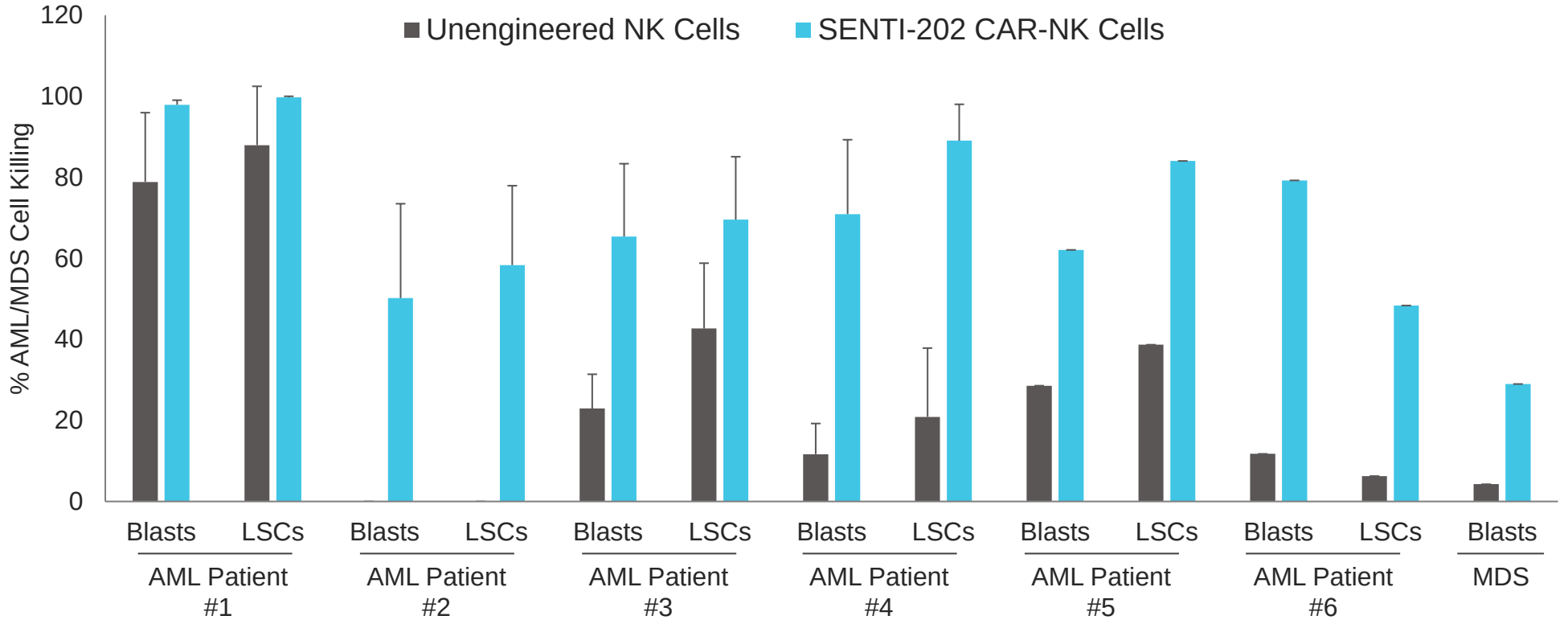

**Cancer killing mechanisms:**

- **A** NK cells innately kill cancer cells
- **B** CD33 CAR targets AML blasts
- **C** FLT3 CAR targets AML LSCs

- Targeting FLT3 and CD33 addresses ~95% of AML patients
- **SENTI-202 is the only CAR-NK clinical program utilizing the OR Logic Gate to target both CD33 and/or FLT3 for AML**

CRi: complete response with incomplete blood recovery
[1] Paczulla Nature 2019; [2] Huang Journal of Hematology & Oncology 2023; [3] Third-party data

# SENTI-202 Has Shown Robust Preclinical In Vitro Cancer Killing Against Patient Samples

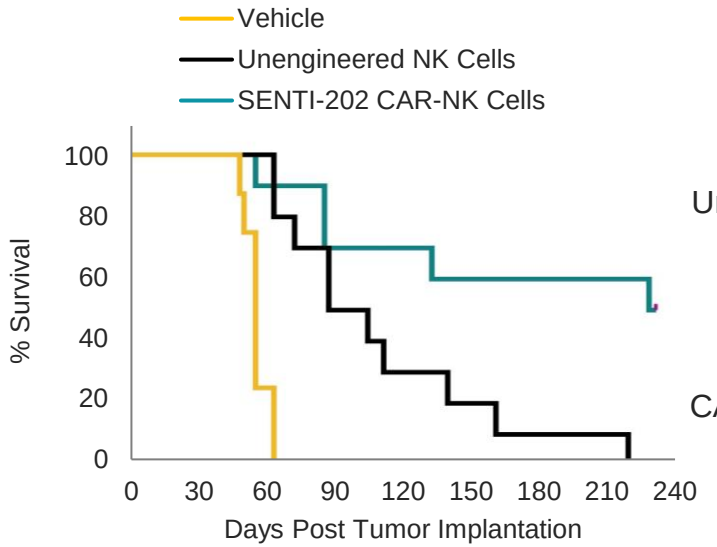


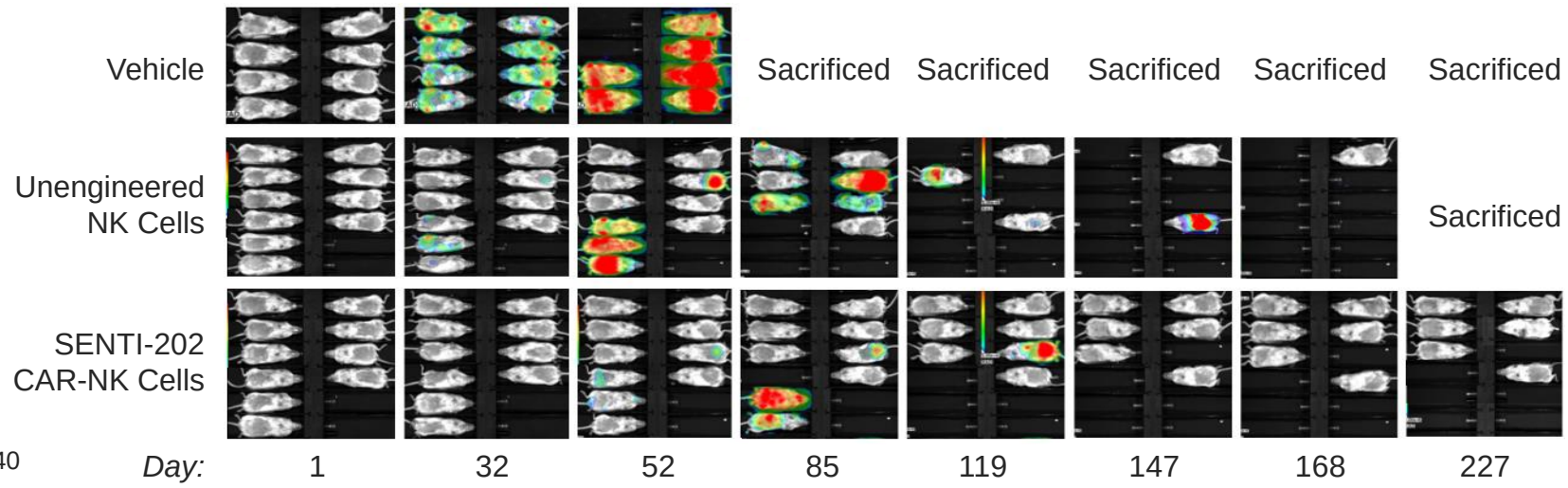

**Broad *in vitro* killing of primary CD33+ and/or FLT3+[1] AML and MDS tumor cells compared to unengineered NK cells**

[1] Both FLT3 wild-type and mutated AML patient samples

# SENTI-202 Has Shown Robust Preclinical In Vivo Cancer Killing Activity

## MV4-11 AML Human Transgenic NSG Mouse Model




| Group | Vehicle | Unengineered NK Cells | SENTI-202 CAR-NK Cells |
|---|---|---|---|
| **Median Survival (Days)** | 56 | 97 | 230 |

