A Wakeup Call for Exhausted CAR T Cells – Targeted Delivery of an Immune Stimulant

Significance: Chimeric antigen receptor (CAR) T cell treatment has shown promising results in suppressing hematopoietic cancers. However, its application to treat solid tumors is limited by CAR T cell exhaustion, triggered by the chronic exposure to tumor antigens. Exhausted CAR T cells regain their ability to lyse cancer cells upon treatment with an immune stimulant such as TLR7-3. However, these nontargeted agents are too toxic for systemic administration due to global activation of the immune system. To avoid this toxicity, TLR7-3 was fused to fluorescein via a self-immolative linker to enable selective targeting to anti-fluorescein CAR T cells.

Comment: Fluorescein-TLR7-3 was prepared from primary alcohol TLR7-3 by transesterification followed by disulfide bond formation. The conjugate is internalized by anti-fluorescein CAR T cells – universal CAR T cells that recognize cancer cells via bispecific adaptor molecules – via CAR-mediated endocytosis. TLR7-3 is released in the reductive environment of the endosome upon reductive cleavage of the disulfide bond in the presence of glutathione. In a solid KB tumor mouse xenograft, fluorescein-TLR7-3 reversed the exhausted CAR T cell phenotype, leading to a steady decrease in tumor size.