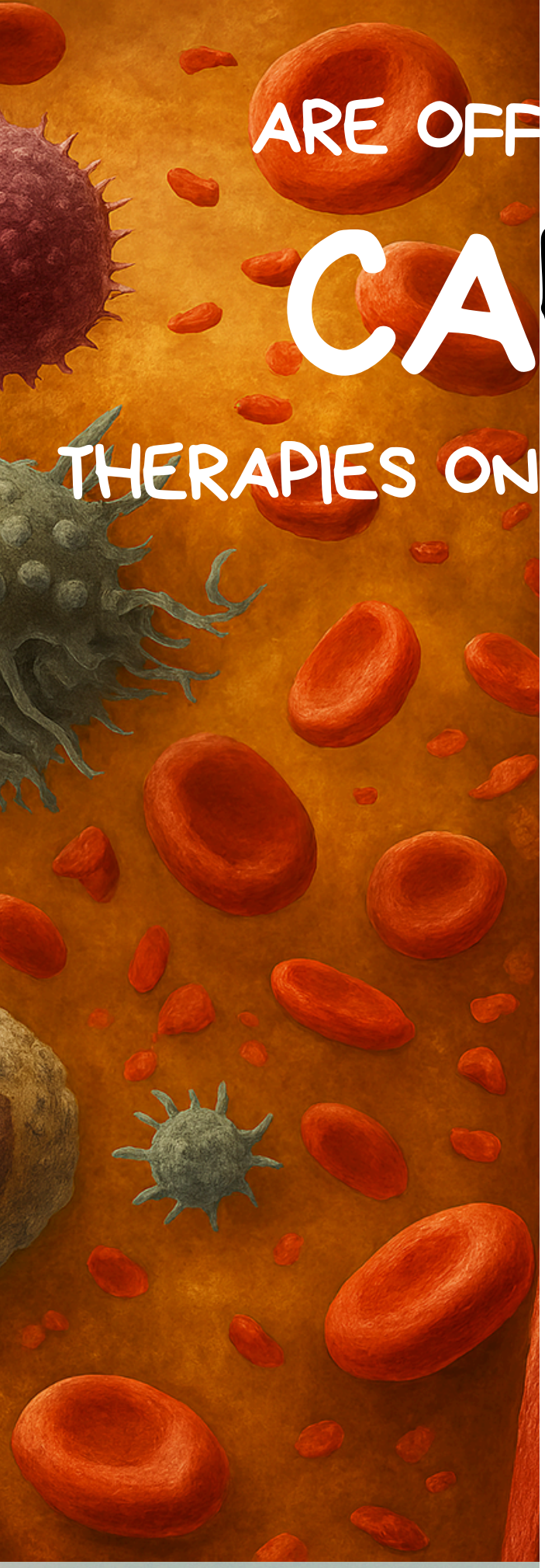


ARE OFF-THE-SHELF CAR-NK THERAPIES ON THE HORIZON ?

by Cliff Dominy PhD

Imagine a cancer therapy that bypasses the immune system and strikes tumours with greater precision. The advantages of a blindfolded immune system could mean reduced therapeutic side effects and delivering more of the drug to where it is needed the most. Now imagine that this potentially safer and highly effective therapy was available on demand. Thanks to a new generation of genetically-modified biologics, it may be closer than we realise.

> THEY KILL CANCER CELLS BETTER AND THEY'RE SAFER." DR JIANZHU CHEN, LEAD INVESTIGATOR

The study, published in Nature Communications, was led by Jianzhu Chen and Rizwan Romee of the Dana-Farber Cancer Institute. The team genetically re-engineered natural killer (NK) cells that can evade the immune system and selectively target lymphoma cells in the blood. These second-generation NK cells were outfitted with an "invisibility cloak" opening the door to safer, more powerful, "off-the-shelf" immunotherapies. If proven safe and effective in humans, the strategy could be an important therapeutic pivot in the treatment of blood-borne cancers.

