Identification and Characterization of an Allogeneic iNKT-CAR Targeting BCMA

Poster 135

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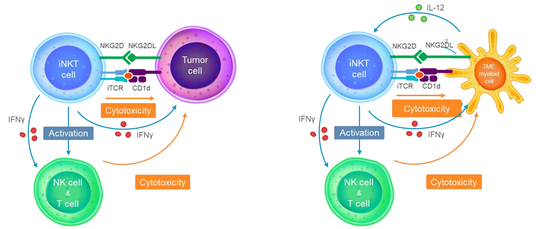
Background

iNKT cells target tumor cells and reshape the TME

iNKT cells directly target tumor cells through:
- The invariant T cell receptor (iTCR), which detects glycolipids presented by CD1d
- NKG2D, which detects stress ligands expressed on tumor cells

iNKT cells indirectly target tumors by:
- Recruiting and trans-activating Natural Killer (NK) cells and T cells
- Targeting myeloid cells in the tumor to repolarize the immunosuppressive Tumor Microenvironment (TME)

Direct Tumor Targeting | **Reshaping of the TME**



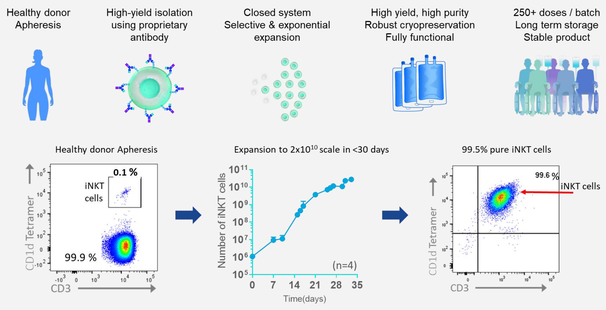
iNKT repolarize the TME via cell-to-cell contacts and soluble mediators. These interactions:
- Promote polarization of Tumor-associated macrophages (TAMs) to a M1 proinflammatory phenotype
- Deplete Tumor-associated neutrophils
- Reduce activity of myeloid-derived suppressor cells (MDSCs)
- Convert Dendritic cells (DCs) from an immature immunosuppressive state into mature DCs
- Induce an IL-12 mediated positive feedback loop which boosts the activity of other tumor-resident immune effector cells, including T cells and NK cells

iNKT cell-based allogeneic cell therapy offers increased benefits over other cell formats

		T cells	NK Cells	iNKT Cells
Potent Cancer Killing	Special population of T cells with NK properties	✗	✗	✓
	Potential for durable anti-tumor immunity	✓	✗	✓
	Orchestrate innate and adaptive immune responses and modulate suppressive myeloid compartment	✗	✗	✓
Enhanced Tolerability	No gene engineering needed for allogeneic application	✗	✓	✓
	Naturally suppresses GvHD/supports engraftment	✗	✗	✓
	Ability to multi-dose	✗	✓	✓
	Administered without lymphodepletion	✗	✗	✓
Possibly Most Scalable and Stable Off-The-Shelf Approach	Ready-made, scalable, off-the-shelf approach with proprietary process for ~99% purity and scaling beyond 10,000 doses/yr	✗	?	✓

*GVHD: Graft vs. host disease
** iNKTs express a molecule known as invariant TCR (iTCR) at their cell surface. iTCRs are highly specific to iNKTs and are not expressed by normal tissue. In the theoretical event that iNKTs trigger severe adverse events in a patient, iTCR can be targeted with a specific antibody to kill iNKTs without killing healthy immune cells. MiNK has IP rights over such an antibody

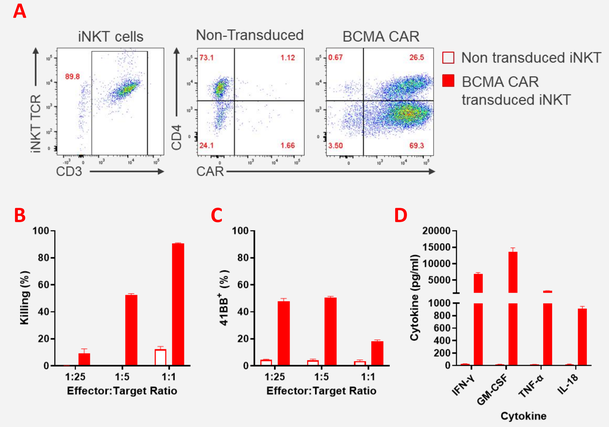
iNKT cell manufacture is scalable



- iNKT cells can be manufactured from healthy donors,
- Scaling up for in-house production of >10.000 doses / year.
- MiNK Therapeutics' iNKT cells (agent-797) are off-the-shelf, scalable, and efficiently transported and stored

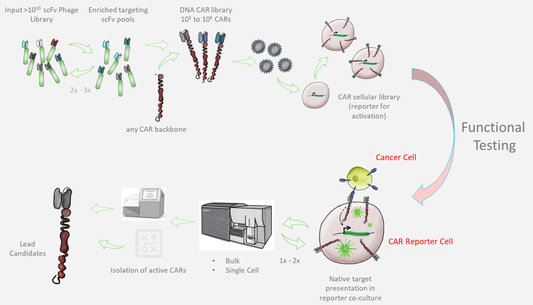
Results

MiNK Therapeutics iNKT cells can be engineered to express CAR receptors and are functional against BCMA+ tumors



