

REVIEW

A Bright Future for Immunotherapy: CAR T-Cell Therapy Promises Revolutionary Changes

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Chimeric antigen receptor (CAR) T-cell therapy is an innovative technology that has fundamentally changed approaches to treating certain forms of oncological diseases. The anticipated development of CAR T cell-based therapies in the near future is expected to broaden the range of therapeutic targets and holds the potential to decrease treatment costs, thereby expanding accessibility for a broader patient population. This review article provides an overview of the practical applications of CAR T-cell therapy in clinical settings, describes the global market for commercial CAR T-cell products and offers insights into the future landscape of CAR T-cell therapy. We focus on emerging therapies, novel targets and strategic approaches to improve treatment efficacy and reduce costs. Furthermore, we discuss the progress of CAR T-cell therapy in Russia, where this type of therapy is in the early stages of development but already demonstrates promising potential.

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Introduction

Gene and cell therapy based on innovative gene engineering and cellular products represents a promising area of modern biomedicine. These approaches open new horizons in the treatment of oncological and other life-threatening diseases where traditional therapies have proven ineffective.¹⁻⁵ Among these innovations, therapy involving the use of chimeric antigen receptors (CARs) is a leading medical technology at the intersection of gene therapy, cell therapy and immunotherapy, marking a breakthrough in the treatment of hematologic malignancies. CAR T-cell therapies are advanced therapy medicinal products (ATMPs) that represent a new generation of personalized cancer immunotherapy. They involve the genetic modification of T cells to create a powerful tool against relapsed or refractory hematological malignancies, such as lymphoma, leukemia and multiple myeloma.⁶⁻¹⁵ In this process, T cells are modified to recognize tumor-specific antigens such as CD19 or B-cell maturation antigen (BCMA) without the involvement of the major histocompatibility complex (MHC), resulting in high activation and antitumor responses.^{16,17}

Over 500 clinical trials on therapies targeting hematological malignancies and solid tumors are currently underway globally, with the United States and China at the forefront of CAR T-cell research.^{18,19} Emerging therapies include bispecific and modular CARs that target multiple antigens simultaneously or incorporate switchable designs to address antigen escape, heterogeneity and off-target effects, thereby improving safety and efficacy.^{20,21} Furthermore, allogeneic CAR T-cell therapies, which use healthy donor cells, present a scalable and cost-effective alternative to patient-specific autologous CAR T cells.²² CAR T-cell technology is also expanding into autoimmune disease treatment,²³ employing chimeric autoantibody receptor T cells (CAAR) and other constructs to target disease-specific immune responses. CAR-natural killer (NK) cell therapy, which combines NK cell cytotoxicity with engineered specificity, is emerging as a complementary approach, particularly for solid tumors and neurodegenerative diseases.²⁴

The commercial CAR T-cell market has grown significantly, with several products targeting hematological malignancies, including lymphoma and multiple myeloma. The manufacturing of CAR T cells in accordance with good manufacturing practice (GMP) standards is essential for ensuring their safety, efficacy and scalability. Advancements in automated production technologies and the development of centralized manufacturing models contribute to reducing treatment costs and expanding accessibility.

As these therapies continue to evolve, their integration into standard clinical practice has the potential to transform patient outcomes globally. This article presents an overview of recent advancements in CAR T-cell therapy, including emerging therapeutic targets and global market dynamics, with a

focus on the contributions of Russia and China. It explores the regulatory landscape and legal frameworks shaping CAR T-cell development, addresses challenges and innovations in production processes and analyzes the economic and social implications, as well as prospects for this innovative technology.

CAR structure and mechanisms of CAR T-cell activation

The CAR construct is derived from the T-cell receptor (TCR) and includes an extracellular domain, typically a single-chain variable fragment of an antibody (scFv), intracellular signaling domains such as the CD3 ζ chain and costimulatory molecules ([Figure 1](#)).²⁵⁻²⁹ The activation of CAR T cells begins when the extracellular domain recognizes tumor-associated antigens (TAA), such as CD19 or BCMA, on tumor cells. Antigen binding triggers receptor dimerization, which activates an intracellular signaling cascade, leading to the release of cytokines such as interleukin-2 (IL-2), which promote cell proliferation and activation. Activated CAR T cells induce tumor cell apoptosis through the secretion of perforin, granzymes and various proinflammatory cytokines, as well as the expression of Fas ligand (FasL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).

CAR T cells can be classified into five generations based on the evolution of their intracellular signaling domains, with each generation designed to overcome specific limitations of its predecessors ([Figure 1](#)).²⁵ The first-generation CARs contained only the scFv and CD3 ζ for signaling. Its major drawback was the absence of costimulatory domains, resulting in low cytokine production, inadequate T-cell proliferation and a limited lifespan. The second- and third-generation CARs contain additional costimulatory molecules such as CD28, CD134 (OX40) and CD137 (4-1BB) to promote anti-tumor potential. The fourth-generation CARs, also known as TRUCKs (T cells Redirected for Universal Cytokine Killing), are designed to secrete cytokines to enhance the therapeutic efficacy of CAR immunotherapy. The fifth-generation CARs incorporate domains designed to activate specific intracellular signaling pathways, such as the STATE3/5 signaling axis, to further promote cytokine signaling independently of external factors.

Targets and ongoing clinical trials of CAR T-cell therapy

CAR T-cell therapy is rapidly evolving from an experimental cancer treatment to a widely developing therapy approach, with more than 500 registered clinical trials in hematologic malignancies and solid tumors, with the majority of these being conducted in the United States and China.^{18,19} While fundamental scientific work in the CAR T-cell field has mainly been carried out in the United States, China leads in the total number of CAR T-cell therapies conducted, with Europe ranking third. In China, the relatively lenient legislative policy for clinical trials in comparison with other countries has enabled these clinical trials to closely resemble treatment processes.

