SENTI-301A, an Off-the-Shelf Multi-Armed Preclinical CAR-NK Cell Therapy for the Treatment of GPC3 Expressing Tumors

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Abstract #2905

Background

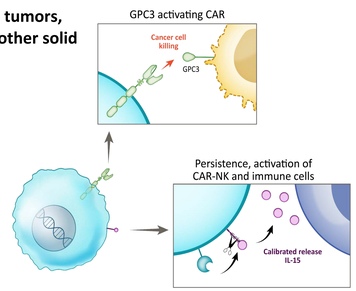
SENTI-301A is a novel off-the-shelf chimeric antigen receptor (CAR) NK cell product candidate in preclinical development designed to potentially address unmet clinical need in GPC3 expressing solid tumors such as hepatocellular carcinomas (HCC). SENTI-301A is designed to express a Multi-Arming gene circuit, a targeted GPC3 CAR and a calibrated-release interleukin-15 (crIL-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. crIL-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. crIL-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

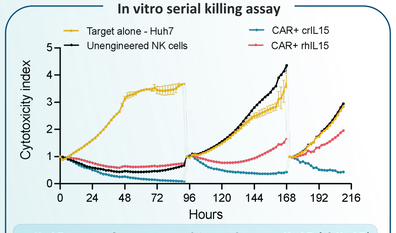
SENTI-301A is designed to target GPC3 expressing tumors, addressing unmet clinical need in HCC, as well as other solid tumors including lung, HNSCC, and breast cancer.

- 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+)[1] and other solid tumors (29-54% GPC3+)[2].

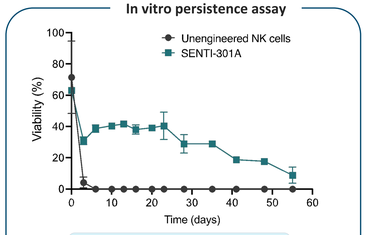
[1] Zheng 2022, [2] Moek 2018



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



crIL-15 outperforms recombinant human IL-15 (rhIL-15) within an incucyte-based serial killing assay.



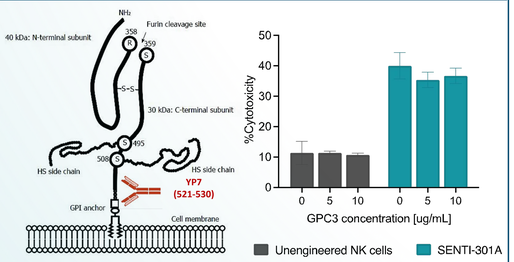
crIL-15 increases in vitro persistence of CAR- NK cells.

SENTI-301A Maintains Anti-tumor Function in the Presence of Soluble GPC3

Soluble GPC3 has been reported to neutralize GPC3-specific CAR-T cells via competitive binding to targets[3].

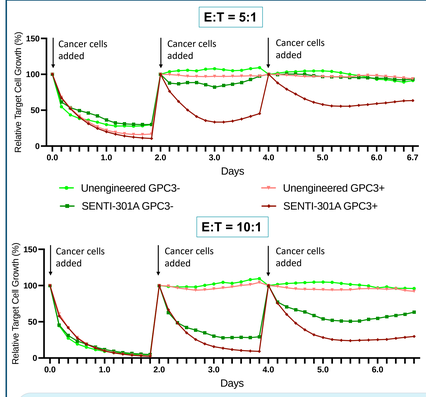
GPC3 is cleaved by furin at S359[4], while the SENTI-301A binder (YP7) recognition site is close to the cell membrane, which may allow SENTI-301A to avoid inhibition by soluble GPC3.

[3] Sun 2021, [4] Ho 2011

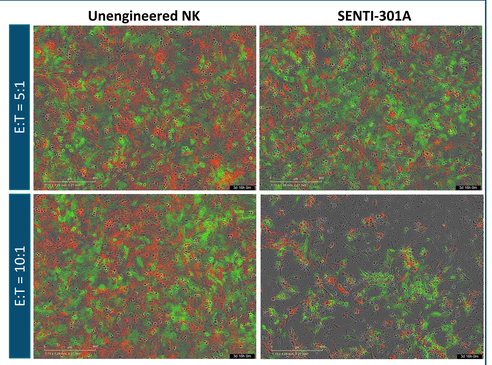


SENTI-301A cytotoxicity against Huh7 target cells is preserved in the presence of soluble GPC3. (1:1 E:T – 18 hours LDH assay)

