**SENTI-301A Demonstrates Tumor Infiltration**

- SENTI-301A infiltrates into the tumor microenvironment and demonstrates enhanced persistence and anti-tumor function in HCC tumor models.

**Background**

SENTI-301A is a novel off-the-shelf chimeric antigen receptor (CAR) NK cell product candidate in preclinical development designed to potentially address unmet clinical need in GPC3 expressing solid tumors such as hepatocellular carcinomas (HCC). SENTI-301A is designed to express a Multi-Arming gene circuit, a targeted GPC3 CAR and a calibrated-release interleukin-15 (cilr-15) engineered onto allogeneic healthy adult peripheral blood NK cells. The activating CAR is designed to target GPC3, an antigen overexpressed in several cancers, such as HCC. cilr-15 is a unique technology where IL-15 cytokine molecules are released from the cell in a calibrated fashion via a protease ubiquitously expressed by the cell, wherein the release rate is calibrated by engineering modifications to the protease cleavage site. cilr-15 is designed to simultaneously stimulate surrounding immune cells and promote CAR-NK cell expansion, persistence, and tumor killing.

**SENTI-301A: A Multi-Armed CAR-NK candidate Targeting GPC3**

- SENTI-301A is designed to target GPC3 expressing tumors, addressing unmet clinical need in HCC, as well as other solid tumors including lung, HNSCC, and breast cancer.
  - Glypican-3 (GPC3) is a membrane-bound protein normally expressed in fetal tissues such as liver and placenta.
  - GPC3 is not expressed in healthy liver tissue or other organs after birth but is overexpressed in different tumor types such as in HCC (70-90% GPC3+), and other solid tumors (29-54% GPC3+).

**cilr-15 Increases CAR-NK Serial Killing of Cancer Cells and In Vitro Persistence**

- cilr-15 increases CAR-NK persistence and anti-tumor function in vitro and in vivo.

**SENTI-301A Demonstrates Effective Serial Killing of GPC3 Expressing HCC Cell Lines**

- SENTI-301A shows significant increase of CAR-mediated killing against GPC3+ target cells, which further augments intrinsic NK cell cytotoxicity against GPC3- cells.

**SENTI-301A Demonstrates In Vivo Enhanced Persistence and Anti-tumor Function**

- In two separate HCC xenograft models, SENTI-301A shows enhanced persistence, antitumor function, and increased survival in comparison to unengineered NK cells.

**Soluble GPC3 has been reported to neutralize GPC3-specific CAR-T cells via competitive binding to target.**

**Summary**

SENTI-301A is armed with cilr-15 to stimulate surrounding immune cells and promote CAR-NK cell expansion, persistence, and tumor killing. SENTI-301A has innate killing ability against non-GPC3 expressing targets, which is further enhanced by the GPC3 CAR for GPC3-expressing targets. SENTI-301A promotes the serial killing of tumor cell lines, including both Huh7 and HepG2 and non-HCC (FU97) cell lines, along with the release of cytokines and cytotoxic proteases. SENTI-301A infiltrates into the tumor microenvironment and demonstrates enhanced persistence and anti-tumor function in HCC tumor models.