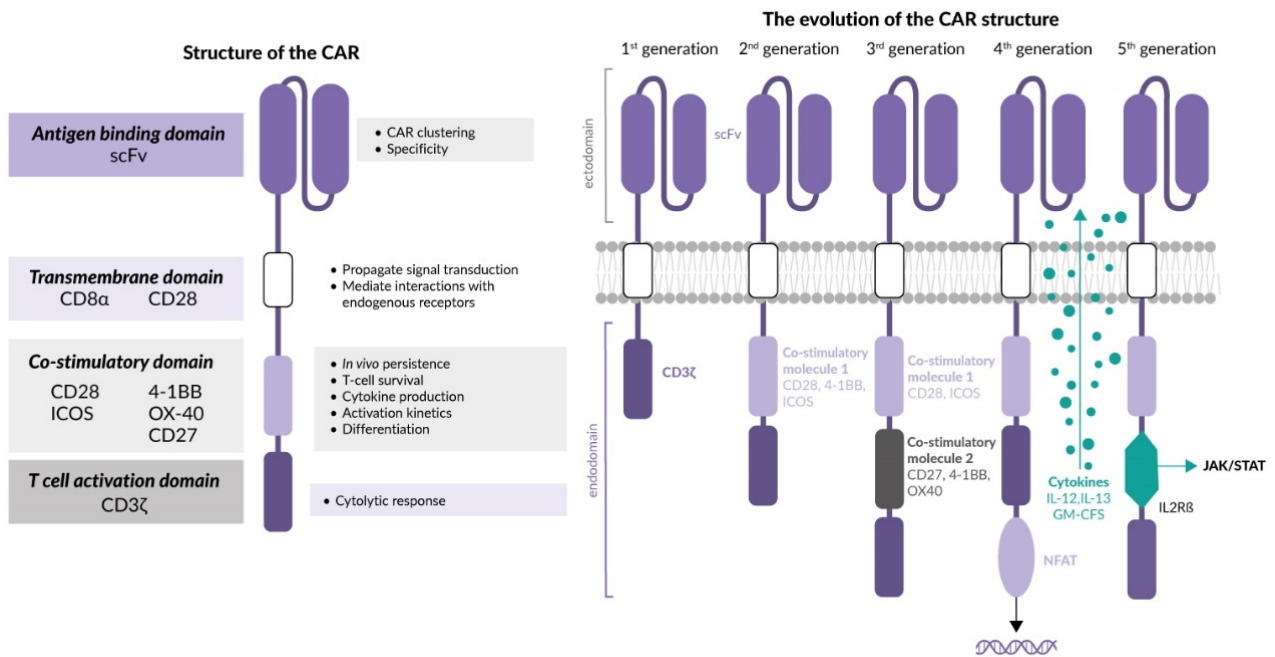


Figure 1. Basic chimeric antigen receptor (CAR) structure and five generations of CARs.

Adapted from McErlean et al. 2024.³⁰

Table 1. List of selected antigen targets for chimeric T-cell receptors.

Disease	Target antigen
Acute lymphoblastic leukemia	CD19, CD20, CD22, CD123
Acute myeloid leukemia	CD33
Chronic lymphoblastic leukemia	CD19
Non-Hodgkin lymphoma	CD19/CD20
Anaplastic large cell lymphoma	CD30
Hodgkin lymphoma	CD19/CD30
Multiple myeloma	BCMA, CD269/CD138

Drug targets for hematological malignancies, such as BCMA, CD19 and CD22, continue to be the most prominent targets, according to data from 2022.¹⁴ The development of extracellular domain focuses on the identification of suitable targets, which are usually surface antigens with epitopes unique to cancer cells. Among these target proteins, CD19 is the most extensively studied target antigen. It is a lineage-specific tissue antigen expressed at virtually all stages of B-lymphocyte differentiation, except for plasma cells ([Table 1](#)). CD19 is considered an ideal target for CAR T-cell immunotherapy for the treatment of B-cell tumors due to its specific expression on various B-cell malignancies and B-cell precursor cells, with no expression on normal tissues and cells. The first successful therapeutic outcomes were achieved using CD19-targeted CAR T cells.²⁹

The expression patterns of CD20 resembles those of CD19, making CD20-targeted CAR T cells a potential option for adoptive immunotherapy of hematological tumors. Currently, anti-CD20 CAR T-cell therapy has also been used as a therapeutic treatment in several studies on acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma.^{14,29} In addition to CD19 and CD20, CD22 is being investigated in clinical trials and has been shown to be a potential therapeutic target. For example, CD22-directed CAR T cells have shown beneficial effects in patients who are not eligible for CD19-targeting CAR T-cell therapy.³¹

Currently, a large number of clinical trials are being conducted worldwide to evaluate the efficacy and safety of CAR T-cell therapy in patients with hematologic and non-hematologic malignancies. Some examples of ongoing and recently completed studies are included in [Table 2](#). Notably, more than 63% of newly developed CAR T-cell therapies target proteins in hematological malignancies and approximately 37% target solid tumors. The top three tumor types investigated in clinical trials are gastrointestinal (10%), breast (6%) and nervous system (6%) tumors.³²

In Russia, the Federal State Budgetary Scientific Institution “Research Institute of Pediatric Hematology, Oncology and Immunology” is conducting a study of the safety and efficacy of autologous CD19/CD22 CAR T lymphocytes in a cohort of children and young adult patients with relapsed/refractory (R/R) ALL ([NCT04499573](#)).³³ A similar approach was utilized in phase I [NCT03233854](#) trial which demonstrated overall responses in all participating adult patients with R/R ALL, including minimal residual disease (MRD)-negative complete remission (CR) rate of 88%.²⁰ In adult patients with large B-cell lymphoma (LBCL), the overall response rate was 62%, with a CR rate of 29%.

A significant proportion of studies are being conducted in China.^{18,34} Clinical trials of CAR T-cell drugs are aimed at treating various solid tumors, such as hepatocellular carcinoma,³⁵ lung cancer³⁶ and gastric cancer,³⁷ using various CAR modifications targeting CEA, epidermal growth factor receptor EGFR/EGFRvIII, GD2, human epidermal growth factor receptor 2 (HER2), MSLN, MUC1 and other antigens. Neuroblastoma therapy with anti-GD2-CAR T cells has demonstrated antitumor activity, but relapse rates after CAR T-cell infusion were high.³⁸ Treatment of renal cell carcinoma with anti-CAIX CAR T cells has been shown to be ineffective, with virtually no clinical response.³⁹ Similar data have been obtained for retinoblastoma with anti-CD171 CAR T cells,⁴⁰ metastatic pancreatic carcinoma with anti-EGFR CAR T cells⁴¹ and colon cancer with anti-HER2 CAR T cells.⁴²

Table 2. Examples of currently ongoing or recently completed clinical trials of chimeric antigen receptor (CAR) T-cell cancer therapy.

