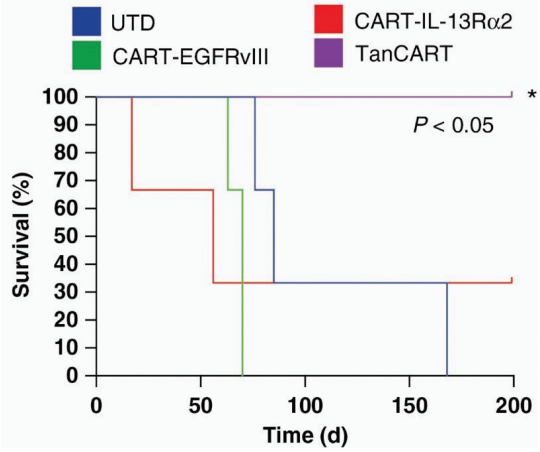

Fig. 1: Kaplan-Meier survival analysis demonstrating survival of TanCART-treated GBM patient-derived xenograft mice compared to untransduced and monospecific CAR-T cell groups, CART-EGFRvIII and CART-IL-13R2. Statistical significance

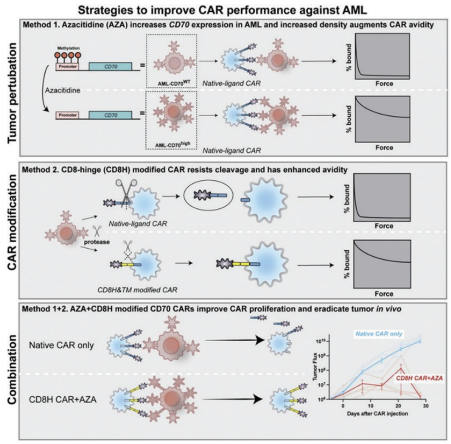

Fig. 2: Strategies to overcome CAR performance against AML

Novel CAR-T cells engineered to overcome obstacles observed in the clinic

Marcela Maus, MD, PhD
Director, Cellular Immunotherapy, MGH; Associate Professor, HMS
mvmaus@mgh.harvard.edu

Using the immune system as a cancer treatment, T cells can specifically kill target cells they recognize and can persist in the body for many years, presenting the potential for long-term protection. CAR-T therapies comprise T cells that are re-engineered to produce chimeric antigen receptors (CARs), which help the T cells target specific antigens on cancer cells. CAR-T therapies have shown great promise for B cell malignancies (e.g., leukemia and lymphoma) in the clinical setting, but barriers remain, and their successful application to other cancers likely requires refinements in the molecular and clinical technologies.

The Maus laboratory and the MGH Cellular Immunotherapy Program use genetic engineering to overcome obstacles observed in the clinic, creating a pipeline of next-generation CAR-T therapies. We are developing novel receptors targeting multiple antigens on tumor cells to better attack heterogenous tumor cell populations, prevent antigen-negative relapse, and decrease effects on healthy cells. In a recent study, we developed a tandem CAR-T (TanCART) cell that simultaneously targets both EGFRvIII and IL-13Rα2, two tumor antigens that are abundant on glioblastoma (GBM) cells but absent from normal brain tissues. In patient-derived heterogeneous GBM xenografts, TanCART achieved long-term, complete, and durable responses while monospecific CAR-T cells did not (Fig. 1).

Leveraging studies that shed light on mechanisms of CAR-T resistance in the inhibitory tumor microenvironment, we aim to re-engineer CAR-T therapies with enhanced resilience. For example, acute myeloid leukemia (AML) resists CD27-ligand-based CAR-T therapy by secreting an enzyme that cleaves the CD27 ligand responsible for targeting the CD70 expressed on AML cells; this cleavage renders CAR-T cells inactive. To overcome this barrier, we modified the most potent previously described CAR targeting CD70 to stabilize its binding to CD70, leading to more potent in vivo activity (Fig. 2).

We envision next-generation CAR-T cells working synergistically with other drugs to enhance their efficacy. For example, we combined the modified CD70-targeted CAR-T therapy described above, which was only modestly effective against AML in animal models, with an FDA-approved AML drug, azacytidine, that increases the density of the CD70 antigen on cancer cell surfaces. This combination exhibited significantly greater efficacy than the CAR-T alone (Fig. 2). In the future, we aim to discover and test additional drug–CAR-T combination therapies with improved safety and efficacy.