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CCR5-Engineered γδ CAR-T Cells as a Platform for HIV-Associated B-Cell Lymphoma Therapy

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Abstract:

Mune-based cell therapy has emerged as a powerful strategy against cancer, yet autologous CAR-T production remains slow, expensive and tailored to each individual. γδ T cells combine innate cytotoxic functions with natural enrichment in tumor types linked to better outcomes, making them ideal candidates for off-the-shelf CAR-T applications. Development of γδ CAR-T has been limited by low starting numbers, resistance to genetic modification and advanced differentiation following expansion, all of which reduce clinical feasibility. To overcome these barriers, we established an optimized in vitro activation and expansion protocol for peripheral γδ T cells that enables efficient gene editing and stable CAR insertion. Stimulation with engineered antigen-presenting-cell mimics preserves a less differentiated phenotype while supporting robust effector function. By integrating a clinically validated CAR into the CCR5 locus, the modified γδ T cells gain protection from HIV-mediated depletion, creating a novel option for HIV-associated B-cell malignancies. These γδ CAR-T products exhibit potent tumor-killing activity in vitro and drive regression of established tumors in vivo. Together, these results offer preclinical proof-of-concept for scalable, allogeneic γδ CAR-T therapies in both oncology and infectious-disease settings.