*convertible*CAR™-T Cells Provide Dose Control of Activity and Targeting Flexibility

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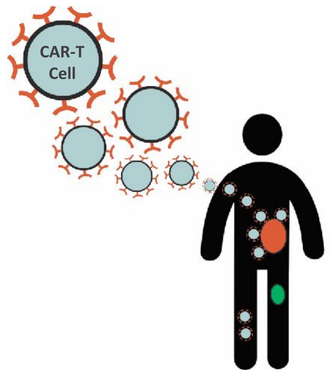
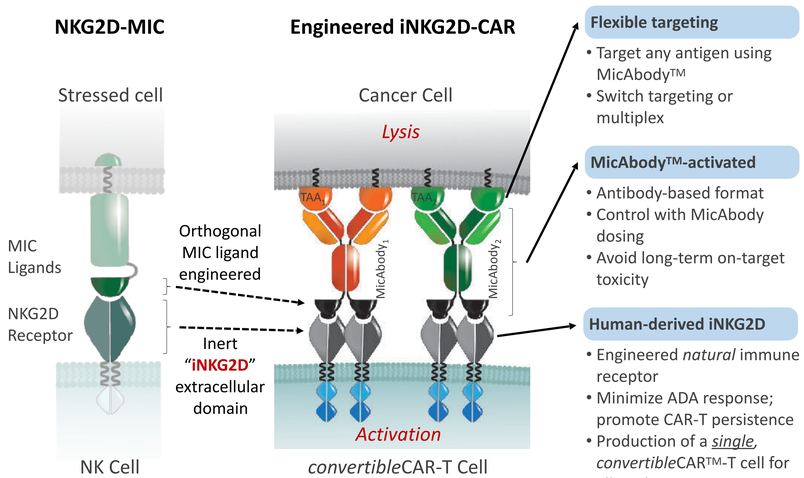
Xyphos' solution to CAR limitations



Limitation	Solution
Single purpose, non-human scFv receptor – one target, one function	Multi-functional receptor – facile retargeting of cytotoxic function; selective delivery of agents to CAR cell
No dose control	Dose-dependent control of function
No mechanism to address antigen loss	Multiplex targeting

*A*dvanced *C*ellular *C*ontrol through *E*ngineered *L*igands

Engineering a privileged partnering

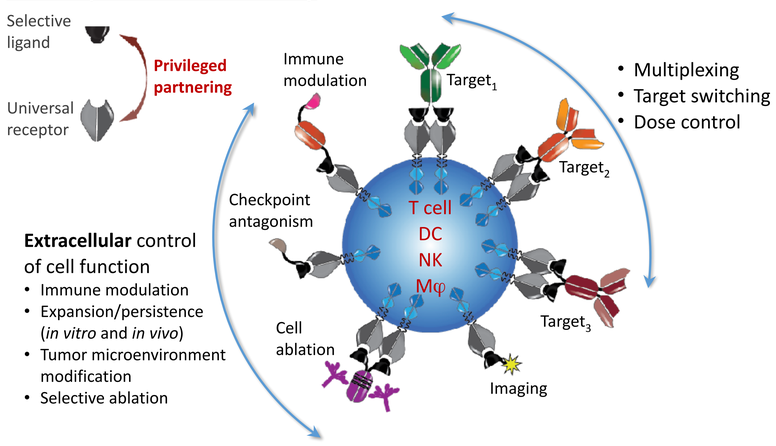


Flexible targeting
- Target any antigen using MicAbody™
- Switch targeting or multiplex

MicAbody™-activated
- Antibody-based format
- Control with MicAbody dosing
- Avoid long-term on-target toxicity

Human-derived iNKG2D
- Engineered *natural* immune receptor
- Minimize ADA response; promote CAR-T persistence
- Production of a *single*, *convertible*CAR™-T cell for all applications in a patient

ACCEL platform versatility

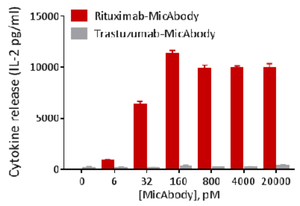


Extracellular control of cell function
- Immune modulation
- Expansion/persistence (*in vitro* and *in vivo*)
- Tumor microenvironment modification
- Selective ablation

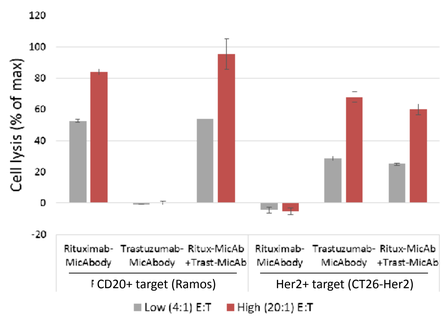
- Multiplexing
- Target switching
- Dose control