Disease	CAR T-cell strategy	Examples of studies
Hematological malignancies		
B-cell and B-precursor ALL	CD19, CD22, CD19/CD22-specific CAR T cells	NCT04499573 , ³³ NCT06343090 , ⁴³ NCT02614066 , ⁴⁴ NCT06647329 ⁴⁵
NHL (DLBCL, HGBCL, PMBCL, FL, TFL, MZL, MCL)	CD19, CD19/CD22 CAR T cells (including in combination with PD-1 antibodies)	NCT02348216 , ⁴⁶ NCT02926833 , ⁴⁷ NCT03287817 , ⁴⁸ NCT02601313 , ⁴⁹ NCT02631044 , ⁵⁰ NCT03310619 , ⁵¹ NCT03568461 , ⁵² NCT03105336 , ⁵³ NCT06647329 ⁴⁵
Multiple myeloma	BCMA- and GPRC5D-specific CAR T cells	NCT04271644 , ⁵⁴ NCT04133636 , ⁵⁵ NCT03318861 , ⁵⁶ NCT04555551 , ⁵⁷ NCT04155749 , ⁵⁸ NCT03288493 ⁵⁹
Solid tumors		
HER2-positive sarcoma	HER2-specific CAR T cells	NCT00902044 ⁶⁰
Neuroblastoma	GD-2-specific CAR T cells	NCT01822652 ⁶¹
Pancreatic cancer	Mesothelin/GPC3/GUCY2C-specific CAR T cells, autologous CAR T cells targeting B7-H3	NCT05779917 , ⁶² NCT06158139 ⁶³
GD2- and PSMA-positive tumors	GD2/PSMA-specific CAR T cells	NCT05437315 ⁶⁴

ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD-1, programmed cell death protein 1; PMBCL, primary mediastinal large B-cell lymphoma; PSMA, prostate-specific membrane antigen; TFL, transformation follicular lymphoma.

Side effects and limitations of CAR T-cell therapy

Effective CAR T-cell therapy faces several challenges, including severe treatment-related toxicity, antigen escape and the immunosuppressive tumor microenvironment. CAR T-cell therapy induces adverse reactions by various mechanisms, such as on-target/on-tumor, on-target/off-tumor and off-target/off-tumor toxicities.⁶⁵ The most common type of adverse events associated with CAR T-cell therapy is the occurrence of cytokine release syndrome (CRS), an inflammatory condition caused by excessive production of IFN γ and IL-6, which can manifest as fever, hemodynamic changes and organ damage.⁶⁶ Another frequent toxicity is immune effector cell-associated neurotoxicity syndrome (ICANS), a neurological condition caused by overactivation of the peripheral immune system, inflammation and blood–brain barrier dysfunction. ICANS can manifest with multiple clinical symptoms of varying severity, such as encephalopathy, seizures and cognitive impairments. In addition, the development of anaphylaxis, macrophage activation syndrome, CAR T-cell infusion-associated infections and tumor lysis syndrome (TLS), as well as many other adverse reactions is possible.⁶⁵⁻⁶⁸ Toxicity associated with CAR T cells can be overcome by altering CAR structure. For example, cytokine secretion can be modulated by modifying the hinge and transmembrane regions of the chimeric receptors. Furthermore, CAR immunogenicity can be reduced by utilizing human/humanized antibody fragments derived from mice.

Adverse events associated with CAR T-cell therapy can substantially impact patients' well-being, particularly in the acute phase following infusion. Studies have indicated that patients may experience a high symptom burden during or immediately after CAR T-cell infusion, with concerns regarding treatment efficacy and adverse reactions contributing to treatment-related distress.⁶⁹ Nevertheless, longitudinal assessments have revealed that, despite early declines health-related quality of life (QoL) due to treatment-related side effects, many patients report a return to baseline or improved QoL in subsequent months, especially among those achieving remission.⁷⁰ The integration of patient-reported outcomes (PROs) into clinical practice would facilitate personalized interventions and improve overall treatment outcomes. Despite these benefits, challenges remain in the routine implementation of PROs, particularly during acute treatment phases in patients experiencing neurological toxicities. Additionally, there is a lack of comprehensive PRO data to guide the monitoring and capture of delayed effects of CAR T-cell therapy in long-term survivors.⁷¹ Ongoing research aims to develop feasible PRO assessment tools tailored to the CAR T-cell therapy context, ensuring that patient-centered care remains a cornerstone of treatment paradigms.

One of the major obstacles for CAR T-cell therapy is tumor resistance to single-antigen-targeted CAR constructs. Although CD19-targeted CAR T-cell therapy has shown promising results in a significant proportion of patients with R/R ALL, recent data show that many patients develop resistance to treatment after disease relapse. The general mechanism of this resistance involves downregulation or loss of the CD19 antigen on tumor cells.⁷² Similar mechanisms of resistance associated with antigen escape have been observed in solid tumors. For example, in a study of CAR T-cell therapy targeting IL13Ra2 in glioblastoma, it was found that recurrent tumors had reduced IL13Ra2 expression.⁷³ To reduce the relapse rates after CAR T-cell therapy, many strategies are currently based on targeting multiple antigens using either dual CAR constructs or tandem CARs containing two scFvs. Clinically, both strategies have shown promise in achieving long-term, sustained remission.

The selection of an antigen for CAR T-cell therapy requires careful consideration due to the potential expression of tumor antigens in healthy tissues. The goal is to identify an antigen specific to tumor cells while minimizing side effects on healthy tissues. One approach to address this challenge is to search for unique post-translational modifications characteristic of tumor cells. An example of such modifications are truncated O-glycans, which are overexpressed in solid tumors.⁷⁴

Solid tumor therapy is limited by the ability of CAR T cells to navigate and penetrate the tumor because the immunosuppressive tumor microenvironment and physical barriers limit CAR T-cell entry and motility. One strategy to address these limitations is to express chemokine receptors on

CAR T cells that respond to tumor-derived chemokines. For example, CAR T cells engineered to express CXCR2 or CXCR1/CXCR2 exhibit enhanced trafficking and significantly increased antitumor efficacy.⁷⁵ Another strategy is to engineer CAR T cells to improve penetration through tumor stroma. CAR T cells expressing heparanase⁷⁶ or fibroblast activating protein,⁷⁷ have demonstrated enhanced infiltration and antitumor activity.