***In vivo* suppression of tumor and increased mouse survival in multiple mouse models including MV4-11 AML and venetoclax resistant AML[1]**

[1] Muftuoglu ASH 2023

# SENTI-202 is Designed to Address the Lack of Clean AML Targets to Improve Selectivity

## Treatment Challenges

### 3 Healthy cell toxicity

Many AML therapies kill cancer cells and HSCs because target antigens are expressed on both

### 4 Treatment tolerability

Killing of healthy HSCs leads to prolonged aplasia and myelosuppression

**Other CAR-based therapies targeting AML antigens kill healthy cells, leading to adverse events and tolerability issues**

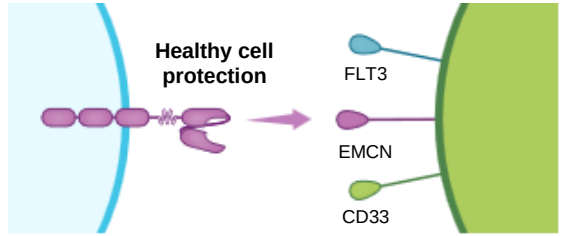
**Antigen expression on cells[1]**

| Antigen | LSCs | Blasts | HSCs |
|---|---|---|---|
| CD33 | +/- | + | +/- |
| FLT3 | + | +/- | + |
| CLL-1 | +/- | + | - |
| CD123 | + | + | +/- |
| CD38 | - | + | - |
| NKG2DL | - | + | - |

## Senti's Solution

**SENTI-202 incorporates an inhibitory CAR designed to protect healthy HSCs, even when expressing FLT3 or CD33**

Endomucin inhibitory CAR to protect healthy cells

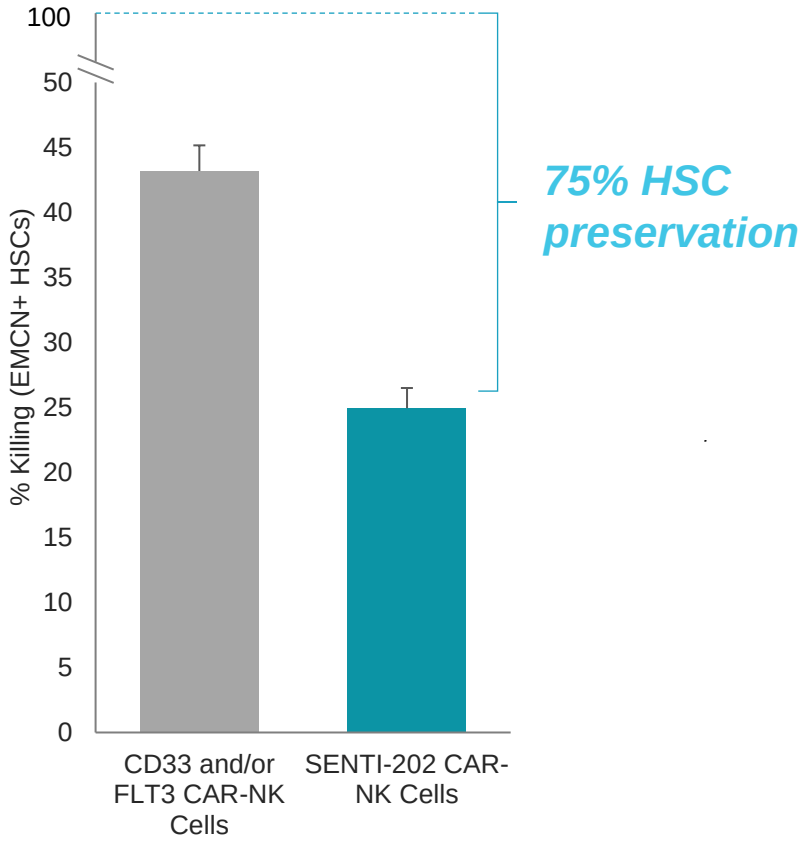



- EMCN was identified and validated as a protective antigen that is expressed on up to 76% of HSCs, but not on LSCs or blasts
- **SENTI-202 is the only known CAR-NK clinical program utilizing the NOT Logic Gate to protect healthy cells in AML**

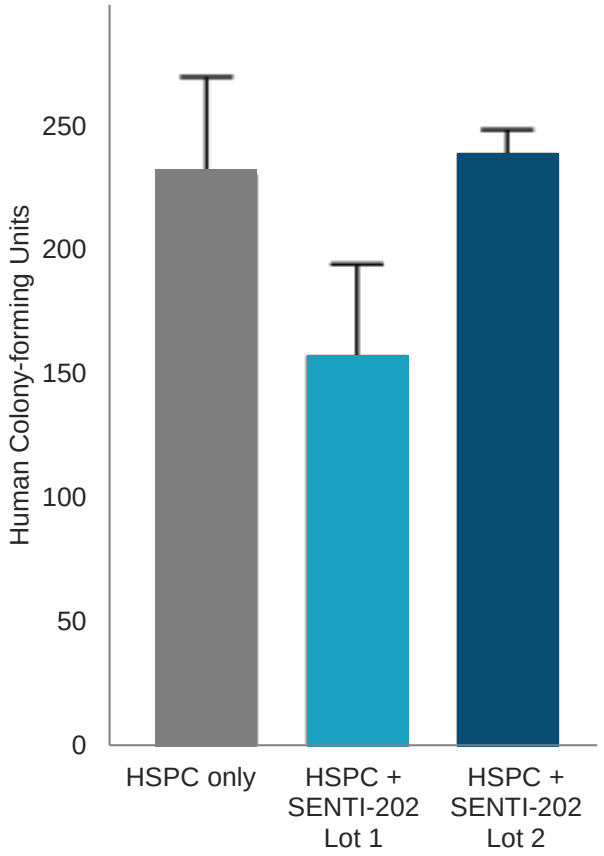
NKG2DL: NKG2D ligands

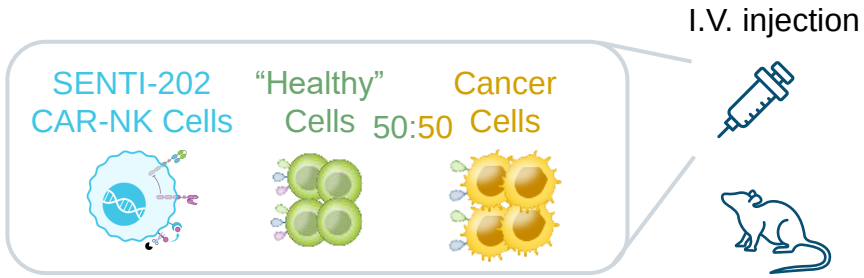
[1] Valent Stem Cell Translational Medicine 2020; Yoshimoto Blood 2009; Walter Blood 2012; Paczulla Nature 2019; Haubner Nature 2018; Pollyea Blood 2017