In vitro characterization

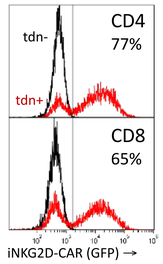
I. Precise control of activation
*convertible*CAR-T cells : CD20+ target cells



II. Multiplex targeting
Pre-armed *convertible*CAR-T cells : CD20+ or Her2+ target cells

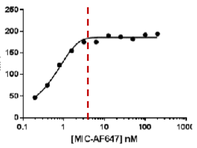


III. Efficient expression

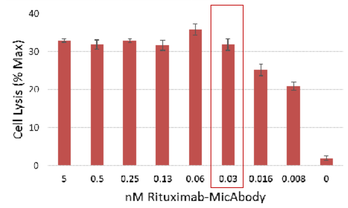


IV. Abundant iNKG2D-CAR on surface
Pre-armed at different MicAbody concentrations

Saturation at 5 nM

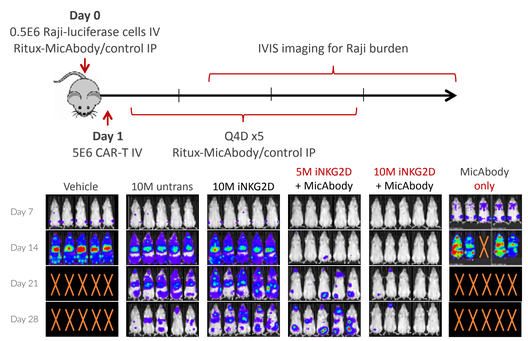


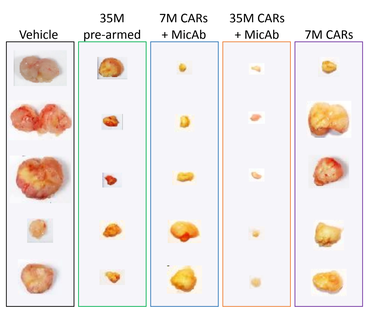
Maximum cytolysis at 30 pM



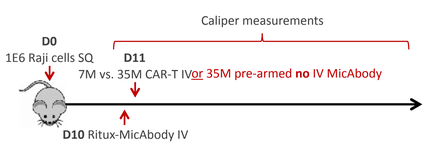
In vivo Raji B-cell models in NSG mice

Disseminated model:
- *convertible*CAR-T cell or MicAbody alone inactive – both required for tumor control
- Greater *convertible*CAR-T cell infusion leads to greater efficacy

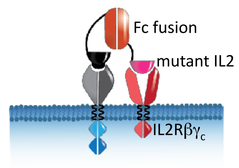




Subcutaneous lymphoma model:
- 35M *convertible*CAR-T cells with IV Ritux-MicAbody effectively controls tumor
- 35M pre-armed also efficacious and may benefit from additional MicAbody dosing



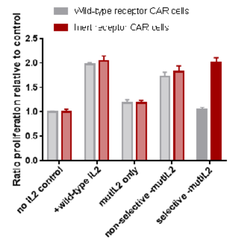
Targeted delivery of cytokines



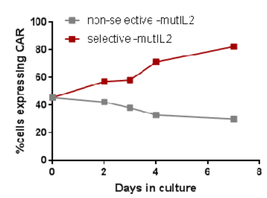
*convertible*CAR-T cell

I. Targeted delivery of IL2 to iNKG2D-CAR expressing cells

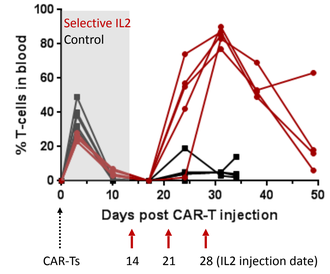
Selective *in vitro* proliferation

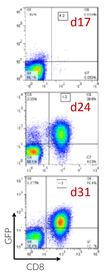


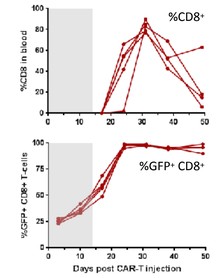
Targeted *in vitro* expansion



II. Selective *in vivo* expansion of *convertible*CAR-T cells







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. *convertible*CAR™-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 *convertible*CAR-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 *convertible*CAR 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 *convertible*CAR-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 *convertible*CAR-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

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