Senti Bio Highlights Preclinical Data on Cancer-Killing Allogeneic CAR-NK Cells in Three Presentations at ASGCT Annual Meeting

May 18, 2022

-SENTI-202 oral presentation details systematic optimization of Logic Gating Gene Circuit technology in allogeneic CAR-NK cells to more precisely target tumor cells in acute myeloid leukemia, while sparing healthy cells -

- SENTI-301 poster presentation highlights optimization of Multi-Arming and Regulator Dial Gene Circuits to improve the cytotoxicity of allogeneic CAR-NK cells and immune stimulation in hepatocellular carcinoma -

- Smart Sensor Gene Circuit oral presentation describes strategies for developing novel cell-state-specific activation promoters to control payload expression when targeting cancer, thereby maximizing anti-tumor activity while minimizing systemic toxicity -

SOUTH SAN FRANCISCO, Calif., May 18, 2022 —Senti Bio, a leading gene circuit company, today announced three presentations at the American Society of Gene and Cell Therapy (ASGCT) annual meeting being held in Washington D.C., May 16–19, 2022. The presentations highlight new data related to the application of gene circuit technology to enhance efficacy and safety of cancer-killing allogeneic chimeric antigen receptor (CAR) natural killer (NK) cells.

“This year's ASGCT presentations mark significant progress across our pipeline of allogeneic gene circuit-enabled CAR-NK cell product candidates, particularly for our two lead programs in acute myeloid leukemia and hepatocellular carcinoma,” said Tim Lu, MD, PhD, Chief Executive Officer and Co-Founder of Senti Bio. “Our next-generation cell therapies, powered by our proprietary gene circuit technology, are designed to target multiple disease pathways to overcome the tumor microenvironment and provide enhanced cancer-killing activity. Importantly, we have further optimized the gene circuit components for our lead programs, SENTI-202 and SENTI-301, and we are excited to be in the final stages of development candidate selection, with anticipated IND filings for both of these programs in 2023.”

SENTI-202 Presentation: Logic Gated FLT3 OR CD33 NOT EMCN CAR-NK Cell Therapy (SENTI-202) for Precise Targeting of AML (Oral presentation, Garrison et al.)

- This presentation describes refinement of individual components in the SENTI-202 product candidate, which employs two types of Logic Gating as a novel therapeutic approach to treating acute myeloid leukemia (AML). Within SENTI-202, “Logic Gating” refers to the concurrent use of activating and inhibitory CARs to integrate multiple target antigen inputs that enable CAR-NK cells to better identify and kill cancer cells while sparing healthy cells. SENTI-202 is also engineered to express a proprietary calibrated release interleukin-15 (crIL-15) to promote NK cell persistence and tumor killing.
    - OR GATE: Bivalent FLT3 OR CD33 Logic Gated activating CAR (aCAR) is engineered to increase AML leukemic stem cell (LSC) and blast clearance, prevent single antigen tumor escape, and potentially provide deeper and longer remissions.
    - NOT GATE: Endomucin (EMCN) NOT Logic Gated inhibitory CAR (iCAR) is engineered to protect healthy hematopoietic stem cells which are EMCN positive (EMCN+) from off-tumor toxicity, potentially increasing therapeutic specificity and improving post-treatment regeneration of a healthy hematopoietic system.
    - Calibrated release interleukin-15: The crIL-15 construct is designed to simultaneously produce both membrane-associated and fully secreted IL-15, to enable both autocrine cytokine signaling (to increase CAR-NK cell proliferation and persistence) and paracrine cytokine signaling (to stimulate the patient's surrounding immune cells).
- New *in vivo* CAR-NK cell activity data demonstrate significant bivalent FLT3 OR CD33 CAR-NK cell killing of AML tumor cells and increased animal survival within an AML xenograft mouse model.
- New *in vitro* CAR-NK cell iCAR screening data demonstrate that Senti Bio has tested more than 20 different NOT GATE architectures to identify the most robust intracellular functional domain for the SENTI-202 NOT GATE circuit.
- *In vitro* data demonstrate significant NOT GATE-mediated protection of primary healthy hematopoietic stem cell (HSC)-enriched cells from off-tumor toxicity via CAR-NK cell recognition of the HSC-expressed EMCN healthy antigen; *in vivo* data also demonstrate significant NOT GATE-mediated protection of healthy model cells from CAR-NK cell toxicity.
- Based on literature that represents years of successful hematopoietic cell transplantation clinical procedures, the authors believe that as little as 10-20% protection may be sufficient to reconstitute a healthy immune system in the absence of hematopoietic cell transplantation, currently the only cure for AML.
- Researchers believe that incorporating Logic Gating technologies into the SENTI-202 gene circuit may enable the achievement of greater tumor clearance with less off-tumor toxicity, and ultimately deeper and longer remissions.