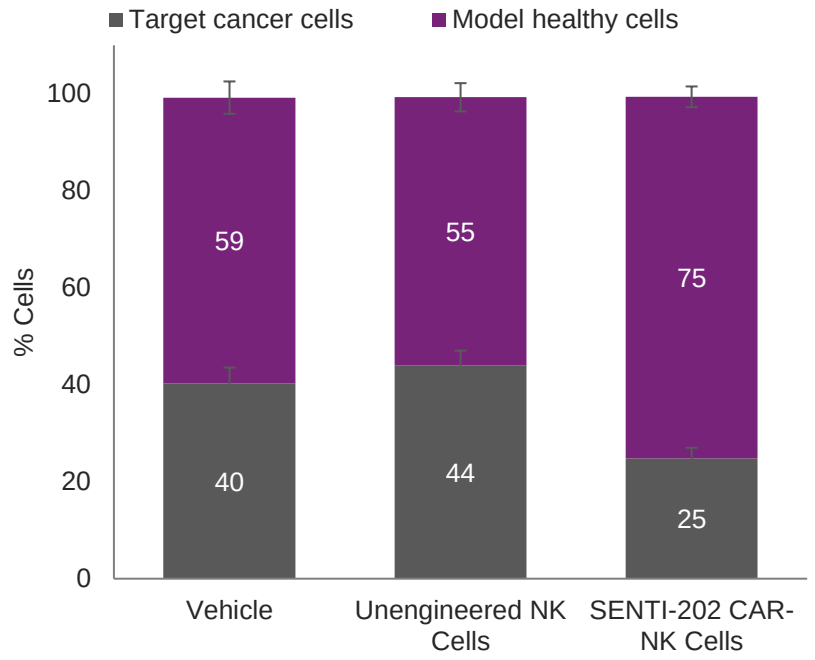
# SENTI-202 Has Shown Strong Preclinical Anti AML Selectivity and HSC Protection




***75% HSC preservation***



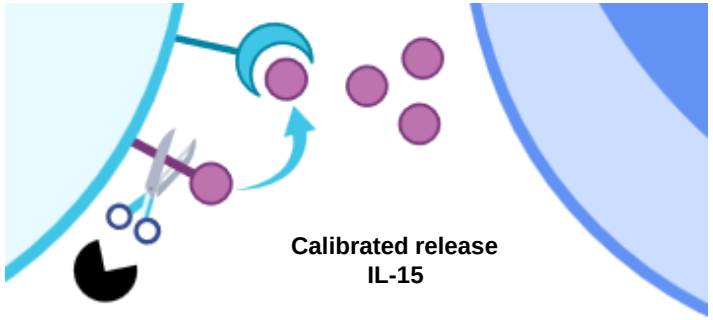

**_In vitro_ protection of primary human HSCs expressing EMCN**

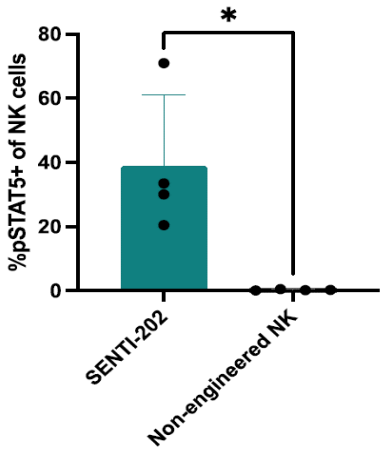
**Preservation of colony forming activity of HSPCs**

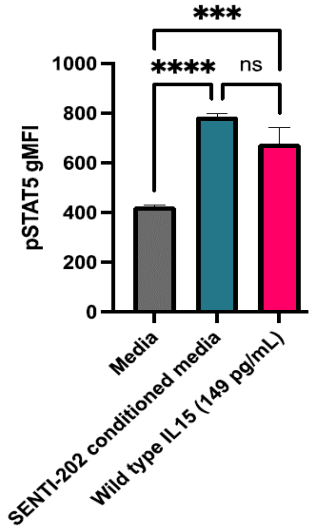
**Killing target cancer cells and protecting model healthy cells**

# SENTI-202 Has Enhanced Proliferation and Persistence in Preclinical Studies and Can Activate Host Immune Cells

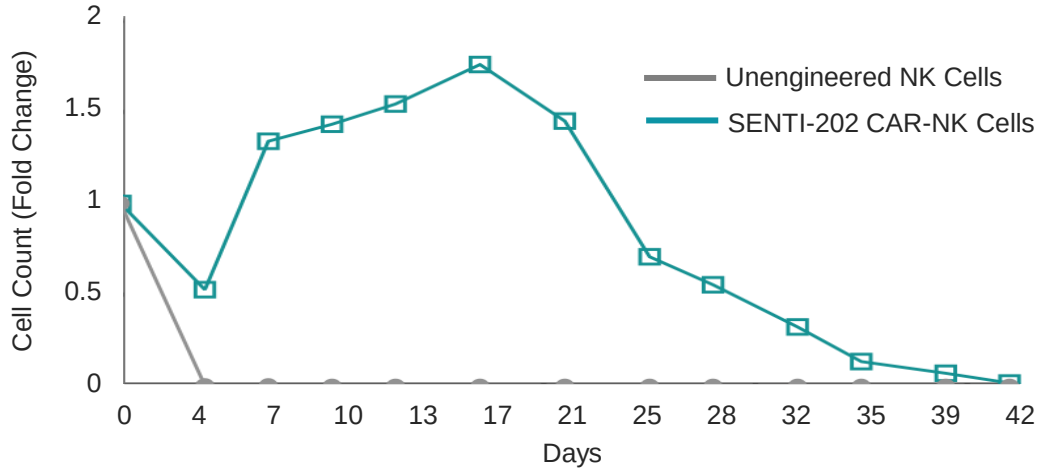
**crIL-15: calibrated release by local proteases → enhanced NK cell persistence**