SENTI-301A Promotes In Vitro CAR-driven Killing of GPC3 Expressing Cell Lines

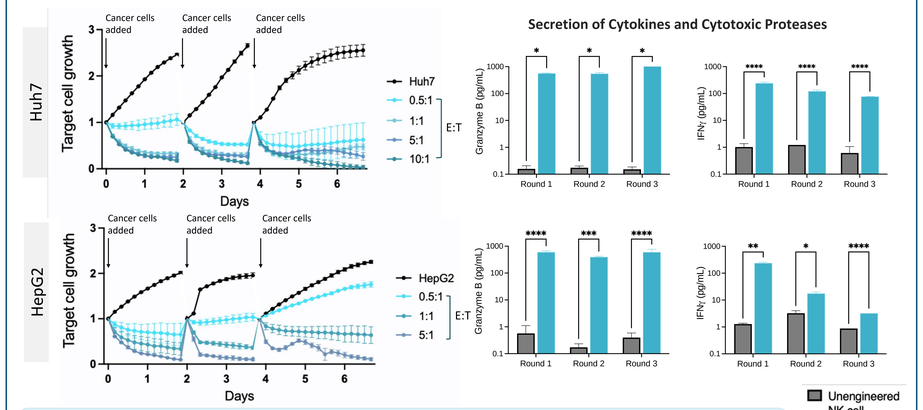


SENTI-301A shows significant increase of CAR-mediated killing against GPC3+ target cells, which further augments intrinsic NK cell cytotoxicity against GPC3- cells.



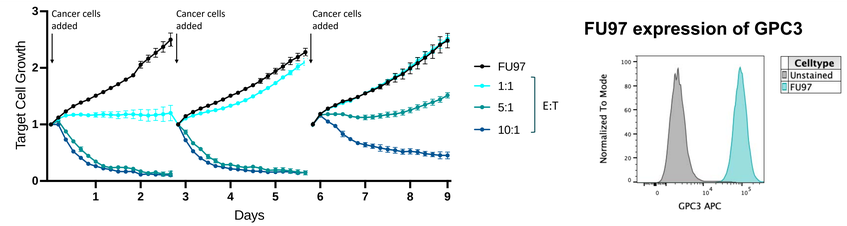
GPC3 negative (green) and GPC3+ (red) target cells were mixed 1:1 and co-cultured with unengineered NK cells or SENTI-301A. Images from 1 NK donor taken at the end of 2nd killing round.

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



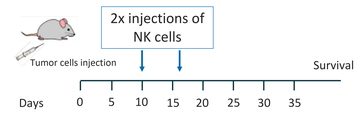
SENTI-301A shows robust antitumor activity against Huh7 and HepG2 cells lines at different effector:target ratios (E:T), with secretion of the effector molecules Granzyme B and IFNγ.

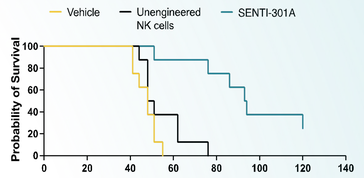
SENTI-301A Demonstrates Serial Killing of GPC3 Expressing Non-HCC Cell Line

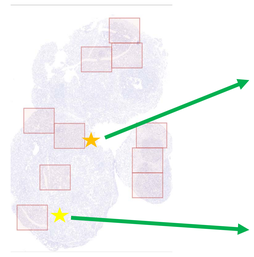


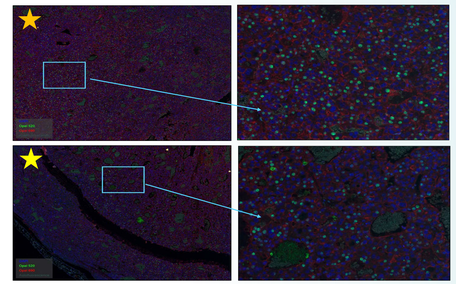
SENTI-301A shows serial killing activity against the GPC3-expressing gastric adenocarcinoma cell line FU97 at different effector:target ratios (E:T).

SENTI-301A Demonstrates Tumor Infiltration



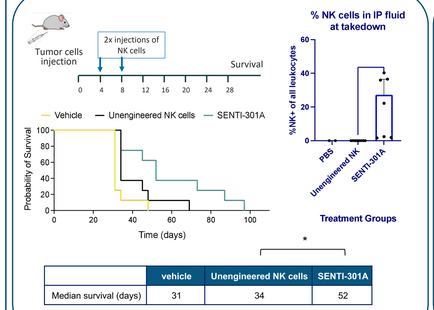






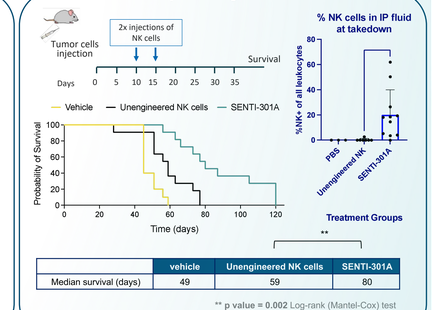
Tumors treated with SENTI-301A showed accumulation of NK cells deep within the tumor tissue.

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



	vehicle	Unengineered NK cells	SENTI-301A
Median survival (days)	31	34	52

* **p value = 0.0385** Log-rank (Mantel-Cox) test



	vehicle	Unengineered NK cells	SENTI-301A
Median survival (days)	49	59	80

** **p value = 0.002** Log-rank (Mantel-Cox) test

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

Summary

- SENTI-301A is armed with crIL-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 HCC (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.

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