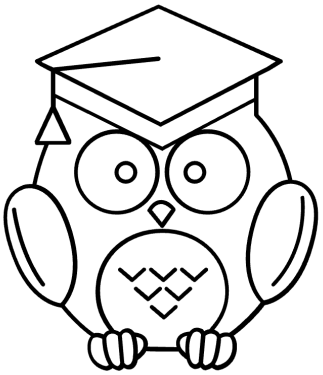

TLDR

Advancements and Challenges in Developing In Vivo CAR T Cell Therapies for Cancer Treatment

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The Big Idea:

CAR T cell therapy offers a promising alternative to conventional treatments like chemotherapy by genetically engineering a patient's T cells to recognize and attack cancer. Although the therapy is still largely in its preclinical stage with many challenges to iron out, it has great potential to revolutionize cancer treatment as we know it today.

Key Terms and Concepts:

T cell: A type of white blood cell that is responsible for germs, disease, and cancer in your immune system.

In vivo: Processes that happen inside a living organism.

Ex vivo: Processes done outside of a living body, typically a lab.

Chimeric Antigen Receptors (CARs): Specially-engineered proteins that help T cells recognize cancer.

Leukapheresis: A procedure to collect white blood cells from a patient using a specialized medical machine, called the *apheresis machine*.

Culture: The process of growing cells in a controlled environment.

Infusion: Delivering substances into the body, usually by IV (intravenous) therapy.

Viral vectors: Modified viruses that are made harmless and used to deliver genetic material into cells.

Nanocarriers: The umbrella term defining tiny particles that are used as a delivery vehicle to transport substances into cells.

T cell-specific ligands: Molecules that help viral vectors target and enter T cells.

Off-target toxicity: Unwanted side effects caused when a treatment accidentally harms healthy cells.

Immunogenicity: A substance's ability to trigger an adverse immune response.

Models: A variable, can be living, used to study and predict how something works in real life. For example, mice models refer to mice used in an experiment.

Key Findings:

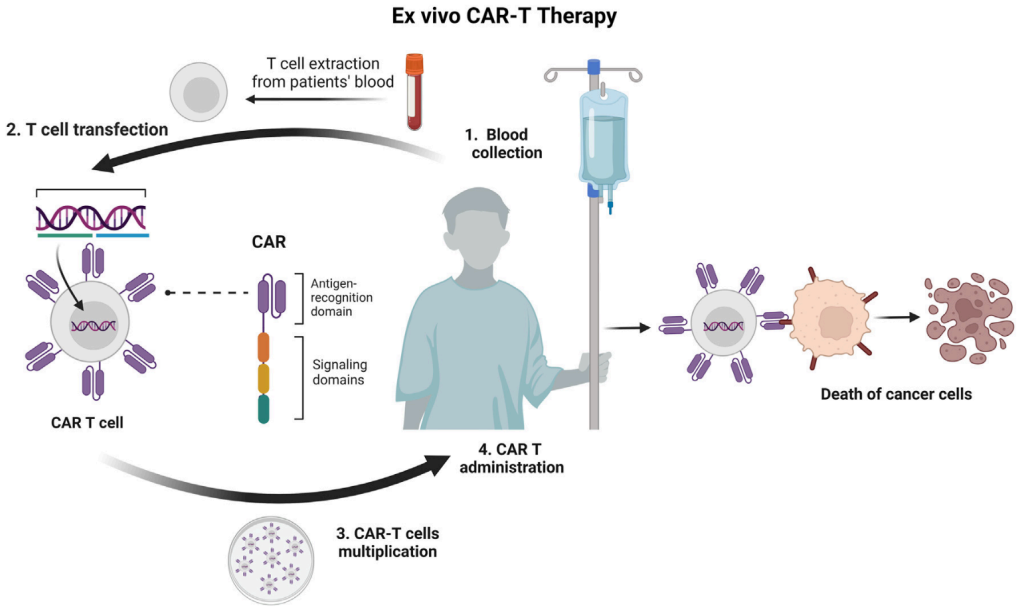
- Conventional cancer treatments (such as surgery, radiation and chemotherapy) are limited by their inability to effectively target cancers that resist treatment through genetic mutations or other mechanisms.

- Therefore, scientists have pushed the development of several novel immunotherapies, with CAR T therapy showing the most promise.