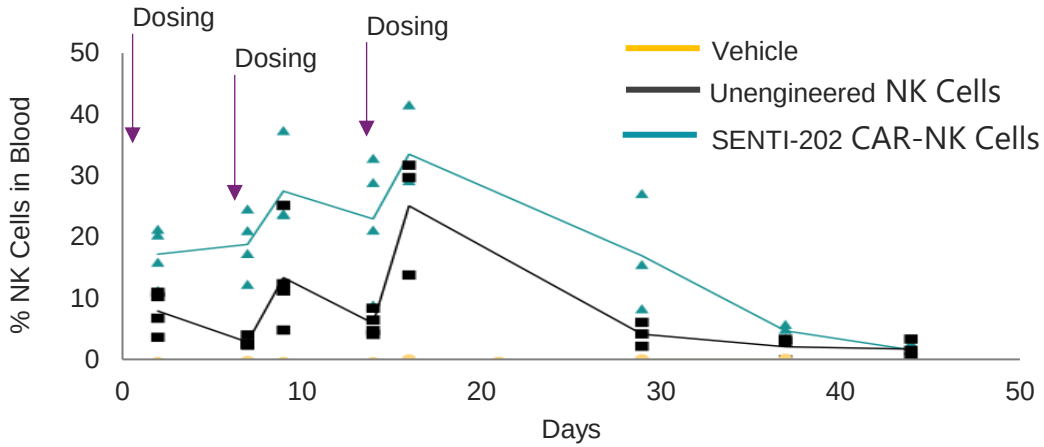



**SENTI-202 demonstrated improved signaling in pSTAT5 assay**

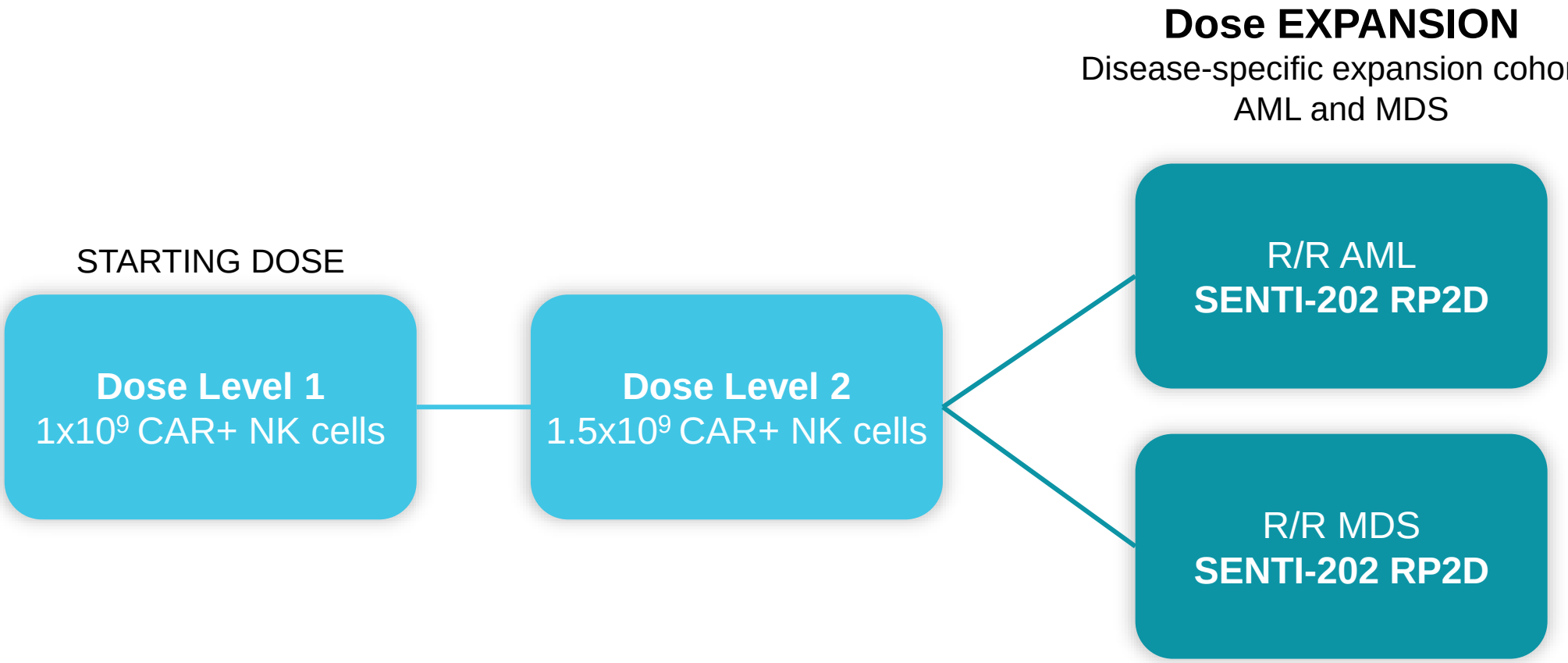



**crIL-15 increased persistence of SENTI-202 CAR-NK cells vs unengineered NK cells in vitro and in vivo**

# SENTI-202 Trial Design Incorporates Prior CAR-NK Trial Findings

## Disease Specific Lymphodepletion, Multi-Dose and Multi-Cycles



# SENTI-202 Phase 1 Trial Design

## Patient Population

- Adult patients
- R/R CD33 and/or FLT3 expressing heme malignancies
- 2 of 3 patients at each dose level with AML
- Received 1-3[1] prior AML treatments including targeted agents if FLT3, IDH1/2 mutation+

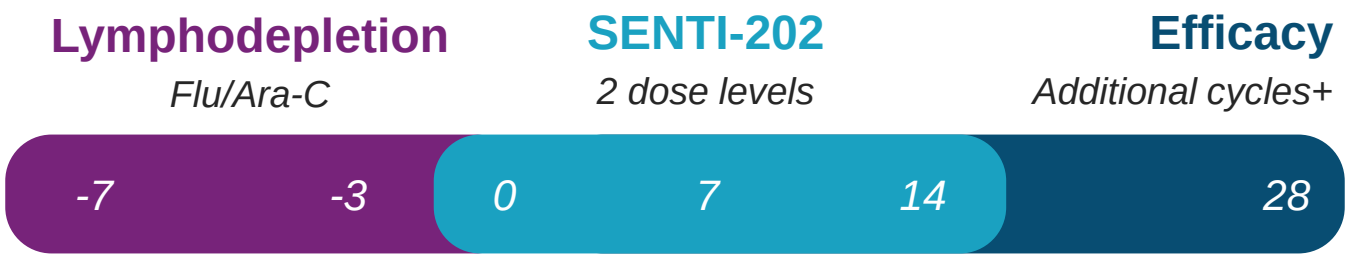
## Study Design

- "3+3" study design
- Dose escalation followed by disease-specific expansion cohorts for AML and MDS
- Starting dose $1x10^9$ CAR+ NK cells and target dose $1.5x10^9$ CAR+ NK cells
- Plans to transition from Phase 1 to pivotal study

## Planned Endpoints

- Safety, DLT, identify recommended Phase 2 dose
- Efficacy, including bone marrow recovery and MRD
- Pharmacokinetics (PK), pharmacodynamics (PD), biomarkers to supplement efficacy and immunogenicity

## Multi-Dose & Multi-Cycle Dosing



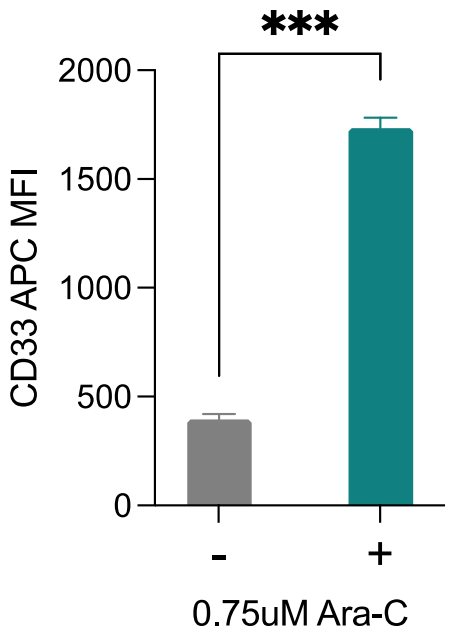

- ✓ Seamless Phase 1 to pivotal design
- ✓ Two initial dose levels
- ✓ Adaptive design with option to open IL2 cohort from emerging data

[1] 1-2 prior for MDS

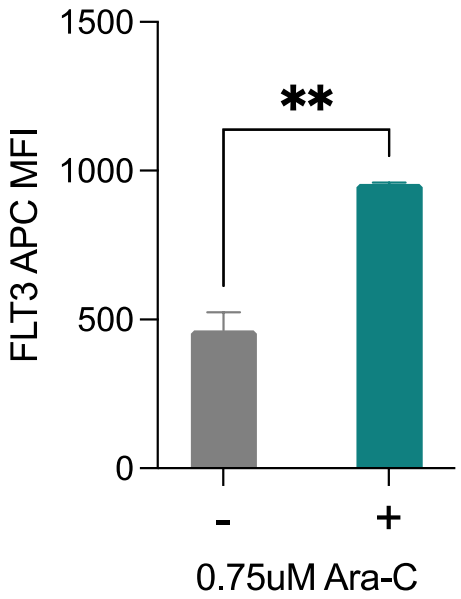
# Ara-C Sensitized KG-1a Cells to SENTI-202