In addition to the above-mentioned challenges, CAR T-cell therapy faces several other significant obstacles, including immune inhibition and tumor resistance, limited persistence and sustainability of CAR T cells and insufficient tumor infiltration. Together, these limitations can significantly restrict the therapeutic potential of CAR T-cell therapies and require further research to improve their broader application, clinical efficacy and safety.

New strategies in CAR T-cell therapy production and application: An overview of current trends

Programmable and controllable CARs

CAR T-cell therapy has revolutionized cancer treatment, but a key challenge remains: maximizing its effectiveness while preventing side effects. Conventional CARs are limited by their inability to switch easily between different tumor antigens, which critically restricts their clinical application. This limitation arises from their design, as traditional CARs consist of a scFv targeting a specific antigen and a fixed signaling domain and therefore is capable of recognizing only one specific target. Modular CAR approaches address this weakness by utilizing universal CARs, which allow the separation of antigen recognition and CAR activation into two distinct, controllable stages.⁷⁸ This design enables the precise activation and re-targeting of universal CAR T cells using molecular switches, allowing them to target multiple tumor antigens with greater flexibility and control, potentially avoiding toxicities, overcoming antigen avoidance and reducing production costs. The separation of antigen recognition from the signaling domain enables the flexibility to switch target antigens without the need to re-engineer CAR T cells, making this approach versatile and cost-effective.⁷⁹

The modular design of universal CARs functions like a two-piece puzzle. The first component is the signaling module, which contains binding sites for a specific epitope. The second component is the switch module, which includes a single binding domain targeting a tumor-associated antigen (TAA) and an epitope that is specifically recognized by the signaling module. These CAR T cells remain inactive until a special switch molecule links them to tumor cells expressing the target antigen. This switch molecule acts as a bridge between the CAR T cells and the tumor cells, activating the CAR T cells and directing them to eliminate the tumor.^{80,81} The therapeutic strategy of switching CAR is particularly promising against highly heterogeneous and immune-evading solid tumors. Furthermore, the dose of the switches

determines the intensity of therapy. To date, a variety of switchable CARs have been designed. The switchable modular designs include dimerizing platforms that use leucine zippers, biotin-avidin system, sortases, conjugates of single-chain monoclonal antibodies with small molecules and others.

An example of a controllable and switchable CAR construct is the biotin-binding immunoreceptor (BBIR), which consists of an extracellular avidin motif linked to an intracellular signaling domain.⁸² The switch molecule is a tumor-specific ligand, such as scFv or a monoclonal antibody that selectively binds to avidin within the BBIR. Binding of the biotinylated switch molecules and tumor cells activates BBIR-engineered CAR T cells and leads to tumor cell lysis.

RNase toxin barnase is an example of a targeting module that inherently provides cytotoxic effects. The barnase-barstar toxin-antitoxin system is controlled by RNase toxin barnase and is inactivated by the related antitoxin barstar, exemplifying molecular switching based on the exceptional affinity of the barnase-barstar complex.⁸³ In this approach, the interaction between barnase and barstar was utilized to direct barstar-modified CAR (BsCAR) T cells to tumor cells using barnase-based molecular switches. Barnase was fused with designed ankyrin repeat proteins (DARPs) that are specific for the tumor antigens HER2 and EpCAM. The resulting DARPin-barnase (DARPin-Bn) proteins enabled T cells modified with universal BsCAR to specifically target tumor cells. The high binding affinity between barnase and barstar provides unique regulatory potential for CAR T-cell therapy *in vivo*. This approach can enhance CAR technology with therapeutic modalities, including redirecting T-cell cytotoxicity against combinations of multiple tumor antigens.

The recently developed switches G3-Bn and 9.29-Bn have demonstrated specific binding to the HER2 receptor on the surface of tumor cells.⁷⁸ The anti-HER2 DARPin proteins (G3 and 9.29) fused with barnase were used as molecular switches to direct BsCAR T cells against HER2-positive tumor cells. It has been reported that DARPins G3 and 9.29 interact with different domains of the HER2 receptor, which is often overexpressed in solid tumors. The DARPin-Bn fusions exhibit significant RNase activity, leading to dose-dependent death of HER+ tumor cells. Further clinical use of many universal and programmable CARs requires detailed studies on the pharmacokinetics and immunogenicity of DARPin-Bn switches in the context of BsCAR T-cell therapy. Based on these findings, customizable BsCAR T cells directed by personalized sets of DARPin-Bn switches could provide promising opportunities for controlled elimination of solid tumors by simultaneously targeting multiple tumor antigens.

CAR T cells targeting solid tumors have received significant scientific and clinical attention.^{84,85} However, the tumor microenvironment (TME) presents substantial challenges that limits their efficacy. These challenges

include physical barriers that hinder CAR T-cell infiltration and an immunosuppressive environment that inhibits CAR T-cell activity. To overcome these obstacles, ongoing research focuses on strategies to increase the number of CAR T cells. In particular, methods such as intratumoral injection of CAR T cells, the use of peptide and nanoparticle vaccines and the development of mechanisms for controlled expansion of the CAR T cell population using cytokines are being considered.⁸⁶⁻⁸⁹ Approaches to target TME include the use of oncolytic viruses to modulate the immunosuppressive nature of TME and *ex vivo* enhancement of CAR T cells using CRISPR–Cas9 and other genome editing approaches.⁹⁰

Bispecific and multi-specific CAR T-cell therapy

Targeting multiple molecules is a promising strategy to overcome antigen escape after single-target CAR T-cell therapy.⁹¹ This approach includes both simultaneous and sequential infusions of different single-target CAR T cells, as well as CAR T cells targeting different antigens simultaneously. Bispecific CAR T cells can be further categorized based on their structure into bivalent CAR T cells, where a single CAR incorporates VH domains that bind to multiple antigens while sharing costimulatory and intracellular signal, and dual CARs, where T cells carry two separate CARs, each functioning independently. There are also co-transducing CAR T cells, in which different CAR-expressing viruses are mixed and transduced into T cells simultaneously, resulting in a product that contains both single- and multi-target parallel CAR T cells.

