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NICHE-CAR-T: NR2F6 IMMUNE CHECKPOINT HARNESSING TO ENHANCE CAR-T EFFICACY

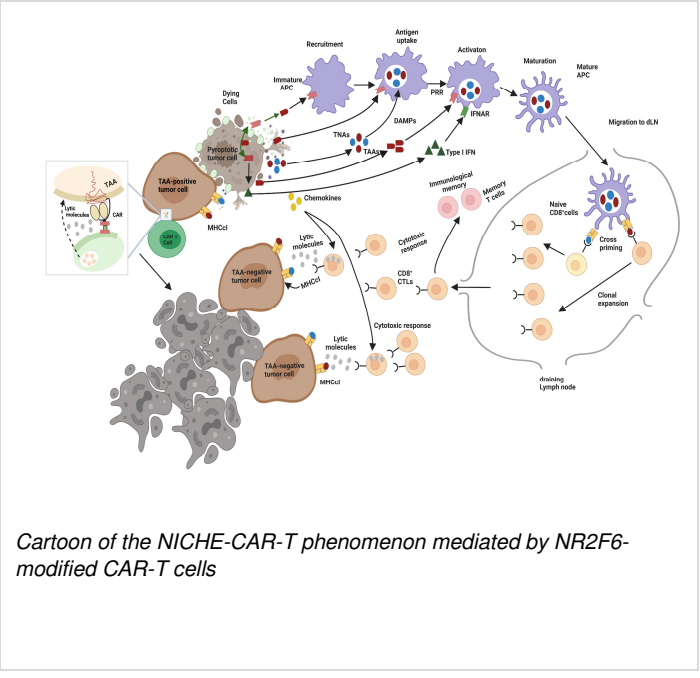
Keywords: CAR-T, NR2F6 silencing, solid tumor therapy, cross-priming, epitope spreading

INVENTION NOVELTY

While CAR-T therapies have revolutionized treatment for hematological cancers, their efficacy in solid tumors remains limited due to both an immunosuppressive tumor immune microenvironment (TIME) leading to terminal T cell dysfunction and an inherent tumor antigen heterogeneity. These current limitations of CAR-T hamper durable responses and limit accessibility for patients with advanced solid tumors like non-small cell lung cancer (NSCLC), which remains a leading cause of cancer-related deaths. It was surprisingly found that inhibition of NR2F6 (Nuclear Receptor Subfamily 2 Group F Member 6) activity in CAR-engineered T cells showed reduced sensitivity to exhaustion resulting in efficient killing of tumor cells.

VALUE PROPOSITION

For the first time, the strategy of selectively targeting NR2F6 in CAR-T cells uniquely enables durable, antigen-agnostic tumor clearance while reducing vein-to-vein time to a single day using a non-genomic, GMP-compatible protocol. This enhanced patient accessibility supports clinical testing of Nr2f6-modified CAR-T cells for the treatment of antigenically heterogeneous tumors such as NSCLC.



Cartoon of the NICHE-CAR-T phenomenon mediated by NR2F6-modified CAR-T cells

TECHNOLOGY DESCRIPTION

The NICHE-CAR-T platform introduces a novel approach by transiently engineering CAR-T cells to inhibit the NR2F6 immune checkpoint, overcoming key resistance mechanisms in solid tumors. The combination of mRNA-mediated CAR expression and siRNA-mediated NR2F6 silencing prevents T cell exhaustion and induces a localized immunological cell death (ICD) process within the TIME resulting in effective tumor antigen cross-priming (epitope spreading). Such a process can promote an anti-tumor immune memory response by the endogenous host immune system that is no longer limited to the tumor surface antigen targeted by the transgenic CAR receptor.

COMMERCIAL OPPORTUNITY

NICHE-CAR-T addresses the €8.2 billion NSCLC market by providing a cost-effective, scalable and curative CAR-T therapy for solid tumors. The one-day manufacturing process enables decentralized, in-hospital production, significantly reducing costs and expanding patient access. The technology is open for collaborative co-development or licensing.

DEVELOPMENT STATUS

Preclinical studies demonstrate complete tumor remission and ICD-induced epitope spreading in a preclinical mouse model of solid tumors, achieving TRL 3-4. The project aims to validate GMP manufacturing and initiate CTA/IND submissions for Phase I trials by 2027.

PATENT SITUATION

A PCT application has been filed in September 2024 with priority of Sept. 14, 2023.

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