## Upregulated CD33 and FLT3

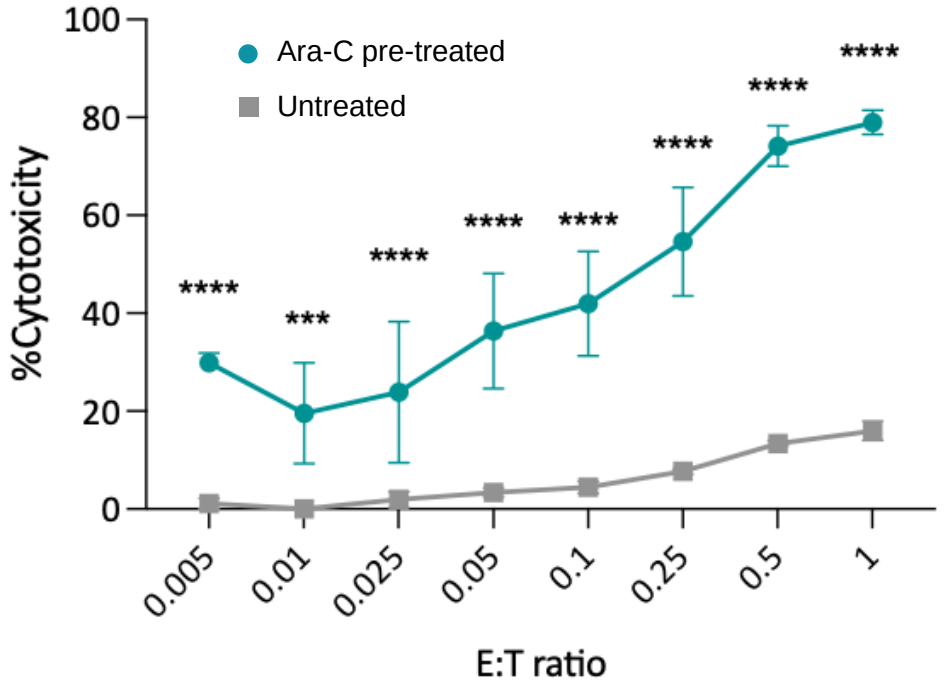
### CD33 Expression




### FLT3 Expression




### Enhanced In vitro Cytotoxicity




- In the CD33 low/FLT3 low KG-1a cell line, 72h Ara-C treatment significantly upregulated CD33 and FLT3 MFI
- Ara-C pre-treated KG-1a cells are sensitized to SENTI-202-mediated cytotoxicity

# SENTI-202 Mechanism of Action and Preclinical Data Could Result in Differentiated Clinical Profile

## 2024 Accomplishments

✓ First patient dosed in 2Q 2024

## Anticipated Clinical Catalysts

- Initial clinical efficacy data by year-end 2024
- Durability data in 2025

- Serial killing of LSCs and blasts *in vitro* and *in vivo*
- Pre-treatment with Ara-C sensitized CD33/FLT3 low AML
- Addition of EMCN shown to protect healthy hematopoietic stem cells
- crIL-15 engineered to increase persistence multiple times more compared to unengineered NK cells

**SENTI-202 was designed to integrate validated mechanisms into one solution, engineered to solve key outstanding problems in AML**

More detailed SENTI-202 data can be referenced in our Cell Reports publication titled:

**Precision off-the-shelf natural killer cell therapies for oncology with logic-gated gene circuits**

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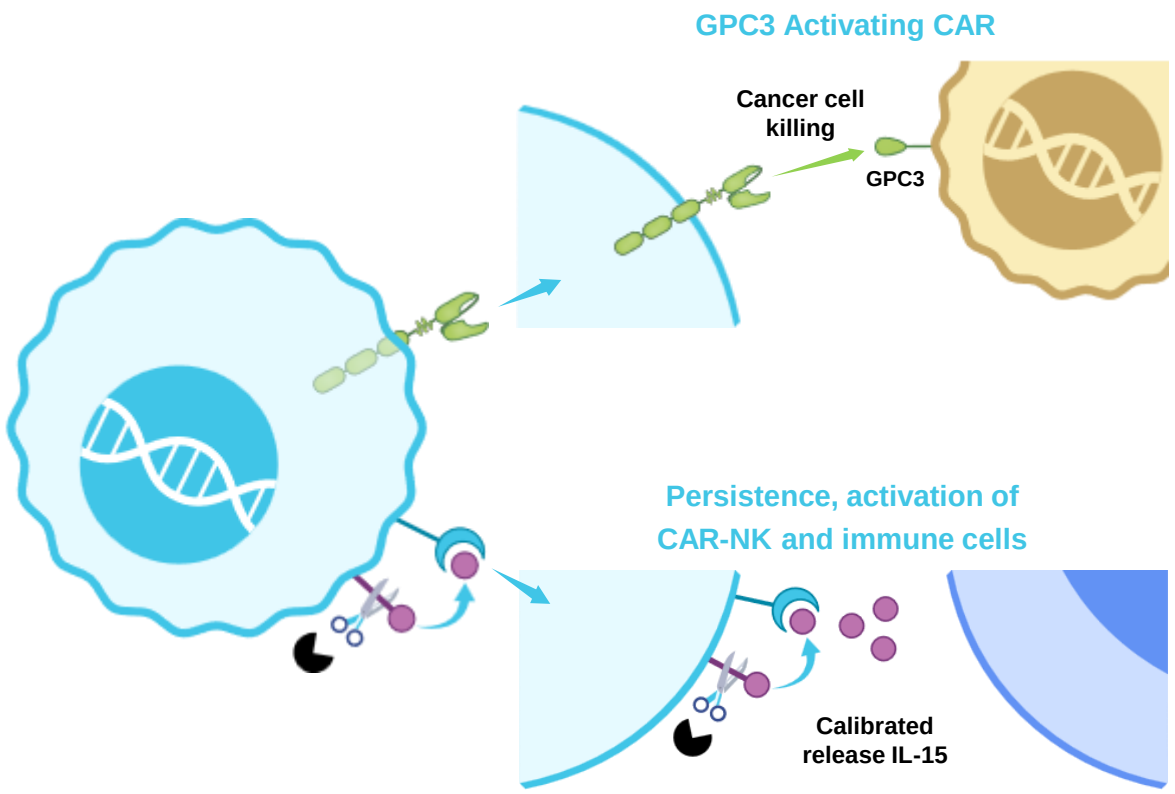
# SENTI-301A

# SENTI-301A Aims to Address Unmet Needs in Solid Tumors With a Focus on HCC




## Activating CAR "kill" signal

- GPC3 for hepatocellular carcinoma (HCC) and other solid tumors

## Calibrated release IL-15

- Potential for increased cell expansion, persistence, and tumor killing

**Strategic collaboration with Celest Therapeutics for clinical development of SENTI-301A to treat solid tumors in China, starting with HCC**

# Collaboration with Celest Therapeutics to Develop SENTI-301A for HCC in China

## Key Transaction Terms

- Up to $156 million in development milestones and potential tiered royalties post-commercialization
- Pilot trial to begin in mainland China with first patient dosing expected in 4Q 2024
- Potential to expand into Hong Kong, Macao, and Taiwan, with Senti retaining all commercialization rights outside of those regions and mainland China


Dose-finding trial design, with two dose levels

9 initial patients with advanced GPC3 expressing liver cancer (HCC)

Pilot trial to include safety and efficacy endpoints

~370,000 new cases of liver cancer in China in 2022, which was over 40% of all liver cancer cases worldwide[1]