Early clinical trials have confirmed the efficacy and safety of multi-specific CARs, as well as their ability to prevent antigen loss in lymphoma patients.^{20, 21}

A clinical trial evaluating anti-CD19/CD20 tandem CAR T cells for the treatment of non-Hodgkin lymphoma ([NCT03097770](#)) demonstrated notable results.⁹² Another study utilizing anti-CD19/CD20 tandem CAR T cells also showed high effectiveness.⁹³ Dual targeting of CD19/CD22 is investigated in ALL and LBCL.^{20,33}

In preclinical models of glioblastoma, studies have demonstrated that tandem CAR T cells targeting HER2 and IL13R α 2 exhibit activation levels similar to single-target CAR T cells when encountering individual antigens.⁹⁴ However, their activation is further enhanced when exposed to both antigens simultaneously. Tandem CAR T cells exhibit prolonged persistence, resistance to exhaustion, reduced antigen escape and enhanced efficacy in treating glioblastoma.⁹⁵ Currently, preclinical investigations are underway for trivalent CAR T cells targeting HER2, IL13R α 2 and EphA2 in glioblastoma. The utilization of nanobodies in CAR design presents a promising solution to certain challenges encountered with bispecific CAR T cells, such as overly large structures exceeding the packaging capacity of viral vectors and the

potential for incorrect pairing of variable light and heavy chains from different scFv.⁹⁶ The preclinical study investigated the use of anti-CD5/CD7 bispecific CAR T cells based on nanotubes to address the issue of antigen evasion in T-cell malignancies. This study compared the functional characteristics of tandem and dual CAR T cells, demonstrating that tandem CAR T cells exhibit a more streamlined and elegant structure along with enhanced long-term efficacy.⁹¹ These results highlight the potential advantages of nanotube-based approaches in overcoming the current limitations of bispecific CAR T-cell therapy.

Bispecific CARs play a crucial role in addressing several issues in immunotherapy, including antigen evasion, lineage switching and trogocytosis. Simultaneous targeting of CD19 and FLT3 has become an effective strategy for mitigating antigen evasion in B-cell AML. This approach leverages the unique properties of bispecific CARs to enhance therapeutic efficacy and overcome resistance mechanisms in leukemia treatment.^{97,98}

Additionally, a dual CAR system can include both an activating CAR that recognizes tumor antigens and an inhibitory CAR to prevent self-recognition by CAR T cells. The former autonomously targets tumor cells, while the latter transmits a protective “don’t kill me” signal among CAR T cells during trogocytosis.⁹⁹

Multispecific CAR T cells have been used for other types of oncological diseases, including glioblastoma¹⁰⁰ and other types of cancers.¹⁰¹

These results indicate that multispecific CAR T-cell therapy may be a promising strategy. However, multispecific CAR T cells require more advanced technical support but offer advantages in terms of cost and labor.

Allogeneic CAR T cells

The use of cells from healthy donors, known as “off-the-shelf” allogeneic (allo) CAR T cells, presents a promising solution for several challenges associated with autologous (auto) CAR T cells. Allo-CAR T cells offer many advantages, such as reduced costs through industrial, scalable manufacturing processes, where a large number of CAR T cells can be obtained from a single donor.²² Additionally, allo-CAR T cells can be produced in batches of cryopreserved T cells, simplifying the process of introducing multiple cell modifications into a single-cell product and standardizing the CAR T cell product based on donor selection and processing. Unlike autologous CAR T cells, which require patient-specific collection, allo-CAR T cells allow for product batches that can be used for re-dosing as needed.

In addition to these production advantages, allo-CAR T cells offer several clinical benefits for patients with hematological malignancies compared with auto-CAR T cells. For example, allo-CAR T cells are associated with less severe CRS, while showing comparable efficacy to auto-CAR T cells in

patients with AML.²² Another notable benefit of allo-CAR T cells is the elimination of the need for bridging therapy. Bridging therapy, recommended for patients with progressive cancers, is administered in the interval between leukapheresis and autologous injection of CAR T cells to control the tumor burden.⁵¹ This therapy incurs additional treatment costs and may be less effective if patients develop resistance to previous drugs. However, these patients can successfully receive allo-CAR T cells without requiring bridging therapy within five days after enrollment.¹⁰² Allo-CAR T-cell therapy can thus also reduce the costs of hospitalization and interventions. Additional advantages of allogeneic products include the use of T cells that have not been compromised by previous immunosuppressive or cytotoxic treatments, as well as the absence of the risk of transducing autoreactive T cell clones. The availability of ready-to-use products also reduces the risk of disease relapse caused by sudden discontinuation of immunosuppressants for autologous lymphocyte apheresis.

Since the use of allo-CAR T cells involves certain risks, Chen et al.¹⁰³ addressed several critical aspects in the development of these allogeneic products. To prevent graft-versus-host disease (GvHD), TCR is removed through genetic ablation of the TCR alpha constant chain (TRAC) gene, thereby preventing the expression of the TCR/CD3 complex. To reduce allogeneic activity and enhance the resilience of CAR T cells, the expression of specific class I MHC molecules and all class II MHC molecules is eliminated by knocking out HLA-A, HLA-B and the class II major histocompatibility complex transactivator (CIITA), while preserving HLA-C, HLA-E and HLA-G to avoid NK cell-mediated elimination. Programmed cell death protein 1 (PD-1) is also knocked out based on the assumption that programmed death-ligand 1 (PD-L1) is often activated in inflamed tissues, which can lead to premature aging of CAR T cells.

CAR T-cell therapy for autoimmune diseases

In the past few years, CD19- and BCMA-based CAR T-cell therapies have been used to treat various B cell-mediated autoimmune diseases, including systemic lupus erythematosus (SLE), idiopathic inflammatory myopathy, systemic sclerosis, neuromyelitis optica spectrum disorder, myasthenia gravis and multiple sclerosis.^{23,104,105} Autoimmune diseases are characterized by a loss of immunological tolerance to self-antigens, partly due to deficient regulation of aberrant immune responses by regulatory T cells. In recent years, significant efforts have been directed toward using regulatory T cells to treat autoimmune diseases.

