Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Review

CAR-T cell therapy for rheumatoid arthritis: current status and molecular insights

Alexander V. Blagov[1*], Elizaveta M. Pleshko[1], Olga N. Maltseva[2], Alikhan Z. Asoyan[1], Alessio L. Ravani[3], Alexander N. Orekhov[1,4]

[1] *Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Moscow 125315, Russia*
[2] *Institute of Experimental Medicine, 12, Academician Pavlov Street Street, 197022, Saint Petersburg, Russia*
[3] *Institute for Atherosclerosis Research, Osennyaya Street 4-1-207, 121609 Moscow, Russia*
[4] *Faculty of Biology and Biotechnology, National Research University Higher School of Economics, 33, Profsoyuznaya Street, Building 4, 117418 Moscow, Russia*

Article Info

Article history:

Received: March 19, 2025
Accepted: May 14, 2025
Published: June 30, 2025

Use your device to scan and read the article online

Abstract

Chimeric antigen receptor (CAR)-T cell therapy, a breakthrough in hematological cancer treatment, is now being explored for autoimmune diseases like rheumatoid arthritis (RA). RA, characterized by chronic joint inflammation and autoantibody production, presents a compelling target for CAR-T cell therapy due to its potential for precise targeting of aberrant immune cells and restoration of immune tolerance. This review analyzes current strategies in CAR-T cell therapy for RA, focusing on molecular mechanisms and clinical implications. We discuss approaches such as CD19-targeted B cell depletion, simultaneous targeting of B cells and memory plasma cells, and the use of chimeric autoantibody receptors (CAARs) to target specific autoantigens. Furthermore, we explore the latest advancements in CAR-T cell engineering, including novel costimulatory domains, dual-targeting strategies, and the development of regulatory CAR-T cells (CAR-Tregs). This review provides insights into the efficacy and safety of CAR-T cell therapy for RA, highlighting its potential to revolutionize clinical applications and future directions in the field.

Keywords: CAR-T therapy, Autoimmune disease, Rheumatoid Arthritis, T cells, Molecular mechanisms, Cell therapy.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the joints, leading to progressive joint damage and disability [1]. The pathogenesis of RA involves a complex interplay of genetic, environmental, and immunological factors, resulting in the dysregulation of immune responses and the breakdown of self-tolerance. Key molecular mechanisms implicated in RA include the aberrant activation of T and B lymphocytes, the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and the dysregulated activity of intracellular signaling pathways like the JAK-STAT pathway. Post-translational modifications, such as citrullination, play a significant role in the pathogenesis of RA by generating neo-antigens that drive autoantibody production [2, 3].

Conventional treatments for RA, including disease-modifying antirheumatic drugs (DMARDs) and biologic agents, aim to suppress inflammation and alleviate symptoms. However, many patients do not achieve sustained remission or experience adverse effects from these therapies. Therefore, innovative therapeutic strategies are needed to target the underlying molecular mechanisms of RA and restore immune homeostasis [4].

Chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising approach for treating hematological malignancies and is now being explored for autoimmune diseases, including RA. CAR-T therapy involves genetically engineering a patient's T cells to express a synthetic receptor that redirects their cytotoxic activity towards specific target cells. The CAR molecule typically consists of an extracellular antigen-binding domain (usually a single-chain variable fragment, scFv), a hinge region, a transmembrane domain, and intracellular signaling domains. First-generation CARs contained only the CD3ζ signaling domain, while second-generation CARs incorporate additional costimulatory domains such as CD28 or 4-1BB to enhance T cell activation, proliferation, and persistence. Third-generation CARs combine multiple costimulatory domains, and fourth-generation

* Corresponding author.
E-mail address: al.blagov2014@gmail.com (A. V. Blagov).
Doi: http://dx.doi.org/10.14715/cmb/2025.71.6.11

CARs (also known as TRUCKs) are engineered to secrete cytokines or express other effector molecules to enhance their therapeutic efficacy. Recent advances in CAR-T cell engineering include the development of dual-targeting CARs, which recognize multiple antigens simultaneously, and regulatory CAR-T cells (CAR-Tregs), which suppress immune responses and promote tolerance. The manufacturing of CAR-T cells involves several steps, including T cell isolation, activation, transduction with a viral vector encoding the CAR gene, expansion, and infusion back into the patient. Techniques such as flow cytometry, quantitative PCR, and ELISA are used to monitor CAR-T cell phenotype, expression, and function during the manufacturing process and after infusion [5, 6].

