CAR therapy beyond the CD19 paradigm

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T cell engineering provides a means to rapidly generate therapeutic T cells of any specificity. In oncology, its purpose is to generate potent, tumor-specific T cells that overcome immune barriers in the tumor microenvironment and eradicate tumor cells. T cell engineering is predicated on methods to safely and effectively genetically modify human T lymphocytes, and the transduction of suitable receptors to redirect T cell specificity and function. Chimeric antigen receptors (CARs) are synthetic receptors that mediate antigen recognition, T cell activation, and, in the case of second generation CARs, costimulation that is intended to augment the functionality and persistence of engineered T cells. We demonstrated over a decade ago that human T cells engineered with a CAR specific for CD19 eradicated B cell malignancies in mice. In multiple phase I clinical trials, CD19-specific, second generation CARs have now demonstrated remarkable activity against a range of B cell malignancies, particularly acute lymphoblastic leukemia (ALL). Second generation CARs that encode either CD28 or 4-1BB cytoplasmic domains have both yielded consistent responses in patients with chemorefractory ALL, but they differ in their kinetics. CD28-based CARs (28z) appear to be more potent while 4-1BB-based CARs (BBz) further extend T cell persistence. They also differ in their susceptibility to PD1/PD-L1 checkpoint blockade. We have investigated novel engineering modalities in order to capture the best features of these two CARs, including new CAR designs and CRISP/Cas9-mediated CAR delivery. We found that T cells co-expressing the 19-28z CAR and 4-1BBL are especially potent, which is in part attributed to IRF7-dependent activation of the T cell IFN-I response pathway. Thus, 28z CAR T cells that co-express 4-1BBL are not only cytotoxic agents but can also serve to recruit and redress the endogenous immune response against the tumor, diversifying its antigen diversity beyond single CAR target, and stimulate immunity that outlives the CAR T cells themselves. These properties are likely to be useful to advance CAR therapy to tackle a broad range of cancers, including solid tumors.