Advancing innovative technologies for the engineering and preclinical testing of PDGFRA-targeting Chimeric Antigen Receptor (CAR)-T cells in DMGs

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Diffuse midline gliomas (DMGs) are among the deadliest pediatric brain tumors, with poor prognosis and limited treatment options. CAR-T cell therapy has shown promise, but existing approaches, such as GD2-CAR-T, face limitations due to antigen heterogeneity and off-target effects.[1] Here, we present a lipid nanoparticle (LNP)-based platform for *in vivo* generation of PDGFRA-CAR T cells as an alternative strategy with improved specificity for DMG treatment. PDGFRA is strongly expressed in DMG and plays a key role in tumor initiation and progression, making it a rational target for CAR-T therapy.[2] To achieve this, we encapsulate a synthetic PDGFRA mRNA within LNPs to reprogram host T cells. A key focus of this approach is ensuring stable and uniform antibody conjugation onto LNPs, as structural dispersity can lead to aggregation and nonspecific organ uptake. Using azide-DBCO click chemistry, we optimize the conjugation process to minimize size variation while preserving mRNA integrity. Our strategy avoids harsh conditions such as extreme pH shifts or high temperatures, maintaining LNP stability and ensuring efficient transfection. This study advances targeted CAR-T therapy by integrating optimized antigen selection with controlled nanoparticle engineering, improving translational potential for pediatric DMG treatment.

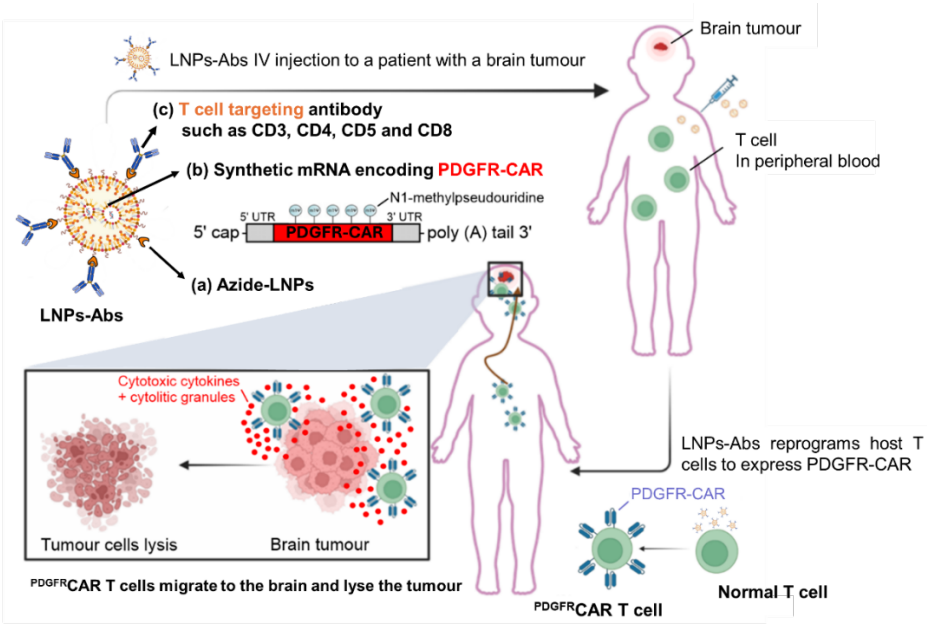

Figure 1: Schematic illustration showing LNPs-antibody therapeutics and predicted mode of action.

References:
[1] S. A. Richman *et al. Cancer Immunol Res* **2018**, *6*, 36-46.
[2] C. Hoeman, C. Shen, O. J. Becher. *Front Oncol* **2018**,8, 191.