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Composition and Methods for Selective Expansion of CAR-T Cells Made in vivo or ex-vivo with the IL9R

Stanford scientists have developed a method to selectively expand CAR-T cells by co-delivering IL9R with CAR genes using a novel platform that enables rapid CAR-T cell engineering through targeted lentiviral delivery. This approach promotes selective expansion of engineered T cells through IL9 cytokine treatment, eliminating the need for traditional lymphodepletion procedures and achieving enhanced anti-tumor efficacy.

Current CAR-T cell manufacturing processes require lymphodepletion prior to infusion to promote CAR-T cell engraftment and expansion in patients. While lymphodepletion creates a favorable microenvironment for CAR-T cell activation and proliferation, it puts patients at significant risk of infections and cytopenia due to the depletion of normal immune cells. Additionally, emerging rapid CAR-T manufacturing platforms enable in vivo engineering but face significant challenges. These approaches cannot utilize traditional lymphodepletion methods, as this would eliminate the T cells targeted for engineering, and the rapid in vivo modification process produces relatively low numbers of CAR-positive T cells compared to conventional manufacturing. Therefore, a method to selectively expand engineered T cells while promoting optimal anti-tumor signaling is essential for successful in-vivo CAR-T cell therapy.

Co-delivering IL9R with CAR genes enables selective expansion of engineered T cells through treatment with IL9, a naturally orthogonal cytokine that specifically targets cells expressing the co-delivered receptor. This approach promotes optimal JAK/STAT signaling for enhanced T cell proliferation and anti-tumor function without affecting non-engineered cells. In preclinical studies, CAR-T cells co-delivered with IL9R demonstrated significantly enhanced expansion and anti-tumor potency compared

to CAR alone in leukemia models. Consequently, IL9R co-delivery has the potential to overcome the key limitations of rapid in vivo CAR-T manufacturing by enabling selective expansion without requiring lymphodepletion, offering a safer and more effective approach to CAR-T cell therapy.

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, and optimizing ex vivo delivery protocols with ultra-short exposure times.

Applications

- Selective expansion of CAR-T cells in vivo without lymphodepletion
- Enhanced ex vivo CAR-T manufacturing with reduced timelines
- Treatment of hematologic malignancies and solid tumors requiring high CAR-T cell numbers or treatment of autoimmune diseases responsive to CAR-T cells
- Development of safer CAR-T therapies with reduced infection risk

Advantages

- Eliminates need for dangerous lymphodepletion procedures
- Enables selective expansion of only engineered T cells through orthogonal cytokine signaling
- Significantly increases CAR-T cell numbers compared to rapid manufacturing alone
- Promotes optimal anti-tumor JAK/STAT signaling profile
- Compatible with both in vivo and ex vivo manufacturing approaches
- Reduces patient risk of infections and cytopenia

Publications

- Hua Jiang, Sam Limsuwannarot, Kayla R. Kulhanek, Aastha Pal, Lea W. Rysavy, Leon Su, Ossama Labiad, Stefano Testa, Heather Ogana, Deepa Waghray, Pingdong Tao, Kevin M. Jude, Christopher S. Seet, Gay M. Crooks, Everett J.

Moding, K. Christopher Garcia, Anusha Kalbasi (2025). IL-9 as a naturally orthogonal cytokine with optimal JAK/STAT signaling for engineered T cell therapy. bioRxiv 2025.01.15.633105.

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