Several new CAR T-cell therapy concepts are currently being developed, with a potential to transform the treatment of autoimmune diseases. One promising approach involves the production and use of allogeneic CAR-expressing cells derived from T cells of healthy donors, cord blood or induced pluripotent stem cells.¹⁰⁶ To prevent alloreactive rejection or graft-versus-host

disease, allo-CAR T cells must be genetically edited, for example, by deleting endogenous TCR and MHC class I and II genes. At the same time, it is important to avoid NK cell-mediated destruction of CAR T cells after MHC class I and II deletion, which can be achieved with strategies such as co-expressing the NK cell-inhibitory ligand HLA-E. Initial data on the efficacy and tolerability of allogeneic CAR-expressing cells have been published in patients with acute leukemia.¹⁰⁶

CAR-based approaches to treat autoimmune diseases vary based on the method of transduction, type of treatment procedure, cellular sources of the product and method of target cell-killing.¹⁰⁷ Various transduction methods are used to introduce CAR genetic information into activated cells, including viral vectors, lipid nanoparticles (LNPs) and CRISPR–Cas9 gene editing. The type of procedure used can also vary. Auto- and allo-CAR T-cell therapies require *ex vivo* transduction of cells, whereas *in vivo* CAR T-cell therapy involves *in vivo* transduction of cells. Although CAR T cells are most commonly used in CAR-based strategies, other cellular sources are also under investigation, including $\gamma\delta$ T cells and NK cells. In addition to these various production strategies, new CAR constructs are being developed to selectively deplete antigen-specific B cells, such as CAAR cells,¹⁰⁸ expressing autoantigen associated with a truncated CAR, and chimeric autoantigen receptor T cells (CATCR).¹⁰⁹

CAR T-cell therapy in autoimmune diseases is already showing signs of clinical efficacy. A case report in 2021 repurposed approved CD19 CAR T cells to target B cells in a patient with SLE, a life-threatening autoimmune disease.¹¹⁰ In 2022, results from five patients were published, showing expansion of the CAR T cells *in vivo*, rapid depletion of B cells and a resolution of SLE symptoms and end-organ damage markers in all patients.¹¹¹ All five patients discontinued their immunosuppressive drug regimen and were declared to be in drug-free remission. Surprisingly, short-term follow-up revealed that naive B cells re-emerge a few months following CAR T cell infusion without the return of disease symptoms.

A recent report also implicated the potential of CAR T cells in the context of severe asthma.¹¹² In two separate animal models, CAR T cells targeted eosinophils and protected from asthma attack. This protection was durable, providing a potential advantage over antibody-based therapies for chronic allergic disorders with pathogenic eosinophils. Emerging evidence also suggests potential efficacy in type 1 diabetes using CAR T cells targeting antigen-presenting cells that activate autoimmune T cells.¹¹³ However, the resolution of diabetes was not durable.

CAR-NK cell therapy

NK cells can be genetically modified to produce a cell population with CAR-NK, which are able to recognize and destroy certain types of cells because of the presence of specific ligands on the surface of target cells. CAR-NK cells are currently used to treat oncological and neurodegenerative diseases.²⁴

CAR-NK cells have several advantages over CAR T cells. NK cells have spontaneous cytotoxic activity and can cause target cell death independently from the tumor antigens they produce, which is important for avoiding tumor cell immune detection.¹¹⁴ NK cells produce cytokines such as IFN- γ , IL-3 and GM-CSF, which differ from the spectrum of pro-inflammatory cytokines secreted by T cells capable of initiating CRS. It is also possible to use allo-NK cells from healthy donors as a source for obtaining cultures and storing them in cryopreserved form. Thus, it is believed that CAR-NK cell lines are more effective and safe for cancer treatment than CAR T cells.¹¹⁵

Between 2020 and 2023, the Food and Drug Administration (FDA) approved several applications for clinical trials of NK therapy drugs. NKGen Biotech has developed an innovative NK-cell based immunotherapy for patients with neurodegenerative and oncological diseases. Clinical studies of NK-cell efficacy and safety are currently being conducted in patients with Alzheimer's disease ([NCT04678453](#))¹¹⁶ and refractory solid tumors ([NCT05990920](#)).^{117,118} Furthermore, the cell therapy company Syena has developed a TCR-modified NK-cell product (NY-ESO-1 TCR/IL-15 NK) for the treatment of R/R multiple myeloma ([NCT06066359](#)),¹¹⁹ synovial sarcoma and myxoid/round cell liposarcoma ([NCT06083883](#)).¹²⁰

The drug CYNK-001 (Celularity Inc.) for the treatment of patients with AML, multiple myeloma and relapsed glioblastoma multiforme is the only drug based on cryopreserved allogeneic cells for NK-cell therapy, which includes CD56⁺ and CD3⁻ NK cells obtained from human placenta. These cells are not genetically modified. Clinical trials of the drug were conducted, including in patients with moderate manifestations of coronavirus infection during the COVID-19 pandemic ([NCT04310592](#),¹²¹ [NCT04365101](#),¹²² [NCT04489420](#),¹²³ [NCT04309084](#)¹²⁴ and [NCT05218408](#)¹²⁵).

Practical applications of CAR T-cell therapy in the clinic

CAR T-cell manufacturing

Despite different designs, the procedure for producing CAR T cells remains consistent across all CAR constructs. This involves collecting T cells from a patient (autologous) or a donor (allogeneic), followed by processing and preparation, including T-cell activation, genetic modification and large-scale expansion ([Figure 2](#)).

