# Abstract

Chimeric antigen receptors (CARs) are synthetic receptors that redirect and reprogram T cells to mediate tumor rejection. The most successful CARs used to date are those targeting CD19, which offer the prospect of complete remissions in patients with chemorefractory/ relapsed B cell malignancies, especially acute lymphoblastic leukemia (ALL). To broaden the applicability of CAR therapy, we are investigating novel CAR designs, novel CAR targets and alternative T cell engineering modalities. To enhance the intrinsic (function, persistence) and extrinsic (action on the tumor microenvironment) potency of adoptively transferred T cells, we are studying the impact of constitutive 4-1BBL expression on therapeutic efficacy.

To identify new CAR targets, we rely on integrated proteomics and transcriptomics to address the challenges of tumor heterogeneity and on-target/off-tumor toxicity based on combinatorial targeting. Using CRISPR/Cas9, we found that directing a CAR to the T cell receptor alpha chain (TRAC) locus not only results in uniform CAR expression in human peripheral blood T cells, but enhances T cell potency by attenuating T cell exhaustion, vastly outperforming conventionally transduced CAR T cells. Using gene editing, we are further inquiring whether allogeneic T cell sources, including induced pluripotent stem cell-derived T cells, can be harnessed to produce therapeutic T cells on a large scale.