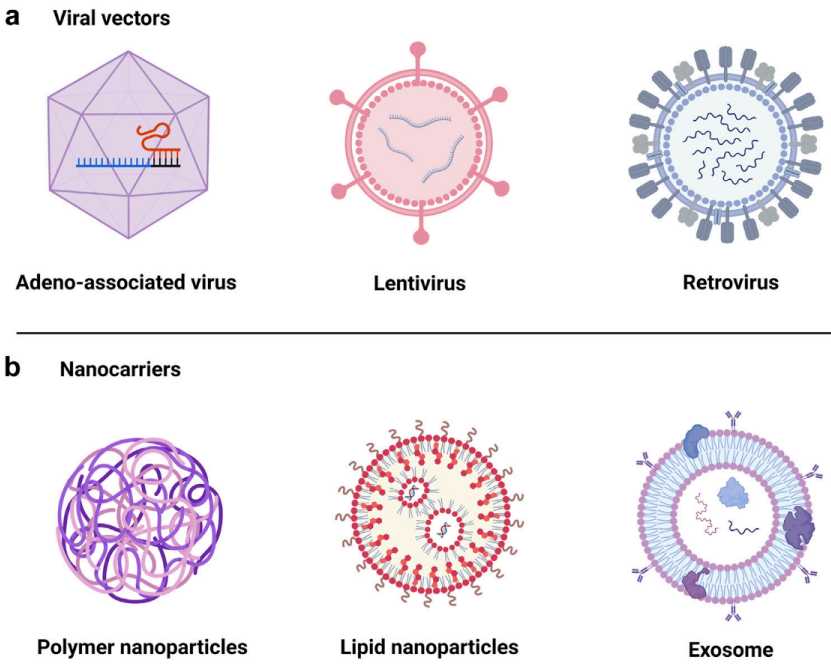
- CAR T therapy involves engineering a patient's T cell, either *in vivo* or *ex vivo*, to produce CARs which help them recognize tumour antigens so that these proteins can locate and destroy the cancer.

