## Title

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# Antigen-presenting nanoparticles for in vivo CAR T cell engineering

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In vivo cell engineering enables chimeric antigen receptor (CAR) production directly within the body. Most in vivo CAR approaches target broad T cell populations. However, antigen-presenting nanoparticles could be used to engineer specific T cell subsets, leveraging the phenotypic and functional properties of the cells for T cell therapy.

Clinically approved chimeric antigen receptor (CAR) T cell therapy requires complex ex vivo manufacturing processes that remain major obstacles for implementing CAR T cell therapy as standard of care for cancer treatment. The convergence of advances in engineered cell therapy and gene delivery enables CAR T cell manufacturing inside the body. In vivo CAR manufacturing is typically achieved using non-viral or viral vectors to deliver a CAR transgene in the form of mRNA or DNA to broad T cell populations. These gene delivery vectors offer better scalability and accessibility than conventional ex vivo CAR T cells, raising the possibility that off-the-shelf in vivo cell engineering approaches could extend CAR T cell therapy beyond highly personalized treatments and to larger patient populations. Furthermore, in vivo cell engineering enables direct manipulation of specific T cell subsets, including early memory T cells and virus-specific T cells, which are challenging to isolate for ex vivo cell engineering yet exhibit favourable characteristics for CAR T cell therapy.

## Targeting T cell subsets for CAR production

Pan T cell-targeting motifs, such as anti-CD5, anti-CD7 or anti-CD8, can be displayed on non-viral or viral vectors to deliver CAR transgenes to circulating T cells. Alternatively, T cell subsets that possess beneficial differentiation and functional profiles for CAR T cell therapy could be targeted. For example, compared to terminally differentiated T cells, early memory lineage subsets, especially stem cell-like memory T cells, exhibit superior proliferation and persistency in vivo, which can translate to better treatment outcomes at lower doses in the context of ex vivo CAR T cell therapy[1]. Virus-specific T cells are another attractive target for CAR T cell engineering owing to their less-differentiated memory phenotypes and native antiviral T cell receptor (TCR) specificity for vaccine boost. Compared to CAR T cells derived from bulk T cell populations, CAR T cells derived from virus-specific T cells offer prolonged persistence in patients after adoptive transfer in ex vivo CAR T cell therapies[2]. Furthermore, the endogenous virus-specific TCRs provide an additional axis of control and boost through TCR-mediated activation, which is being evaluated in clinical trials for its ability to augment the anticancer efficacy of ex vivo CAR T cell therapy (NCT01953900, NCT05432635 and NCT05801913). Increased frequencies of regulatory T cells expressing CARs is correlated to a lack of clinical responses to CAR T cell therapy in patients. Therefore, selective engineering of T cell subpopulations, such as virus-specific CD8 T cells, could avoid CAR expression on regulatory T cells[3]. Collectively, targeting T cell subsets presents an alternative for in vivo CAR production and for therapeutic enhancement of CAR T cell therapy.

## APNs program virus-specific T cells with CARs

Selective targeting to antigen-specific T cell subsets can be achieved using peptide major histocompatibility (pMHC) molecules that selectively engage the TCRs expressed on their cognate T cells. Examples of pMHC molecules for the development of antigen-specific T cell modulations include antigen-displaying viruses, soluble bispecific TCRs and pMHC multimers. Through decoration of pMHC molecules on the surface of lipid nanoparticles (LNPs), antigen-presenting nanoparticles (APNs) were developed to preferentially deliver B cell maturation antigen (BCMA) CAR mRNA to virus-specific T cells in vivo (Fig. 1a,b) with minimal off-target CAR delivery to non-cognate T cell populations, multiple myeloma cancer cells and liver hepatocytes[4,5]. Anti-BCMA CAR T cells engineered using APNs confer antitumour efficacy in xenograft mouse models of human multiple myeloma. The in vivo production of anti-BCMA CAR T cells using APNs could be amenable for translation to other CAR constructs and indications including leukaemia and lymphoma, for which anti-CD19 CAR T cell therapies are already clinically approved.

APNs engage their target T cells through pMHC–TCR interactions and are primarily internalized via TCR-mediated endocytosis, in contrast to conventional LNPs, which enter cells through low-density lipoprotein receptor (LDLR)-mediated pathways. The pMHC–TCR engagement between APNs and virus-specific T cells also enables APNs to activate and expand T cells in vivo through their native virus-specific TCRs. APN-based engineering of CAR T cells leverages the phenotypic advantages of virus-specific T cells and holds the potential to enhance the anticancer efficacy and expand CAR applications to solid tumours.