CAR-T therapy - a primer

The problem: To appreciate the development, it would help to revisit how CAR-T based therapies work, and how they have revolutionized oncology. Chimeric antigen receptor T-cell (CAR-T) immunotherapy has shown much promise in the treatment of B-cell leukemia, multiple myeloma and lymphoma. Indeed, since 2017, several CAR-T therapies have received FDA approval for treating these liquid cancers. But their success comes at a price, with 70-90% of patients experiencing an immune system overreaction to the drug - a so-called cytokine storm. All told, about 3-6% of patients will die from the side-effects of the drug rather than the underlying cancer. Nevertheless, patients with B-cell lymphoma who survive the treatment can expect three additional years of life - with many leukemia survivors enjoying an extra 5-10 years.

The solution: CAR-T therapy is the poster child for personalized medicine, but it can be hazardous, expensive and take ages to produce. Researchers isolate T-cells from a patient with, for example, lymphoma and modify them to recognize the exact cancer present in the patient. It's a treatment made just for that person. The modified cells are incubated in the laboratory for several weeks until they have multiplied to a therapeutically useful level. Once reinfused back into the body, they hunt down the cancer and do what cytotoxic T-cells do best - kill it.

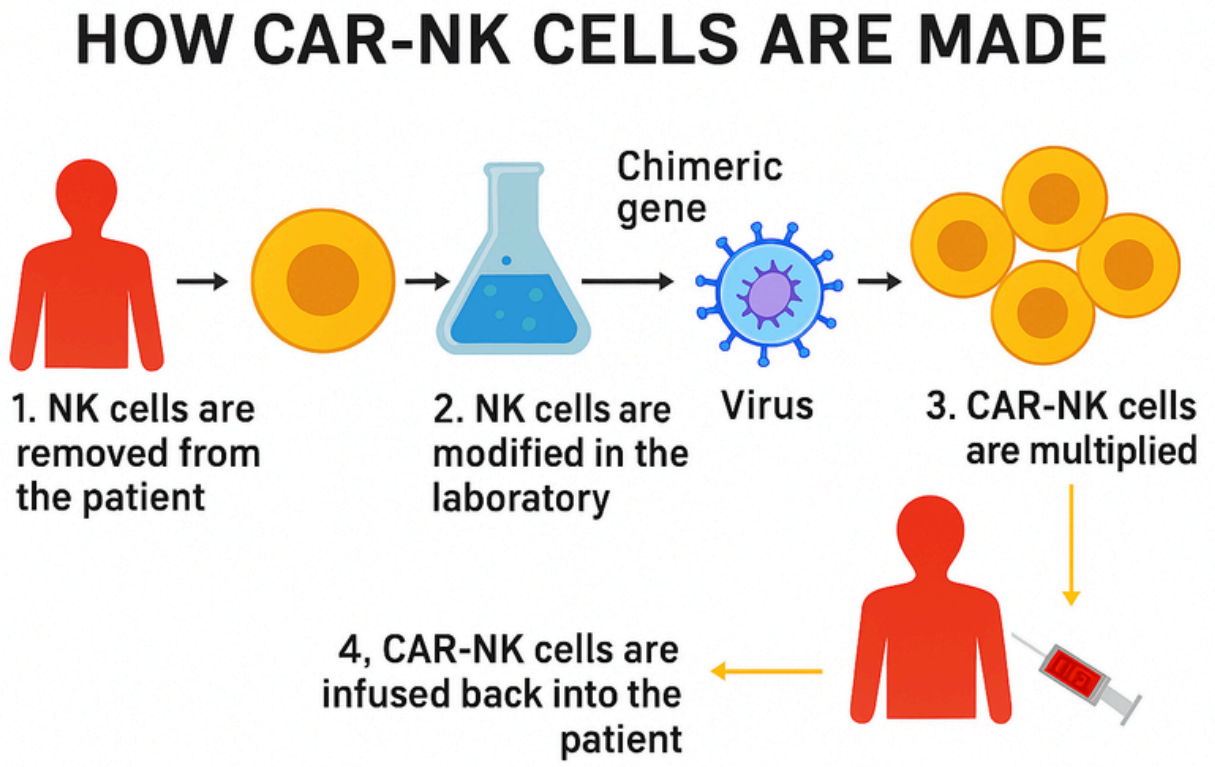
Why CAR-NK might be better

Unlike T-cells, natural killer (NK) cells are a component of the innate immune response, and genetically engineered versions are less likely to be recognized and rejected by the body. They simply fly fewer foreign flags from their surface. There are currently several gen-1 CAR-NK therapies being evaluated in clinical trials, but none approved by the FDA.

Like the CAR-T approach, they require several weeks of culturing between extraction and reinfusion, an often critical delay. The goal of the New England group was to remove the immune recognition flags from a healthy donor of NK cells and to monitor the fate of these foreign cells once infused into the patient. If accepted by the host's immune system, the approach would remove the several-week culturing phase of the cells. Dr. Jianzhu Chen of MIT noted: “This enables us to do one-step engineering of CAR-NK cells that can avoid rejection by host T cells and other immune cells. And they kill cancer cells better and they’re safer.”

How to modify an NK cell

The team's approach followed the path of current immunotherapies - with two key additions to the cells. Like earlier CAR-T and CAR-NK therapies, the cells were genetically modified by introducing an antibody gene fragment that recognises the tumour-dominant CD19 protein.