The underlying causes and mechanisms of the disease are not entirely clear, but research suggests that the process of citrullination may play a role. The presence of anti-citrullinated protein antibodies in the blood is highly specific for RA and is associated with the severity and progression of the disease [7, 8]. RA is a gradually progressive disease, and without proper treatment, it can lead to irreversible joint damage, affecting physical and emotional well-being, as well as increased mortality due to complications and comorbidities [9-11].

Advances in pharmaceuticals have led to new therapeutic approaches for the treatment of RA, but the lack of understanding of the molecular mechanisms is a challenge in finding a cure. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and targeted synthetic DMARDs are available to maintain joint function, but their use is associated with many significant side effects and requires careful monitoring [12]. Targeted synthetic DMARDs, such as JAK inhibitors, have shown promise as a new class of drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are also used as adjunctive therapies to relieve inflammation and pain. The goal of RA therapy is to achieve a state of remission and minimize any potential harmful side effects [13].

Despite the availability of treatment options, a significant number of RA patients still do not respond to current therapies. Thus, the development of new treatments and the adoption of a more personalized treatment approach are becoming very important. CAR-T therapy involves genetically modifying a patient's T cells to express chimeric antigen receptors (CARs) that target specific antigens. CD19 is the most studied target for CAR-based therapy. It is expressed in normal and neoplastic B cells and is maintained at high levels throughout all stages of B cell development [14]. CD19+ malignancies were the first cancers to be eliminated using CAR-engineered human T cells administered intravenously to mice. Various CD19 CARs successfully eliminated B cell tumors, leading to ongoing clinical trials and FDA approval. Similarly, B cell depletion may also be a promising therapeutic strategy for the treatment of autoimmune diseases. Moreover, other strategies such as limited B cell depletion by targeting self-antigens, dual targeting and engineering of regulatory T cells (Tregs) are also being explored [15].

This review aims to analyze the current status of CAR-T therapy in RA, focusing on the molecular mechanisms, clinical applications, and future directions of this innovative therapeutic approach. We will discuss the different CAR-T cell strategies being developed for RA, including targeting B cells via CD19, simultaneously targeting B cells and plasma cells, and targeting specific autoantigens using chimeric autoantibody receptors (CAARs). Additionally, we will explore the latest advances in CAR-T cell engineering and their potential to improve the efficacy and safety of CAR-T therapy for RA.

2. Mechanisms and advances in CAR-T therapy: From molecular design to clinical application

Chimeric antigen receptors (CARs) are modified receptors that alter the specificity and activity of T lymphocytes and other immune cells by fusing the variable regions of high-affinity monoclonal antibodies with intracellular signaling components of the T cell receptor (TCR) complex. Their modulatory structure consists of four domains: ligand-binding, spacer, transmembrane, and cytoplasmic domains [16]. CARs bind antigens through an extracellular portion consisting of a ligand-binding domain and a spacer, typically constructed using single-chain variable fragments (scFv) derived from antibodies, library Fab fragments, or natural ligands. Most commonly used scFvs can function autonomously or as modular units for CAR T cell therapy, determining the ability of modified T cells to recognize and target desired antigens [17]. CAR-mediated recognition is independent of the major histocompatibility complex, allowing it to overcome tolerance to self-antigens and target any chosen antigen expressed on the cell surface. CARs also control T cell growth and persistence, influencing both efficacy and safety. Linking CARs to co-stimulatory ligands, chimeric co-stimulatory receptors, or cytokines can improve T cell efficacy, specificity, and safety [18].

T cells expressing first-generation CARs lacking a costimulatory domain are insufficient for T cell activation and show limited efficacy in vivo. Second-generation CARs have been developed to address this issue by adding a costimulatory domain, typically CD28 and 4-1BB (CD137). Costimulatory domains provide additional signals upon antigen recognition that are critical for enhancing T cell proliferation, cytokine release, cytotoxic activity, memory formation, and persistence [19]. CAR T cells with the intracellular CD28 costimulatory domain demonstrated significantly higher proliferation and persistence compared to cells lacking a costimulatory domain. Moreover, CAR-T cells containing the CD28 domain showed better early growth and cytotoxic activity than cells containing the 41BB costimulatory domain, which showed better long-term survival [20]. Third-generation CARs include multiple costimulatory domains, while fourth-generation CARs are engineered to express additional inducible transgene elements, typically for inducible cytokine secretion, to improve T cell function and reduce off-target toxicity [21].

