

Cell Therapies

175 CAR-T ENGAGER PROTEINS OPTIMIZE ANTI-CD19 CAR-T CELL THERAPIES FOR LYMPHOMA

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Background B cell lymphoma therapy has been transformed by CD19-targeting cellular therapeutics that induce high clinical response rates and impressive remissions in relapsed and refractory patients. However, approximately half of all patients who respond to CD19-directed cell therapy relapse, the majority within six months. One characteristic of relapse is loss or reduction of CD19 expression on malignant B cells. We designed a novel biologic, a CAR T Engager, that binds CD20 and displays the CD19 extracellular domain. This approach increases the apparent CD19 antigen density on CD19-positive/CD20-positive lymphoma cells, and prevents antigen-loss induced relapse, as CD19 bound to CD20 remains present on the cell surface. We demonstrate that this novel therapeutic prevents and reverses lymphoma relapse *in vitro* and prevents CD19-negative lymphoma growth and relapse *in vivo*.

Methods The CTE biologic has three functional domains: a modified CD19 ECD, an anti-CD20 binding domain and an anti-albumin binding domain. The protein, termed a CAR-19-CD20 T cell Engager (CTE-19.20), binds to CD20 and displays the CD19 ECD and increases CD19 antigen density on target lymphoma cells regardless of their level of CD19 expression.

Results CTE-19.20 proteins potently triggered CD19-negative lymphoma cell death in the presence of CAR-19 T cells *in vitro* and prevented antigen-loss relapse in an *in vitro* model of lymphoma escape from CAR-19 therapy. Using *in vivo* modeling we show that CTE-19.20 protein given alongside CAR-19 T cells prevented CD19-negative lymphoma expansion, eliminated disease, and significantly impacted survival. CTE-19.20 was readily expressed and secreted by transfected mammalian cells, was efficiently purified and demonstrated favorable biophysical properties.

Conclusions Patient relapse from CAR-19 therapy occurs rapidly, often within the first months following therapy. The kinetics of relapse offer the potential to intervene using CTE-19.20 protein, using several different clinical designs. In the first instance we are developing this molecule with the goal of treating patients who have already received a CAR-19 therapy, by evaluating their clinical response through the first few months post CAR infusion. Diverse biomarkers can be used to track response and risk of relapse. PET imaging and ctDNA analyses have emerged as sensitive means of tracking lymphoma and leukemia regression. This is an optimal and straightforward approach to productive and sustained activation of CAR-19 T cells, using a potent CD19-anti-CD20 bridging protein with an extended half-life.

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