[1] World Cancer Research Fund International

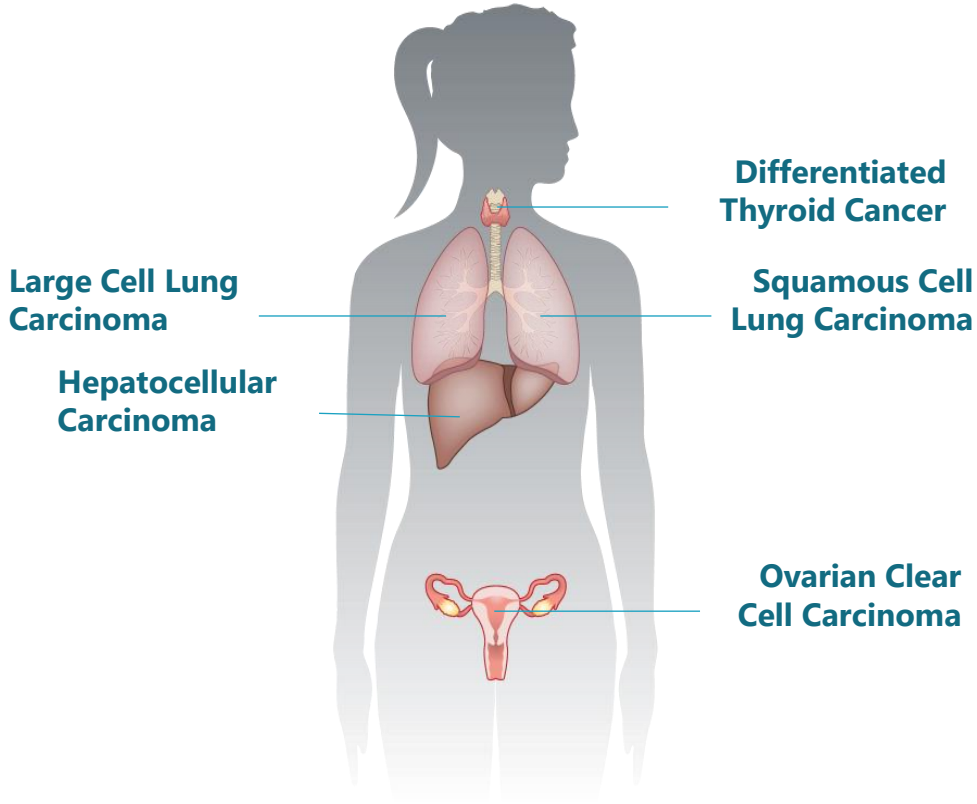
# SENTI-301A Is Designed to Tackle GPC3+ Expressing Solid Tumors

## GPC3 is expressed in multiple solid tumors

- HCC (70-90% GPC3+)[1] and other solid tumors – lung, ovarian, thyroid (29-54%[2] GPC3+)
- Academic GPC3 CAR-T cell trials have shown promising activity but limited by CAR-T toxicities precluding multiple dosing and limited durability[2,3]

## SENTI-301A is designed to target GPC3+ tumors

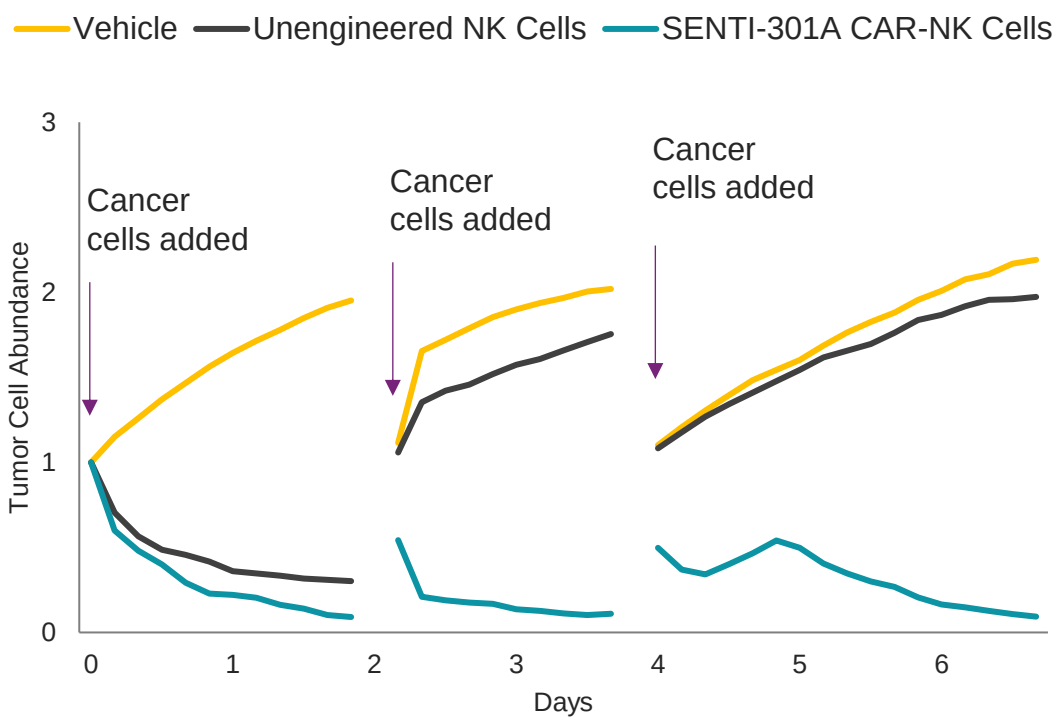
- Tackle multiple solid tumors with high GPC3 antigen expression via NKs multi-armed with GPC3 CAR and crIL-15

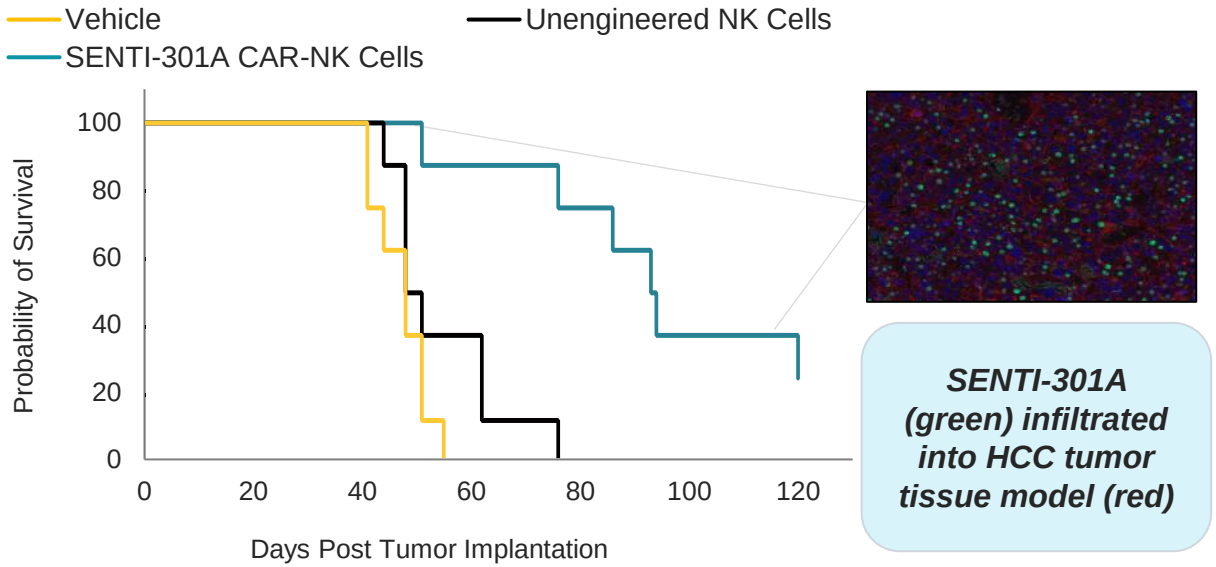



**Common GPC3 expressing tumors**

[1] Zheng Frontiers in Oncology 2022; [2] Moek American Journal of Pathology 2018; [3] Shi Clinical Cancer Research 2020

