_convertible_CAR-T cells provide _in vivo_ dose control of activity with sequential and multiplex targeting

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The excellent oncolytic efficacy of conventional CAR-T cells is burdened by lack of dose-dependent control of activity, fixed targeting, and complex manufacturing. We have designed and pre-clinically evaluated *convertible*CAR-T cells that possess an inert NKG2D receptor that binds *exclusively* to an engineered orthogonal human ligand fused to an antibody-based adapter targeting tumor antigens. The *convertible*CAR-T cells are activated only when an immunologic synapse is formed by the specific adapter, a "MicAbody", bridging the targeted tumor cell and its privileged partner, i.e. the otherwise inert NKG2D-bearing CAR-T cell. Studies in NSG mice have demonstrated MicAbody dose-dependent killing of disseminated and solid tumor malignancies. Targeting can be modified by switching or adding another specific MicAbody without modifying the *convertible*CAR-T cell, and hence, one autologous *convertible*CAR-cell suffices for all targets in the donor patient or one allogeneic *convertible*CAR-cell will suffice for all patients, all targets. The privileged partnering between the inert NKG2D receptor and the orthogonal ligand also enables the exclusive activation or inhibition of the *convertible*CAR-T cell. For example, a mutant IL-2 or mutant IL-15 protein that cannot bind the high affinity subunit of its respective receptor, when fused to the unique ligand, promotes proliferation exclusively of CAR-T cells expressing the otherwise inert NKG2D receptor. Overall, these types of precision controls and flexibility could improve substantially the safety, efficacy and manufacturing of CAR-T cells and expand the applications of potent CAR-T cells to managing diseases in patients with lower risk tolerance than those with life-threatening malignancies.