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Rapid Programmable CAR-T Cell Engineering Platform Using Antigen-Targeted Lentiviral Delivery for Same-Day In Vivo and Ex Vivo T Cell Modification

Stanford scientists have developed the Programmable Antigen-Mediated Cellular Knock-in of T cell (PACK-IT) platform that enables rapid CAR-T cell engineering in hours rather than weeks. PACK-IT uses engineered lentiviral particles with T cell-targeting antibodies to deliver CAR genes directly to T cells in vivo or ex vivo without requiring traditional T cell activation and expansion steps, potentially preserving greater T cell potency for therapeutic applications.

Current CAR-T cell manufacturing requires 1-3 weeks of intensive ex vivo manipulation including T cell purification, activation with antibody-coated beads, lentiviral transduction, and expansion. This lengthy process is costly, labor-intensive, and may diminish T cell potency by depleting their proliferative and functional capacity before therapeutic infusion. The extensive ex vivo culture period forces T cells to undergo multiple rounds of division and activation that can shift them toward exhausted or differentiated states, potentially reducing their effectiveness once reinfused into patients. While newer rapid manufacturing platforms have reduced ex vivo culture time to under 2 days, they still require T cell activation steps and cannot enable direct in vivo CAR-T generation.

PACK-IT employs engineered lentiviral particles with modified envelope proteins that enable targeted delivery of genetic cargo to specific cell types. These particles are equipped with T cell-targeting antibodies that direct viral entry specifically to T cells through binding to T cell surface receptors. This targeted approach enables CAR

gene delivery directly to T cells in vivo through systemic administration or ex vivo with ultra-short exposure times of less than 2 hours, eliminating the need for traditional activation and expansion steps. Consequently, PACK-IT has the potential to drastically reduce CAR-T manufacturing costs and timelines while preserving T cell potency for enhanced therapeutic efficacy.

Stage of Development
Preclinical: in vivo
Continued research: Translating the platform to mouse models for toxicity assessment, evaluating in vivo targeting with different binding molecules, testing various T cell enhancement strategies, delivering alternative genetic cargos including TCRs, cytokines, and transcription factors, targeting additional cellular components within the tumor microenvironment, and optimizing ex vivo delivery protocols with ultra-short exposure times.

Applications

- Rapid CAR-T cell manufacturing with reduced timeline and costs
- In vivo CAR-T cell engineering through direct systemic delivery
- Enhanced ex vivo CAR-T production with ultra-short exposure times
- Manufacturing CAR-T cells with various functional phenotypes
- Delivery of alternative genetic cargos to T cells including TCRs, cytokines, and transcription factors
- Targeted genetic modification of tumor microenvironment components, including tumor cells

Advantages

- Eliminates need for costly T cell activation reagents and antibody-coated beads
- Reduces manufacturing timeline from weeks to hours
- Preserves T cell potency by avoiding extensive ex vivo culture and activation
- Enables direct in vivo CAR-T generation without ex vivo processing
- Modular platform accommodating diverse targeting strategies and genetic cargos
- Potential for simultaneous targeting of multiple cellular components in the tumor microenvironment

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