# SENTI-301A Has Shown Robust Preclinical Activity in Liver Cancer Models




***SENTI-301A (green) infiltrated into HCC tumor tissue model (red)***

| Group | Vehicle | Unengineered NK Cells | SENTI-301A CAR-NK Cells |
|---|---|---|---|
| **Median Survival (Days)** | 48 | 49.5 | 93.5 |

**Effective in vitro serial killing of HepG2 cell line**

**Increased survival, tumor infiltration and response in HepG2 mouse model**

# Planned Early Exploratory Clinical Study Design of SENTI-301A

## Patient Population

- Adult patients
- Advanced GPC3-positive Hepatocellular Carcinoma
- Unresectable stage B or C (per BCLC)
- Failed at least 1 prior line, including PD1/L1 & TKIs

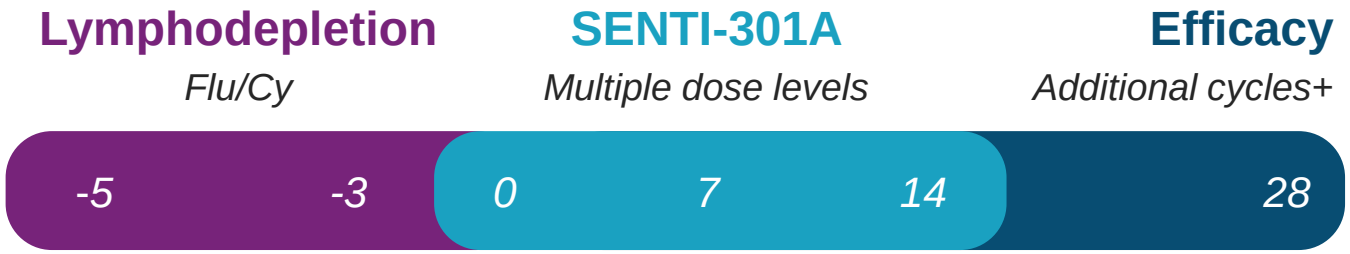
## Study Design

- “3+3” study design
- Dose escalation followed by expansion cohort
- Multiple dose levels
- Opportunity to transition to US clinical study

## Planned Endpoints

- Safety, DLT, recommended Phase 2 dose
- Efficacy, using RECIST v1.1, mRECIST & iRECIST criteria
- Pharmacokinetics (PK), pharmacodynamics (PD), biomarkers to supplement efficacy and immunogenicity

## Multi-Dose & Multi-Cycle Dosing




**First patient dosing in China expected in 4Q 2024**

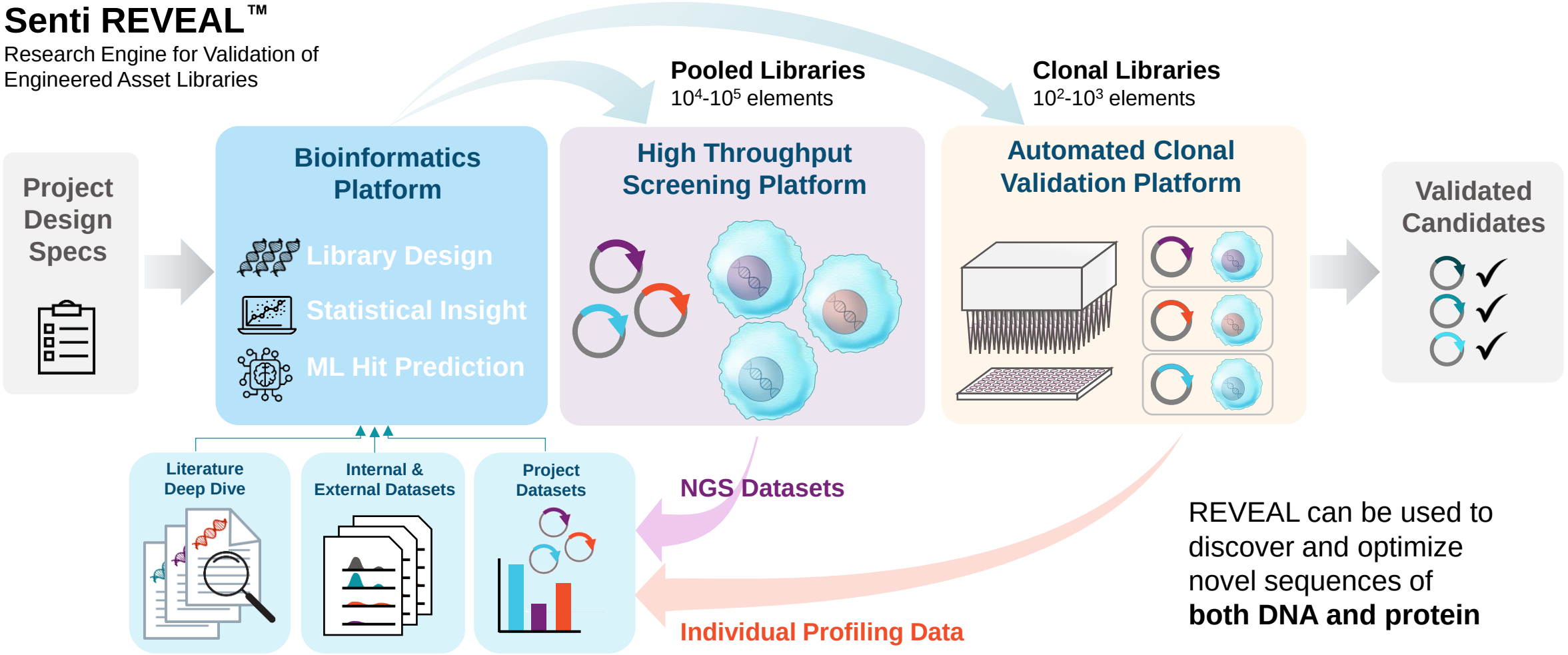
SENTI BIO

# Platform

# Senti's Discovery and Optimization Engine For Novel DNA and Protein Assets

## Senti REVEAL™

Research Engine for Validation of Engineered Asset Libraries



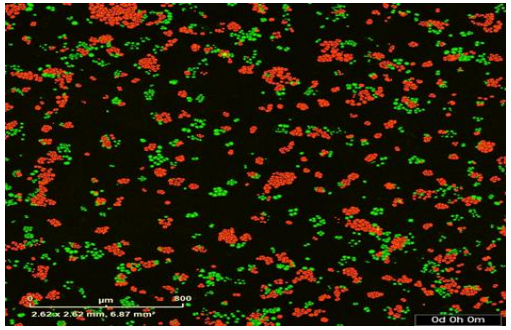

REVEAL can be used to discover and optimize novel sequences of **both DNA and protein**

# Senti's REVEAL Platform Designed to Enable Rapid Optimization of Highly Potent & Protective Logic Gates for NK and T Cells

