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Design, Synthesis, and Targeted Delivery of an Immune Stimulant that Selectively Reactivates Exhausted CAR T Cells
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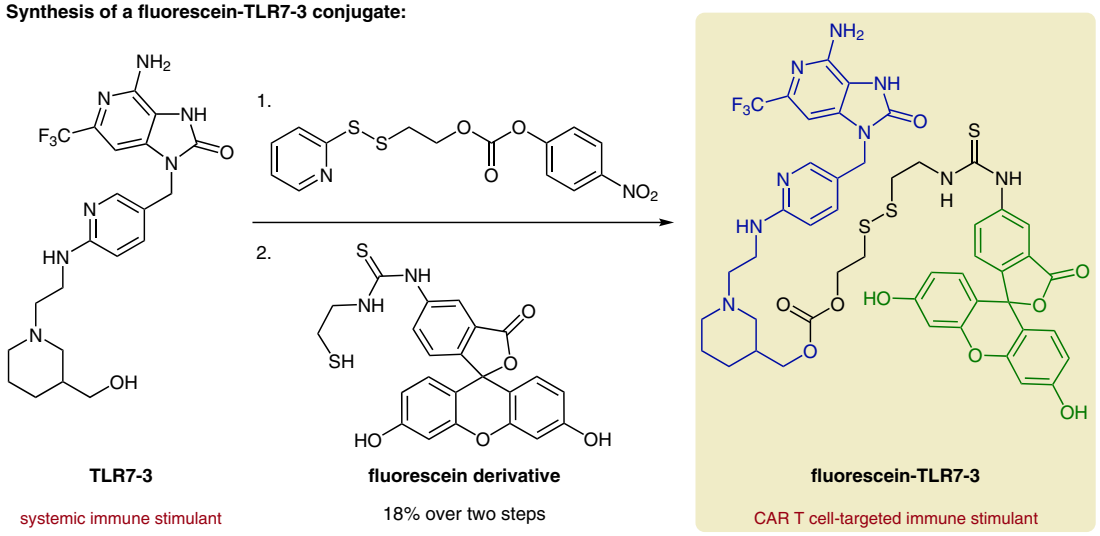
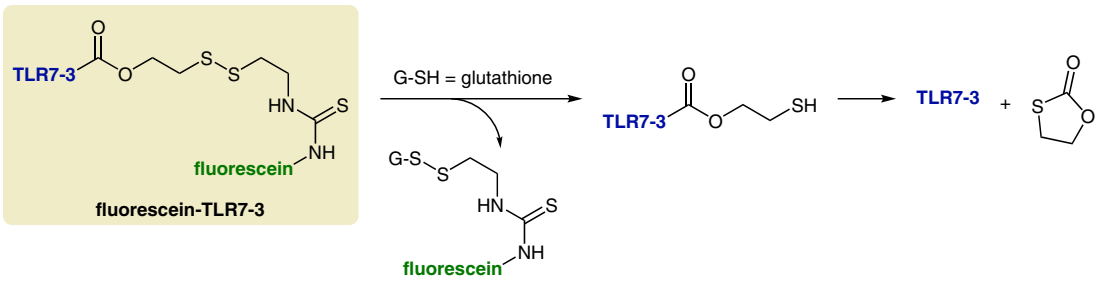
A Wakeup Call for Exhausted CAR T Cells – Targeted Delivery of an Immune Stimulant

Synthesis of a fluorescein-TLR7-3 conjugate:



Release of TLR7-3 inside of an anti-fluorescein CAR T cell endosome:



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.

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Synfact of the Month