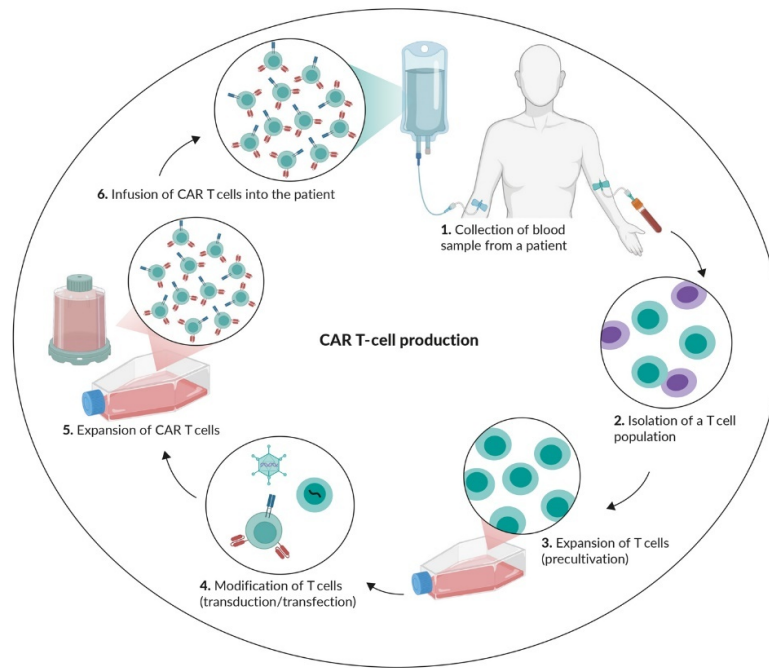


Figure 2. CAR T-cell production and clinical use.

The first step in CAR T-cell therapy is the collection of T cells, which are purified and genetically modified to express the engineered CARs. The engineered CAR gene is transduced into T cells using a variety of methods, including viral (lentivirus or retrovirus), non-viral (transposon or CRISPR/Cas9) and electroporation techniques.¹¹⁸ Once modified, these cells are expanded *in vitro* to achieve the desired quantity and quality. The final product is then infused into the patient's bloodstream, where CAR T cells recognize specific antigens, initiating their antitumor function.¹²⁶

Implementation of good manufacturing practice

CAR T cells for clinical use are classified as advanced therapy medicinal products and their production is regulated by regulations established by bodies such as the European Medicines Agency (EMA) and federal or regional authorities. To achieve therapeutic success and minimize risk, CAR T-cell production requires strict adherence to the Good Manufacturing Practice (GMP) standards.

GMP compliance offers a number of critical benefits. First, GMP ensures that cellular therapies meet stringent quality standards, which is critical given the slightest deviations can lead to serious consequences for patients. Second, GMP compliance guarantees product safety and purity, which includes monitoring production conditions, sterility and prevention of contamination. Third, GMP promotes reproducibility and process stability. This means that each production cycle will yield a homogeneous and high-quality product, which is especially important for therapy based on individualized cells.

GMP compliance is a prerequisite for obtaining regulatory approvals, which facilitate access to clinical trials and commercial markets. As a result, adherence to these standards not only increases the credibility of therapy but also contributes to its successful integration into clinical practice. Therefore, CAR T cell-based preparations should be produced in compliance with GMP and defined as powerful products manufactured safely according to standardized methods under carefully controlled, reproducible and tested conditions.

Regulatory and legal considerations in CAR T-cell therapy

A significant obstacle in the development of CAR T-cell therapy is the lack of comprehensive legal regulations for the application of such innovative treatment methods in most countries. In the legislation of countries such as the USA, European Union, Japan and South Korea, products for gene therapy are regulated as biological medicinal products (MPs).

In the Russian Federation, gene therapy MPs are subject to regulation under the Federal Law “On the Circulation of Medicinal Products”. The fundamental difference in the regulation of different types of gene therapy drugs in the Russian Federation lies in the types and sequence of stages of expert evaluation during state registration.¹²⁷ The CAR T-cell method can, to some extent, be classified under the regulations of Federal Law No. 61-FZ (dated April 12, 2010, as amended on August 2, 2019) “On the Circulation of Medicinal Products,” as it falls under the definition of biological gene therapy MPs.

In the Russian Federation, the production of pharmaceuticals, as well as biomedical cell products (BMCPs), is classified as a licensed activity. Thus, products for *in vivo* gene therapy are regarded as biological MPs, while those for *ex vivo* therapy are classified as BMCPs. It is also important to note that regulatory bodies in foreign guidelines differ in terms of both terminology and mechanisms for recognizing the results of drug development. For example, the term BMCP is not present in the regulatory framework of the Eurasian Economic Union (EAEU), but Decision No. 78 of the EAEU Council introduced the concept of “high-tech medicinal products” (HTMPs).

The global market for commercial CAR T cells

The clinical outcomes of CAR T-cell therapy have been very encouraging, and several commercial treatments are registered worldwide ([Table 3](#)). Currently available CAR T-cell products treat hematological cancers, including B-cell ALL, diffuse large B-cell lymphoma (DLBCL) and multiple myeloma. In March 2022, more than 30% of all approved ATMPs in the United Kingdom and the European Union were CAR T-cell therapies.¹²⁸

Table 3. Commercially available chimeric antigen receptor (CAR) T-cell therapies.

Product	Manufacturer	Target molecule	Indications	Agency and date of approval
Ttisagenlecleucel (Kymriah) ¹²⁹⁻¹³¹	Novartis (Switzerland)	CD19	ALL, DLBCL, HGBCL, FL	FDA and EMA (2018)
Axicabtagene ciloleucel (Yescarta) ^{10,132,133}	Kite Pharma Inc.(USA)	CD19	DLBCL, PMBCL, HGDCL, FL	FDA (2017), EMA (2018)
Brexucabtagene autoleucel (Tecartus) ^{12,15}	Kite Pharmaceuticals, Inc. (USA)	CD19	ALL, MCL	FDA and EMA (2020)
Lisocabtagene maraleucel (Breyanzi) ^{6,7}	Juno Therapeutics, Inc./ Bristol-Myers Squibb (USA)	CD19	DLBCL, HGBCL, HGBCL, PMBCL, FL	FDA (2021), EMA (2022)
Idecabtagene vicleucel (Abecma) ^{11,134}	Celgene Corporation/ Bristol-Myers Squibb (USA)	BCMA	Multiple myeloma	FDA and EMA (2021)
Ciltacabtagene autoleucel (Carvykti) ¹³⁵	Janssen Biotech, Inc. (USA)	BCMA	Multiple myeloma	FDA and EMA (2022)

ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicinal agency; FDA, Food and Drug Administration; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma.