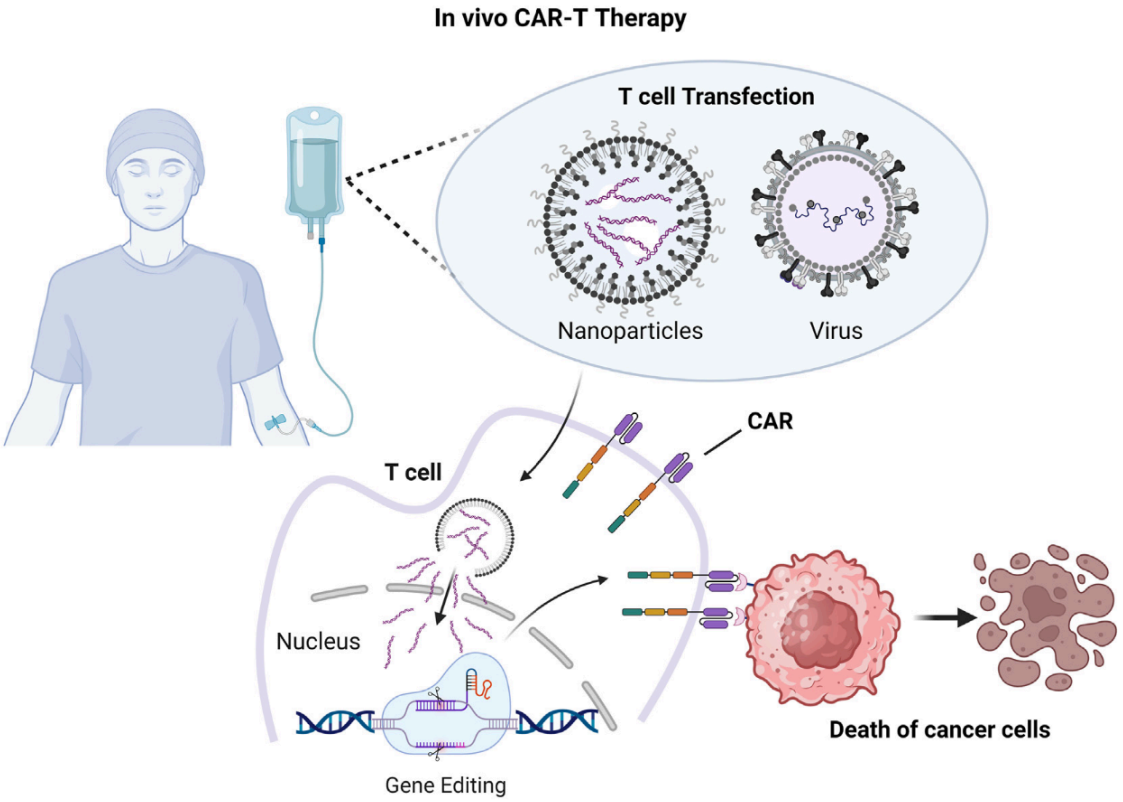
Method	**Notes**

Ex vivo CAR T	• T cell modifications are performed outside of the body.
	• Two distinct strategies:
	  ○ Autologous
	  ■ Uses a patient's own T cells.
	  ○ Allogeneic
	  ■ Uses T cells from a healthy donor.
	  ■ Risks graft rejection, where the patient's immune system recognizes donor cells as foreign and attacks them.
	• T cells are harvested from blood samples via leukapheresis. Then, they are genetically modified with CARs, designed to target specific tumour antigen. These modified cells are left to culture, before being reintroduced into the patient via infusion.
	• Potential for side effects like toxicity and rejection.
	• Tumours can eventually learn how to resist treatment by evading CAR T cell recognition.
	• The entire ex vivo procedure involves isolation, modification, colony expansions, and administration of T cells. This process can span over weeks of intricate work, making it an unviable choice for urgent treatments.
	• The procedure is expensive, which limits accessibility towards lower-income families.



Method	Notes
In vivo CAR T	• T cell modifications are performed directly within the body. • In vivo CAR T therapy is done by delivering genetic material into the patient's T cells using viral vectors or nanocarriers, which provides instructions that tell the T cells how to make CAR proteins. • Viral vectors, most notably the lentivirus, retrovirus, and adeno-associated virus, are currently in the preclinical stage. They show promise because they can be engineered to specifically target T cells by incorporating T cell-specific ligands. But, they risk off-target toxicity and immunogenicity. • Polymers, lipids, and exosomes are the most commonly used nanocarriers for in vivo therapy. Compared to viral vectors, nanocarriers have minimal off-target toxicity and immunogenicity, and can be produced on a large scale. However, they are not as effective as delivering genetic material into cells. .


a
Viral vectors
Adeno-associated virus
Lentivirus
Retrovirus
b
Nanocarriers
Polymer nanoparticles
Lipid nanoparticles
Exosome


In vivo CAR-T Therapy
T cell Transfection
Nanoparticles
Virus
CAR
T cell
Nucleus
Gene Editing
Death of cancer cells

- Researchers are currently discovering new ways to improve the precise targeting of delivery carriers into T cells because it is essential to ensuring efficacy and safety.
    - One study which featured *CD3-targeted biodegradable poly(β-amino ester)-based nanoparticles* saw tumour decline and enhanced survival by 5 days in mice models with leukemia.

- Challenges of in vivo therapy:

    - **Long term effectiveness**. Over time, CAR T cells experience T cell exhaustion (when T cells become less effective due to prolonged activity).

    - **Solid tumours**. Solid tumours *hide* from the immune system, preventing T cells from recognizing and attacking it, which reduces the efficacy of CAR T cells.

Future Directions:

- Setup of elaborate clinical trials to move in vivo CAR T therapy to clinical use.

- Exploration of ways to enhance the long-term effectiveness of CAR T cells.

- Minimisation of unintended off-target effects.

- More frequent utilisation of animal models to more accurately reflect the human immune system.

- Streamline manufacturing processes of CAR proteins.

Sources:

Bui, T. A., Mei, H., Sang, R., Ortega, D. G., & Deng, W. (2024). Advancements and challenges in developing in vivo car T cell therapies for cancer treatment. Elsevier, 106, 105266. https://doi.org/10.1016/j.ebiom.2024.105266

Elsevier. (2024). *Fig. 2: Process of ex vivo CAR T therapies*. Advancements and challenges in developing in vivo CAR T cell therapies for cancer treatment. Retrieved April 28, 2025, from https://doi.org/10.1016/j.ebiom.2024.105266.

Elsevier. (2024). *Fig. 3: Schematic explanation of the in vivo CAR T therapy for cancer treatment*. Advancements and challenges in developing in vivo CAR T cell therapies for cancer treatment. Retrieved April 28, 2025, from https://doi.org/10.1016/j.ebiom.2024.105266.

Elsevier. (2024). *Fig. 4: Delivery vehicles for in vivo CAR generation*. Advancements and challenges in developing in vivo CAR T cell therapies for cancer treatment. Retrieved April 28, 2025, from https://doi.org/10.1016/j.ebiom.2024.105266.