SENTI-301 Presentation: Multi-Arming and Regulator Dial Gene Circuits to Address Key Disease Challenges in HCC (Poster presentation, Guzman Ayala et al.)

- This presentation describes the SENTI-301 product candidate which employs two gene circuits, a Multi-Arming and a Regulator Dial gene circuit, to improve the cytotoxicity and longevity/persistence of CAR-NK cells in treating hepatocellular carcinoma (HCC). Senti Bio has developed a novel calibrated release interleukin-15 (crIL-15) technology to enable both autocrine cytokine signaling (to increase CAR-NK cell proliferation and persistence) and paracrine cytokine signaling (to stimulate the patient's surrounding immune cells). SENTI-301 includes the following:
    - GPC3 CAR: NK cells are engineered to express a GPC3 (glypican-3) CAR to enhance targeting of HCC cells. GPC3 is a biomarker of HCC, high levels of which are associated with poor outcomes for HCC patients.
    - Multi-Arming: CAR-NK cells are armed with crIL-15 and crIL-12, the calibrated release forms of IL-15 and IL-12, two therapeutic cytokines known to stimulate the immune system and which have shown anti-tumor activity in the clinic. In addition, crIL-15 also improves CAR-NK persistence and effector function.
    - Regulator Dial: a gene circuit designed to control expression of calibrated release interleukin-12 (crIL-12) under the control of an FDA-approved small molecule.
- Data presented demonstrate that crIL-15 enhances NK cell persistence and GPC3 CAR-NK tumor killing compared to wild-type secreted IL-15. Optimization of the expression of the GPC3 CAR crIL-15 gene circuit in NK cells also shows higher anti-tumor function compared to unengineered NK cells *in vitro* and *in vivo*.
- Similarly, optimization of the Regulator Dial gene circuit demonstrates the ability of SENTI-301 to control crIL-12 expression via the presence or absence of an FDA approved small molecule for hepatitis C treatment, an NS3 inhibitor grazoprevir (GRZ), as evidenced by a significant increase in release of crIL-12 secretion post GRZ treatment with low levels of released crIL-12 in the absence of GRZ.
- The authors outline the benefits of SENTI-301 to potentially overcome the challenges of the immunosuppressive tumor microenvironment, providing a potentially more efficacious and safe treatment option for HCC patients.

Smart Sensor Gene Circuit Presentation: Activation Regulated Gene Circuit for Controlling Payload Expression in Cell Therapies (Oral presentation, Hung et al.)

- This presentation highlights Senti Bio's "Smart Sensor" gene circuits which are designed to sense a disease state and turn on gene expression in response. The authors describe promoters that drive gene expression in NK and T cells in response to activation through native receptors or CARs. These activation-responsive Smart Sensors may enable NK and T cells to express potent cytokines only when activated by tumor cells, and not systemically, thereby leading to high anti-tumor activity while reducing the toxicity of systemic expression.
- The authors discovered several promoters that exhibited high expression in activated cells (maximizing efficacy) and minimal expression in resting cells (minimizing toxicity).
- One promoter discovery strategy leveraged natural promoter mining resulting in the discovery of a promoter with minimal basal activity and a 20-fold induction in response to T cell activation. Another promoter strategy leveraged high throughput screening of synthetic promoters leading to the identification of four promoters that showed minimal basal activity and greater than 10-fold activation responsiveness.
- Senti Bio's Smart Sensor Gene Circuit can be designed for "cell-state-specific" and "disease-state-specific" response to gene expression, which may be applied to cell and gene therapies across multiple therapeutic areas and modalities.

About Senti Bio

Our mission is to create a new generation of smarter medicines that outmaneuver complex diseases using novel and unprecedented approaches. To accomplish this, we are building a synthetic biology platform that may enable us to program next-generation cell and gene therapies with what we refer to as Gene Circuits. These Gene Circuits, which are created from novel and proprietary combinations of DNA sequences, are designed to reprogram cells with biological logic to sense inputs, compute decisions, and respond to their cellular environments. We aim to design Gene Circuits to improve the intelligence of cell and gene therapies in order to enhance their therapeutic effectiveness, precision, and durability against a broad range of diseases that conventional medicines do not readily address. Our synthetic biology platform utilizes allogeneic chimeric antigen receptor natural killer (CAR-NK) cells, outfitted with these Gene Circuit technologies, to target particularly challenging liquid and solid tumor oncology indications including acute myeloid leukemia, hepatocellular carcinoma, and colorectal cancer. We have also demonstrated the breadth of our Gene Circuits in other modalities and diseases outside of oncology, and have executed partnerships with Spark and BlueRock to advance these capabilities. For more information, please visit the Senti Bio website at https://www.sentibio.com.

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