Personalized clinical manufacturing of CAR-T cells involves several steps followed by quality control testing throughout the process. The first step is the collection of white blood cells from the patient (autologous) or donor (allogeneic) from peripheral blood using leukapheresis, where only white blood cells are extracted and the remaining blood products are returned to the circulation [22]. Second, T cells are augmented, separated and washed with leukapheresis buffer [23]. Third, at the CD4/CD8 composition level, T cell subsets are separated using specific conjugates or markers with antibody-coated beads. The isolated cells are then cultured and activated with puri-

fied allogeneic or autologous APCs or by administration of beads coated with anti-CD3 or anti-CD28 monoclonal antibodies (or both together with feeder cells and interleukins) [24]. IL-2 is the most common growth factor used to induce rapid T cell expansion . A recent study reported that a cytokine cocktail of IL-2, IL-7 and IL-15 induced better expansion of CD4 and CD8 CAR-T cells [25]. Fourth, various methods have been considered to deliver nucleic acids into the derived T cells. Generally, delivery of foreign genetic material (RNA or DNA) into human cells can be accomplished using viral or non-viral vectors [26]. The fifth step is to expand the CAR-T cells using bioreactors that help the cells divide and express the CAR on the cell surface. Finally, when the cells reach the clinically required volume, they are reintroduced into the patient as a therapeutic agent [27].

2.1. Comparison of CAR-T cell generations

The evolution of CAR-T cell therapy is marked by distinct generations, each designed to address limitations in efficacy and safety. As shown in Table 1, first-generation CARs lacked costimulatory domains, leading to limited persistence and efficacy. Second-generation CARs incorporated single costimulatory domains like CD28 or 4-1BB, enhancing T cell activation and survival. Third-generation CARs combined multiple costimulatory domains to further improve T cell function, while fourth-generation CARs, known as TRUCKs, were engineered to express inducible cytokines, enhancing their therapeutic impact [5].

2.2. Molecular mechanisms and signaling pathways

The efficacy of CAR-T cell therapy is rooted in its molecular mechanisms. Table 2 outlines the key components involved in CAR-T cell signaling, including the CD3ζ domain for TCR-like activation and costimulatory domains such as CD28 and 4-1BB. These domains enhance T cell proliferation, survival, and cytotoxic activity through pathways like PI3K-AKT and NF-κB. Understanding these mechanisms is crucial for optimizing CAR design and improving therapeutic outcomes [28].

3. The most promising developments in the field of CAR - T therapy today

3.1. Anti-fluorescein isothiocyanate (FITC) CAR T-cell therapy

In 2020, a proof-of-concept study was published that utilized universal anti-fluorescein isothiocyanate (FITC) CAR T cells that were fused with FITC-labeled RA-immunodominant peptides. This study demonstrated that multiple hybridoma cell strains could be targeted and eliminated by anti-FITC CAR T cells via lysis, depending on the availability of the corresponding FITC-labeled antigen peptides, offering a solution to the diverse nature of RA treatment with CAR T cells. This approach aimed to specifically eliminate different types of autoreactive B cell subsets, providing a more selective and permanent treatment option for RA patients [29].

Moreover, this study also tested the off-target effects of anti-FITC CAR T cells and found no significant toxicity to FcγR+Raw264.7 cells unless excess specific antibody was added. These results suggest that off-target toxicity is unlikely and is primarily caused by low-avidity antibodies alone, which constitute a small fraction of total immunoglobulin G. Moreover, no significant cytotoxic activity was observed for the control groups, demonstrating the high selectivity of this approach and suggesting its potential to target pathogenic autoimmune cells without affecting protective immunity [29].

The main limitation of the study is that it demonstrated the elimination of autoreactive B cells only in vitro and had no evidence of therapeutic effects of the approach in vivo . Another concern is the stability of the peptide mediator [29]. This proof-of-concept study still represents a significant step forward in the field of targeted treatment of systemic autoimmune diseases and opens up opportunities for additional research and development in this area.

