convertibleCAR™-T Cells Provide Dose Control of Activity and Targeting Flexibility

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Xyphos’ solution to CAR limitations

Advanced Cellular Control through Engineered Ligands

Engineering a privileged partnering

In vitro characterization

Targeted delivery of cytokines

In vivo Raji B-cell models in NSG mice

ACCEL summary and opportunities

The excellent oncolytic efficacy of pioneer CAR-T therapies is hampered by lack of dose-dependent control of activity, fixed targeting, and complex manufacturing. To address these limitations, Xyphos has developed a chimeric antigen receptor platform in which the extracellular domain of human NKG2D has been rendered functionally inert (iNKG2D) and to which an engineered, orthogonal human ligand has been developed. convertibleCAR™-T cells, expressing iNKG2D fused to intracellular co-stimulatory domains, are inactive until they are targeted to an antigen by a bispecific comprised of the orthogonal ligand and an antigen recognition domain (MicAbody™). Upon engagement the cells are activated, effectively lyse tumor targets, and can be multiplexed to engage multiple antigens simultaneously. We have demonstrated the ability of convertibleCAR™-T cells to control both disseminated and subcutaneous tumors in a MicAbody-dependent manner. Furthermore, the presence of an invariant universal CAR receptor than can be selectively engaged with a privileged ligand presents opportunities for targeted delivery of molecules to iNKG2D-CAR expressing cells. For example, tethering of the orthogonal ligand to a mutant form of IL2 – which on its own has very little bioactivity – can drive the selective in vitro and in vivo expansion of convertibleCAR™-T cells.

This highly adaptable system greatly potentiates adoptive cell therapies enabling:
- The expression of a universal iNKG2D receptor in any therapeutic immune cell type
- The generation of a single convertibleCAR™-T cell for all indications in a single patient
- The provision of an addressable, universal receptor that is compatible with an allogeneic cell providing a single convertibleCAR™-T for all patients and indications
- Targeted delivery of immunomodulatory molecules to iNKG2D-CAR expressing cells to promote selective expansion both ex vivo during manufacturing (to enrich cells and possibly direct their phenotype) and in situ in the patient (to drive in vivo expansion, encourage persistence, or recall them as needed)
- Multiplex capabilities to not only pursue multiple tumor targets simultaneously but to also target suppressive cells in the tumor microenvironment