Near-term prospects of CAR T-cell therapy in Russia

Currently, clinical trials of several CAR-T therapies are underway in Russia to treat various types of cancer, including leukemia and lymphoma. A study of a bispecific CD19/CD22 CAR T-cell drug ([NCT04499573](#)) is underway at the Federal Research Institute of Pediatric Hematology, Oncology and Immunology.³³ The purpose of this study is to evaluate the safety and efficiency of autologous CD19/CD22 CAR T lymphocytes in a cohort of pediatric and young adult patients with R/R B-lineage acute lymphoblastic leukemia. The Russian National Research Center for Hematology has launched a clinical trial to evaluate the safety, tolerability and efficacy of anti-CD19 CAR T cells in adult patients with B-cell ALL and non-Hodgkin lymphoma.¹³⁶ Russia is actively establishing state-of-the-art manufacturing facilities that comply with GMP standards to facilitate large-scale production of CAR T cells. A significant breakthrough in this field was achieved by the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation. Following a pharmaceutical inspection, it became the first institution in the Russian Federation to obtain a certificate authorizing it to manufacture medicinal products. This certificate confirms the Centre's adherence to the Eurasian Economic Union's (EAEU) GMP requirements and permits the production of Biomedical Cellular Products (BCPs). The Centre has commenced the practical application of BCPs in clinical practice for the treatment of CD19-positive lymphomas and leukemias. The establishment and development of domestic CAR T-cell manufacturing capabilities in Russia will contribute to reducing treatment costs and enhancing its accessibility for patients.

CAR T-cell therapy holds tremendous promise for improving oncological treatment outcomes in Russia. Ongoing preclinical and clinical research, the expansion of manufacturing capacities and governmental support are driving the rapid development and implementation of this therapeutic approach. As current challenges are overcome and CAR constructs are further optimized, it is anticipated that CAR T-cell therapy will become a valuable tool in the fight against cancer in Russia and beyond.

Economic and social prospects

While CAR T-cell therapy is highly effective, its cost remains high. This is largely due to the significant initial investment in the development and research aimed to identify the chimeric receptor and design of the viral vector for its delivery, as well as the subsequent production for clinical use.

Another factor that increases the final cost of CAR T-cell therapy is the mandatory use of GMP-certified materials, reagents and equipment during production. Continuous and reliable supply of serum-free media, cytokines and highly purified growth factors further increase expenses.

An important factor influencing the introduction of CAR T-cell therapy into clinical practice are preclinical studies on animal models with congenital or induced immunodeficiency. This requires special accredited specific pathogen-free (SPF) vivariums, which also contributes to the overall cost of the therapy. As a result, to reduce the cost of CAR T-cell therapy, it is necessary to develop and ensure a closed production cycle at one medical institution, which includes the production of a viral vector and biologically active components, such as cytokines and growth factors. Transport and logistics costs will also be minimized using such a production model.

According to a study by Gribkova et al. (2022),¹³⁷ the average costs of tisa-cel and axi-cel are \$475,000 and \$373,000, respectively. This represents only the drug costs and exclude other costs associated with the therapy. A similar result was obtained in the work of F. Zhu et al.,¹³⁸ which compared the costs of CAR T-cell therapy for the same two diseases. The authors showed that, for the cohort of patients with B-cell lymphomas, all considered costs were lower than those in the ALL group.

Hospitalization for treatment of severe side effects, such as CRS or ICANS, is a significant contributor to the high cost of CAR T-cell therapies. Selection of patients for CAR T-cell therapy to prevent CRS or ICANS involves a thorough review of the patient's medical history, including identification of risk factors such as high tumor burden, rapid tumor growth or a prior history of CRS or ICANS. Laboratory tests, including the assessment of IL-6 and tumor necrosis factor (TNF) cytokine levels, can help identify patients at high risk. Positron emission tomography (PET) scans can reveal high

tumor burden, which is also a risk factor for CRS. Identification of genetic mutations may further aid in recognizing patients predisposed to CRS or ICANS.

Considering the high expenses of the therapy, there are potential ways to reduce their cost. This may include lowering the cost of drugs, blood transfusions, procedures, laboratory tests, medical specialists and hospital treatment. One important approach to cost reduction is the production of CAR T cells directly in healthcare facilities, thereby minimizing external production costs.¹³⁹ Researchers in Germany reported that they have successfully implemented GMP-compliant CAR T-cell production at their clinic, significantly reducing costs.¹⁴⁰ The use of one system for the automated production of CAR T cells has further demonstrated its potential to reduce the total cost of these therapies. Spain's academic CAR T-cell therapy program, led by the Red Española de Terapias Avanzadas (RED TERAV), has developed high-quality treatments at a fraction of the cost of commercial products. For example, the Hospital Clínic de Barcelona produces CAR T-cell therapies for approximately €89,000 per patient, compared to nearly €400,000 for commercial alternatives, demonstrating the feasibility of producing effective and safe CAR T-cell treatments domestically.¹⁴¹

A further opportunity to reduce the cost of CAR-T-therapy is in the development of allo-CAR T cells, which eliminates the need of producing autologous drugs individually for each patient. Companies such as Cellectis and Servier are currently developing therapies based on allo-CAR T cells ([NCT03190278](#)¹⁴² and [NCT02808442](#)¹⁴³). These ready-to-use CAR T-cell therapies can be produced in series.

The cost of CAR T-cell therapy can also be reduced by using automated systems and the transfer of technologies from other countries. Finally, *in vivo* T-cell reprogramming can potentially reduce treatment costs by eliminating the costly production of *ex vivo* T cells. A study by Pfeiffer et al. (2018)¹⁴⁴ using a mouse model demonstrated that auto-CAR CD19 T cells can be obtained directly *in vivo* using the CD8-LV lentivirus vector.

Conclusions

CAR T-cell therapy has led to significant advances in the treatment of hematological malignancies. Due to its high efficacy, CAR T-cell therapy is well suited for widespread clinical use. However, the costs associated with this therapy are still too high.

In particular, CAR T-cell biotechnology requires high material costs, namely automation of the technological process, the need to include GMP conditions in the production process and the “point of care” strategy, which suggests their possible implementation only in large scientific centers. It is

necessary to make CAR T-cell therapy of the future significantly cheaper by using all available methods. According to the literature, the main costs are associated with CAR T-cell products themselves and the relief of adverse reactions.

Perhaps in the future, specialized medical institutions will be able to independently produce drugs for CAR T-cell treatment at lower prices, which will help reduce general costs.

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Conflict of interest

The authors have declared that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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