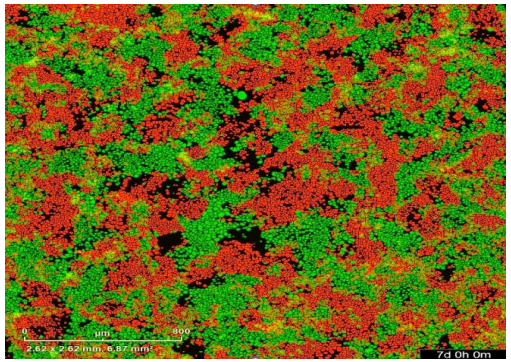
Cancer cells *(VSIG2$^{-}$CEA$^{+}$)*

Model healthy cells *(VSIG2$^{+}$CEA$^{+}$)*

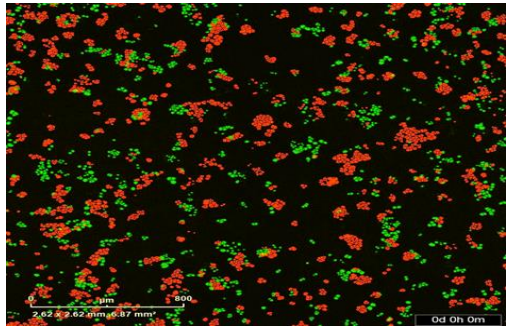
## No NK Cells



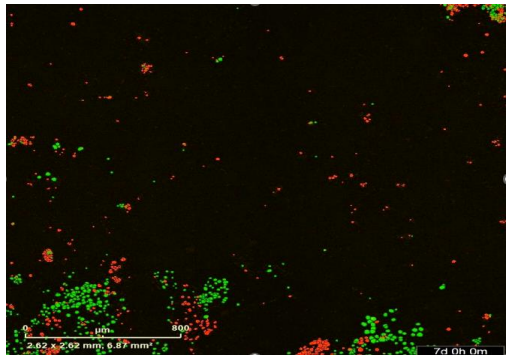
No killing of cancer or healthy cells



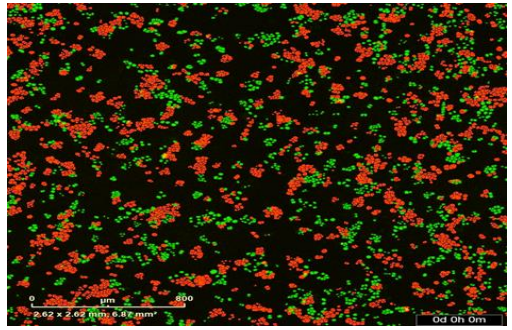
## CEA CAR-NK



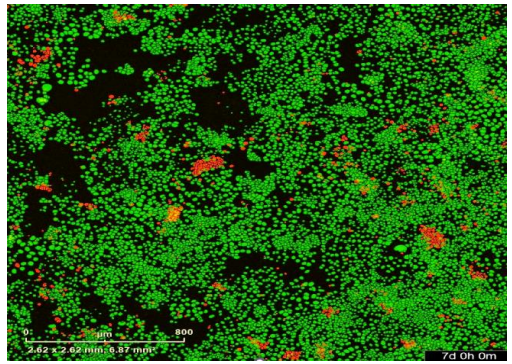
Significant killing of both cancer and healthy cells



## CEA NOT VSIG2 CAR-NK

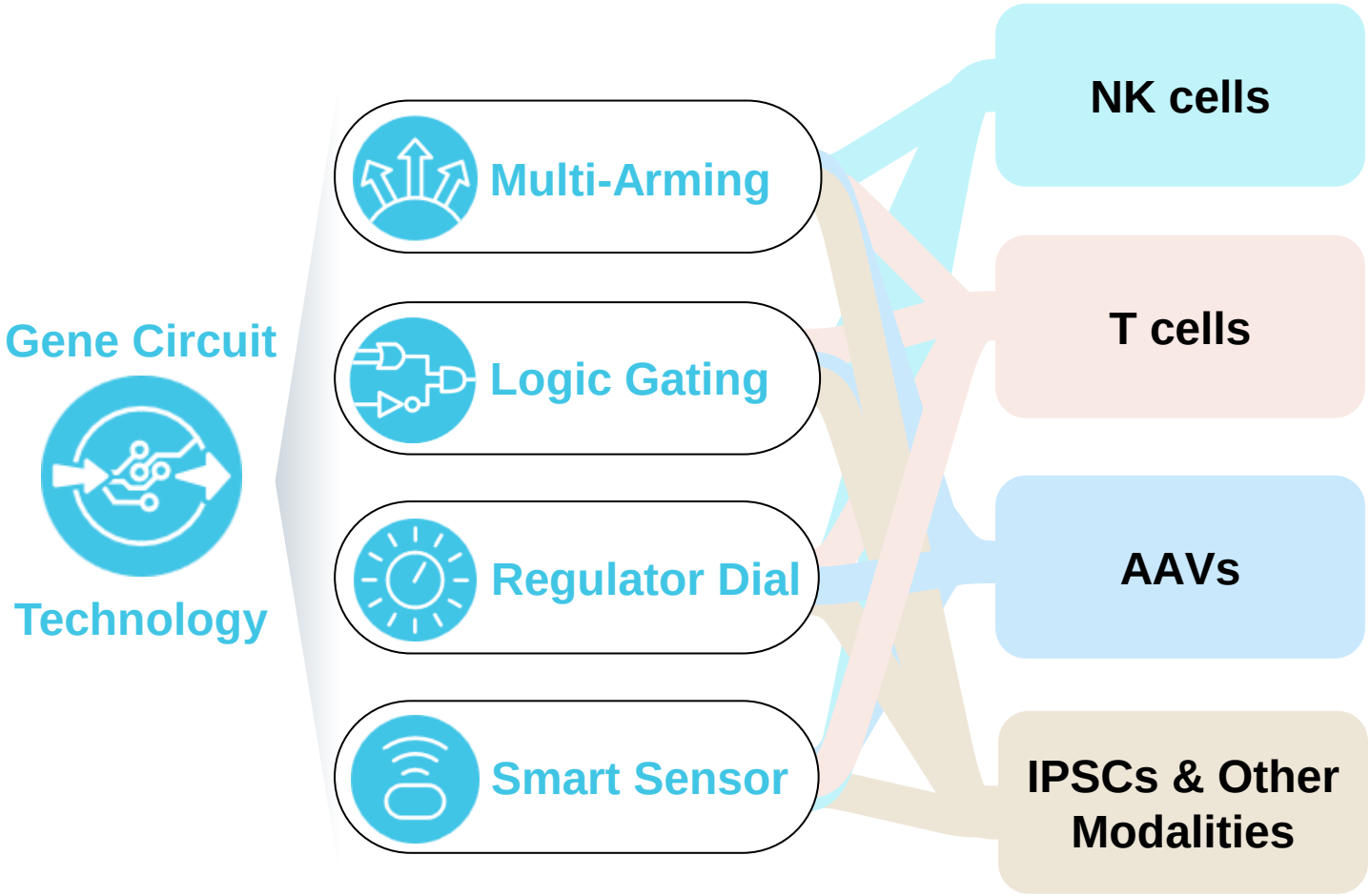


Precise killing of cancer cells while sparing healthy cells



**CEA NOT VSIG2 CAR-NK cells spared VSIG2-expressing model healthy cells while maintaining robust on-target, on-tumor killing of CEA+ cancer cells**

# Executing Towards Bringing Gene Circuit Medicines to Patients




- ✓ SENTI-202 is a potential first-in-class logic gated CAR-NK program for AML
  - ⇨ Initial efficacy data anticipated YE 2024
  - ⇨ Durability data anticipated 2025
- ✓ SENTI-301A first patient expected to be enrolled in China in 4Q 2024
- ✓ Experienced management team with track record of executing on timelines and accelerating innovative therapies
- ✓ Gene Circuit technology has been validated in NK cell, T cell, AAV, and iPSC applications

SENTI BIO

# Thank You!