DEVELOPMENT OF AN ALLOGENIC FAP CAR INKT PRODUCT TO TARGET TUMOR STROMA AND MODULATE THE TUMOR MICROENVIRONMENT

Xavier Michelet*, 1Martyna Popis, 1Shannon Bui, 1Magda Niedzieska, 1Reed Masakayan, 1Efrat Altman Sharoni, 1Paul Ibbett, 1Deborah Wright, 1Barbara Kalinowska, 1Justin Keith, 1Bishnu Joshi, 1Moira Pinzan Rossi, 1Rachel Smith, 1Burcu Yigit, 1Olivier Le Tonqueze, 1Eleni Chantzoura, 1Marc Van Dijk. 1MINK Therapeutics, Lexington, MA, USA; 2Agenus, Lexington, MA, USA; 3MINK Therapeutics, Cambridge, UK

Background The emergence of antibodies targeting checkpoint modulators such as PD-1 and CTLA-4 has revolutionized solid tumor treatment and highlighted the importance of effectively engaging the immune system to drive durable responses. However, well over 50% of solid tumor patients do not respond adequately to checkpoint modulators; due to generally ascribed active immune suppression in the tumor microenvironment (TME). To overcome suppression and increase tumor control, we developed a highly selective and precisely tuned Chimeric Antigen Receptor (CAR), which targets Fibroblast Activating Protein (FAP)) expressed on both tumor cells and immune-suppressive Cancer Associated Fibroblasts (CAFs). This novel allogeneic CAR-iNKT cell (invariant natural killer T cell) product is IL-15 secreting, in addition to being FAP binding, and is intended for treatment of solid tumors. iNKT cells were selected as hosts due to their natural resistance to exhaustion, tissue homing properties, selective cytotoxicity towards M2 macrophages and stimulation of dendritic cell maturation properties which are essential for effective solid tumor directed therapies. In addition, iNKT cells have intrinsic CD1d- and NK receptor ligand targeted cytotoxicity, while not causing Graft versus Host Disease due to the presence of invariant T cell receptors.

Methods Our proprietary CARDIS™ platform combines screening of highly diverse (>10^{10}) fully human scFv libraries with library-based direct functional selection in CAR format using mammalian display. Candidates can be further optimized using affinity tuning to ensure optimal and highly selective on-target/on-tumor activity and full mouse cross-reactivity. We developed a scalable manufacturing approach to engineer and specifically expand CAR and soluble IL-15-expressing allogeneic iNKT cells.

Results Using our CARDIS™ platform, we generated a panel of fully human, potent, and highly selective anti-human FAP CARs with equivalent cross-reactivity towards mouse FAP. In xenograft mouse models our FAP-CAR-IL-15 iNKT cells effectively control FAP-expressing tumors, as well as FAP negative tumors with immune-suppressive stroma mediated by FAP+ CAFs, while soluble IL-15 prolongs persistence in immunocompromised mice. In addition, we show that FAP-CAR-IL-15 iNKT cells mediate the infiltration of tumor-specific T-cells and enhance their anti-tumor activity.

Conclusions We have used our CARDIS™ and iNKT platforms to develop a CAR-iNKT therapy effectively and selectively targeting FAP positive tumor cells and suppressive CAF subsets in the TME. We believe that combining the activity of our FAP-CAR with the potent natural activity of iNKT cells will enable a level of tumor control and immune engagement to solid tumor patients beyond currently available treatments.