Two new immunity-related additions were included with the tumour recognition protein.

- The researchers included a small inhibitory RNA molecule designed to suppress, or “knock down” the surface proteins on the donor NK cells. These are the external flags that the patient's immune system could recognise as foreign, and remove before the treatment could take effect.

- A gene coding for a checkpoint inhibitor was included. Checkpoint inhibitors dampen the immune response and inhibit rejection of the cell. In the study, the authors used two different checkpoint inhibitor genes, PD-L1 and SCE, to investigate whether one was more effective than the other. PD-L1 functions as a “don’t attack me, I'm friendly” flag on the modified cells. By contrast, SCE operates by sending a more covert “nothing to see here, move along” signal to the immune system guards.

Great news … in mice

To test their idea, Chen and Romee turned to a mouse model. The team introduced the therapeutic cassette into genetically modified mice that contained a humanized immune system. Additionally, the mice were injected with active lymphoma cells.

The results, conducted in the animal model and cell culture, were encouraging.

- Both variations of the therapy outperformed conventional CAR therapies because of the immunosuppressive effects of the PD-L1 or SCE genes.
- The immune evasion strategy was highly effective, with cytotoxic CD8+ host cells remaining inactive because of the siRNA molecule altering the surface of the therapeutic cells.
- There were significantly fewer inflammatory cytokines produced by the treatment, suggesting that side effects from cytokine storms were reduced if not eliminated.
- The introduced CAR-NK cells were active for three weeks - longer than typical NK cells.

Future plans

"Our approach represents a promising strategy in enabling off-the-shelf allogeneic cellular immunotherapies." says lead investigator Dr Rizwan Romee. Yes indeed, but he noted that mice with humanized immune systems are still not human. Plans include better understanding the cytotoxic effect of the therapy in animals before transferring the technology into humans.

However, the development of a donor-supplied (allogeneic) therapy, if approved in humans, could reinvent how we deliver cancer immunotherapies - faster, safer, and more effectively.

Reference

Liu F, Tarannum M, Zhao Y, et al. Selective HLA knockdown and PD-L1 expression prevent allogeneic CAR-NK cell rejection and enhance safety and anti-tumor responses in xenograft mice. Nat Commun. 2025;16(1):8809. Published 2025 Oct 8.