## Applications beyond cancer

In the context of autoimmune disease, in vivo non-specific T cell engineering strategies are limited to B cell depletion in B cell-driven conditions. For example, anti-CD19 CAR T cells produced in vivo by pan-T cell-targeting LNPs have been developed to treat systemic lupus erythematosus in an early-stage clinical trial (NCT06801119). Building on this concept, APNs could transfect virus-specific T cells with anti-CD19 CAR for B cell depletion to treat B cell-mediated autoimmune diseases, such as systemic lupus erythematosus, idiopathic inflammatory myositis and systemic sclerosis. Redirecting virus-specific T cells with anti-CD19 CARs could leverage their phenotypic and functional advantages for CAR T cell therapy. APNs have also been designed to deliver mRNA encoding cell executioner proteins (such as caspases) that induce cell death in autoreactive T cells to prevent the onset of

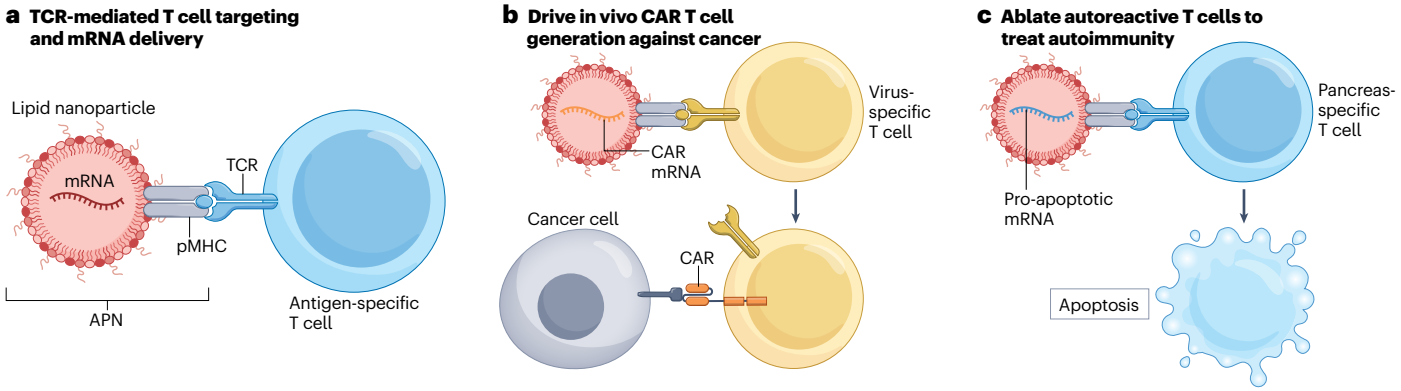


**Fig. 1 | APNs for in vivo engineering of antigen-specific T cell subsets.** **a**, Antigen-presenting nanoparticles (APNs) are a lipid nanoparticle (LNP)-based mRNA delivery system decorated with peptide major histocompatibility complex (pMHC) to target T cells through their T cell receptor (TCR) and to leverage TCR-mediated endocytosis for mRNA delivery. **b**, APNs deliver mRNA encoding a chimeric antigen receptor (CAR) to reprogram virus-specific T cells into anticancer CAR T cells. **c**, APNs ablate autoreactive T cells by delivering pro-apoptotic mRNA to prevent autoimmune disorders.

type 1 diabetes[5], a T cell-mediated autoimmune disease, in a mouse model (Fig. 1c). In the clinic, anti-CD3 antibodies are used to delay type 1 diabetes progression through broad modulation of the T cell compartment, which is associated with lymphopenia-related adverse effects. By contrast, APNs selectively deplete autoreactive T cells without lymphopenia, as shown in a mouse model of type 1 diabetes. APN-based engineering of autoreactive T cells for the prevention of autoimmunity demonstrates the potential of APNs for precision immunotherapy.

## Outlook

Realizing the translational potential of APNs will require addressing challenges related to delivery specificity and the duration of CAR expression on T cells. Although the pMHC decoration on the APN surface tunes the tropism of APNs towards antigen-specific T cells, off-target transfections to phagocytes and hepatocytes are detectable and could pose toxicity risks with long-term repeated dosing. To mitigate this risk, T cell specificity could be further improved by leveraging advances in artificial intelligence-guided LNP engineering for T cell-specific transfection. For example, deep neural networks have been applied to identify ionizable lipids to form LNPs for cell-specific transfection[6]. Additionally, the mRNA cargo could also be engineered to selectively express in T cells using RNA editing systems[7] or to de-target hepatocytes through microRNA-regulated mRNA translation[8]. The combination of cell-specific pMHC targeting motifs, cell-specific LNP formulation and selective expression of mRNA cargo could improve the specificity and safety of APNs for in vivo engineering of T cell subsets.

CAR expression induced by mRNA is transient, warranting multi-dosing of APNs to maintain therapeutic levels of CAR T cells. To reduce the number of required dosing, CARs can be encoded in circular mRNA instead of linear mRNA for more durable CAR expression (>7 days for circular mRNA versus 2–3 days for linear mRNA), owing to the superior stability of circular mRNAs compared to their linear counterparts. Alternatively, APNs can deliver genome editing systems, such as CRISPR–Cas9 and recombinases, for CAR transgene knock-in to the T cell genome for more sustained CAR expression on T cells. For example, co-delivery of Cas9 (by virus-like particles) and CAR donor DNA (by adeno-associated virus) has been shown to achieve in vivo CAR T cell therapy by CAR transgene knock-in, with CAR expression persisting for more than two weeks[9]. This in vivo transgene integration could be used to engineer circulating T cells as 'living' mRNA delivery vehicles[10] that secret APNs as extracellular vehicles containing a CAR transgene in the core and pMHC modifications on the surface to transfect the target T cell subsets.

APNs have demonstrated potential for specific T cell CAR engineering in preclinical models and their clinical translation for in vivo T cell therapy could be further advanced through integration with artificial intelligence-enabled LNP engineering, RNA editing and transgene integration technologies.

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## Competing interests

F.-Y.I.S. is listed as an inventor on patent applications pertaining to the technology (antigen-presenting nanoparticles) described in this Comment.