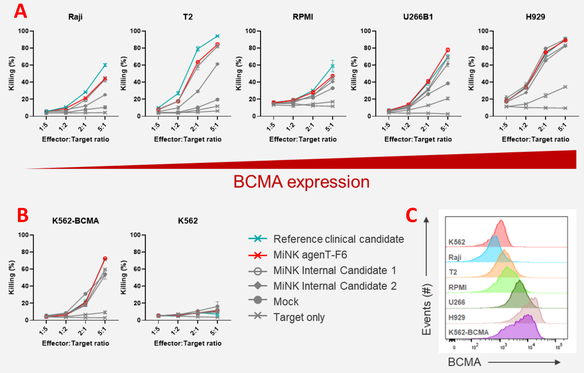
A. iNKT cells are transduced efficiently to express CAR receptors (ranging from 60 to 90%). B-D. iNKT cells expressing BCMA-CAR are co-cultured with Raji tumor expressing BCMA. B. The cytotoxic activity and C. iNKT activation (41BB$^+$ cells) are measured 24 hours post-co-culture. D. Levels of pro-inflammatory cytokines (IFN-γ, GM-CSF, TNF-α and IL-18) are measured post-co-culture

CARDISTM: Next Generation CAR Discovery



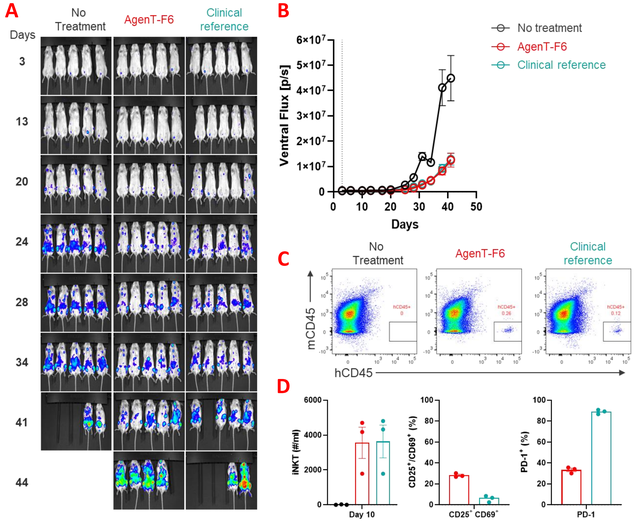
Our proprietary high throughput CARDIS^{TM} platform is a 2-stage discovery approach, where the screening of highly diverse scFV libraries via phage display is followed by functional activity screening of mammalian display libraries in CAR-T format. This high throughput approach enables rapid selection of extremely potent and safe CARs.

MiNK Therapeutics Lead candidate Has Potent Cytotoxic Activity Against Human BCMA+ cell lines *in vitro*



A. iNKT cells expressing BCMA-CAR receptor have been co-cultured with multiple tumor lines expressing different level of endogenous BCMA. The number of dead tumor cell has been recorded by flow cytometry 24 hours later. Cells have been co-incubated at various Effector:Target ratios. MiNK therapeutics lead candidate shows similar cytotoxic activity to the reference clinical candidate. B. iNKT cells expressing BCMA-CAR receptor have been co-cultured with K562 overexpressing or not BCMA. C. Levels of BCMA of the different tumor lines have been recorded by flow cytometry.

MiNK Therapeutics Lead candidate showed partial tumor control comparable to the clinical reference



A, B. iNKT cells expressing MiNK BCMA-CAR and the clinical reference have been administered to NSG-*tg* (hIL-15) mice bearing OPM-2 tumors expressing luciferase. Note the partial tumor control of treated mice. C. At day 10 post treatment iNKT cells are detected in the bone marrow at similar levels for MiNK BCMA CAR iNKT and the clinical reference. D. iNKT numbers and levels of activation indicating anti-tumor activity.

Conclusions

- MiNK Therapeutics (formerly AgenTus Therapeutics) is a clinical stage biopharmaceutical company pioneering the discovery, development, and commercialization of allogeneic, off-the-shelf, invariant natural killer T (iNKT) cell therapies to treat cancer and other immune-mediated diseases.
- MiNK Therapeutics delivered 2 INDs for lead product candidate (agenT-797) targeting heme malignancies (multiple myeloma) and COVID-19.
- MiNK Therapeutics advanced receptor discovery platforms to weaponize iNKTs allow a more rapid and efficient identification of antigen-specific and biologically potent CAR candidates, as shown with our lead BCMA clinical candidate. In addition, a stromal target-CAR-iNKT is in preclinical development.
- MiNK Therapeutics NKT cell platform, naturally lack alloreactivity that enables rapid engineering and expansion of an off-the-shelf CAR product.
- With full access to the entire Agenus' I-O antibody portfolio, weaponized iNKTs have potential as monotherapy or in combination with checkpoint antibodies to further enhance efficacy.

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