Development of an Allogeneic FAP-CAR iNKT Cell Therapy to Modulate the Immunosuppressive Stroma and Improve Anti-tumor Immunity Against Non-Small Cell Lung Carcinoma

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Background
- Lung cancer is the leading cause of cancer-related death in the United States, with non-small cell lung cancer (NSCLC) comprising a majority of cases.
- CAR T cell therapies have demonstrated unprecedented responses in hematologic malignancies. This is in part due to the ability of the CAR T cell to recognize antigen in the absence of MHC presentation and quickly respond. Moreover, recent advances have enhanced the ability of these cells for cytolytic capacity and improved persistence.
- Current limitations facing CAR-based cellular therapies in solid tumors:
  1. Insufficient infiltration of CAR-expressing cells into the tumor microenvironment (TME).
  2. Reduced cytolysis long-term against the tumor.
  3. Presence of the immunosuppressive TME which impedes endogenous anti-tumor responses and long-term tumor control.

INKT cells have the unique capacity to:
- Directly kill tumor cells by recognition of lipid tumor antigens and stress ligands.
- Reestablish the TME through IFNγ secretion, activating dendritic cells, inhibiting/eliminating immunosuppressive myeloid cells, and enhancing T cell/MiNK cell function.
- Naturally home to tissues such as lung and liver (among others).

Can the inherent functionality of INKT cells be leveraged against solid tumors?

Cancer-associated fibroblasts (CAFs):
- Contribute to tumor progression by providing physical support to tumor cells, enhancing tumor cell proliferation and angiogenesis, and promoting endogenous anti-tumor responses.
- Constitute an important part of the TME inSolid tumors such as NSCLC.

A CAR of MINK express fibroblast activation protein (FAP) and FAP-expressing CAFs play a central role in the establishment and maintenance of the immunosuppressive TME through several mechanisms.

FAP+ CAFs represent an attractive therapeutic target for solid tumors such as NSCLC. This approach is further enhanced by combining FAP-targeting with the intrinsic anti-tumor capabilities of INKT cells.

Results

Figure 1. MINK-215 immune cells exhibit antigen-specific cytotoxicity against FAP-expressing tumor cells in vitro. MINK-215 cells kill FAP-expressing tumor cells in vitro (A) or in a mouse orthotopic tumor model (B).

Figure 2. MINK-215 CAR T cells enhance iNKT cell recruitment and T cell activation in the tumor microenvironment. In vivo treatment with MINK-215 CAR T cells results in the significant infiltration of iNKT and T cells into tumor (A), resulting in improved tumor control (B).

Figure 3. MINK-215 CAR T cells increase cytokine capacity of peripheral blood T cells in vivo. MINK-215 CAR T cells are administered, and cytokine release is assessed using anti-IFNγ/FireDyex1 (IFNγ) T cells against A549 FAP-expressing tumor cells in vivo (A) or in an orthotopic tumor model (B).

Figure 4. MINK-215 CAR T cells enhance iNKT cell infiltration and T cell activation in the tumor microenvironment. In vivo treatment with MINK-215 CAR T cells results in significant infiltration of iNKT and T cells into tumor (A, B), resulting in improved tumor control (C).

Figure 5. MINK-215 CAR T cells enhance cytokine capacity of peripheral blood T cells in vivo. MINK-215 CAR T cells are administered, and cytokine release is assessed using anti-IFNγ/FireDyex1 (IFNγ) T cells against A549 FAP-expressing tumor cells in vivo (A) or in an orthotopic tumor model (B).

Figure 6. MINK-215 CAR T cells enhance iNKT cell infiltration and T cell activation in the tumor microenvironment. In vivo treatment with MINK-215 CAR T cells results in significant infiltration of iNKT and T cells into tumor (A, B), resulting in improved tumor control (C).

Figure 7. MINK-215 CAR T cells enhance cytokine capacity of peripheral blood T cells in vivo. MINK-215 CAR T cells are administered, and cytokine release is assessed using anti-IFNγ/FireDyex1 (IFNγ) T cells against A549 FAP-expressing tumor cells in vivo (A) or in an orthotopic tumor model (B).

Figure 8. MINK-215 CAR T cells enhance iNKT cell infiltration and T cell activation in the tumor microenvironment. In vivo treatment with MINK-215 CAR T cells results in significant infiltration of iNKT and T cells into tumor (A, B), resulting in improved tumor control (C).

Conclusion
- Targeting FAP is an effective therapeutic option against solid tumors, especially using INKT cells as cell therapy platform.
- Demonstrates the ability to infiltrate into tumor tissue and kill FAP-expressing tumor cells.

MINK: 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-related diseases. MINK Therapeutics has advanced 3 clinical programs for biopharmaceutical product candidates (agent-870) targeting home malignancies (multiple myeloma), solid tumors in combination with PD-1 checkpoint inhibitors, and COVID-19.

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