3.2. CD4+ targeted CAR T cell therapy

One study used an approach to treating autoimmune diseases that targets only the pathogenic CD4+ T cells responsible for autoimmune disease pathology by incorporating HLA-DRB1×01:01 (DR1) and a model autoantigen as part of the CAR molecular structure. The resulting DR1 CAR T cells lyse CD4+ T cells in an antigen-specific manner, targeting only cells expressing a DR1-restricted TCR specific for an antigen peptide. Studies in a humanized mouse model of RA using DR1-collagen type II (CII) T cells showed that they effectively identify and lyse CII-specific CD4+ T cells and reduce the T cell autoimmune response and RA severity in vivo. DR1 CAR T cells also reduce the severity of RA as well as the B cell autoantibody response [30]. The specificity of CAR T cells can be repro-

Table 1. Comparison of CAR-T cell generations [5].

Generation	Structural Features	Advantages	Limitations
First-Gen	CD3ζ signaling domain	Simple design	Limited efficacy, poor persistence
Second-Gen	CD3ζ + CD28 or 4-1BB	Enhanced proliferation and persistence	Potential for excessive cytokine release
Third-Gen	Multiple costimulatory domains (e.g., CD28 + 4-1BB)	Improved T cell activation and survival	Increased complexity, potential for toxicity
Fourth-Gen (TRUCKs)	Inducible cytokine secretion	Enhanced tumor microenvironment modulation	Complexity in design and regulation

Table 2. Molecular mechanisms and signaling pathways [28].

Component	Function	Signaling Pathway
CD3ζ Domain	TCR-like signaling activation	PI3K-AKT, NF-κB
CD28 Costimulation	Enhanced T cell activation and proliferation	PI3K-AKT, NF-κB, mTOR
4-1BB Costimulation	Long-term survival and persistence	NF-κB, PI3K-AKT
CAR-T Cell Exhaustion	Reduced functionality due to chronic antigen exposure	PD-1/PD-L1 interaction, TGF-β signaling

grammed by altering the antigen peptide sequence, which is an advantage for its use in autoimmune diseases. These results suggest that CAR T cells based on Antibodies recognizing major histocompatibility complex (MHC) class II may have potential for treating autoimmune diseases in an antigen-specific manner [31].

DR1 CAR T cells were found to retain their cytolytic function for 90 days in culture, even when expressing markers associated with CD8 T cell exhaustion. However, although they showed function in vivo, they failed to persist as a memory phenotype due to the low frequency of target cells and the lower affinity of DR1 CAR for the target TCR. The frequency of antigen-stimulated CD4+ T cells was found to be low and the MHC class II binding affinity of the TCR was lower than that of antibodies. Continuous stimulation of DR1 CAR T cells via DR1 CAR was insufficient to maintain the cells in culture for a long time. Thus, novel signaling domains for CARs have been developed to improve clinical efficacy, which may be beneficial for DR1 CAR function [29].

3.3. Dual targeting for optimal treatment of autoimmune diseases

Early in the disease course, CD19-based therapy can prevent the accumulation of autoreactive plasma cells, but later memory plasma cells can accumulate and lead to persistent autoantibody production despite B cell depletion [32]. CD19, one of the earliest and most specific B-lineage cell markers, may not be expressed on all plasma cells. Plasma cells express CD19 heterogeneously, and memory plasma cells are part of the CD19-negative plasma cell population [33]. In addition, the cytokine B-cell activating factor (BAFF), a member of the TNF superfamily, plays a critical role in promoting the survival and function of B cells and memory plasma cells [34]. BAFF can bind to the BAFF receptor (BAFFR), the B-cell transmembrane activator and maturation antigen (BCMA), and these receptors play a distinctive role in regulating B-cell function [35]. Overexpression of BAFF leads to the development of autoreactive B cells and exhibits autoimmune-like symptoms in mice, highlighting the significance of impaired BAFF expression in autoimmunity [36]. Moreover, autoimmune diseases are associated with persistently high BAFF levels, making inhibition of BAFF signaling a promising therapeutic approach. Furthermore, BCMA has been shown to be essential for the survival of plasma cells and memory plasma cells. Therefore, targeting both B cells and memory plasma cells may be more effective, leading to complete clearance of autoantibodies. By combining different types of CD19 CARs, such as BAFF, BCMA or BAFFR, the efficacy of CAR-T cells can be improved. This can be achieved by engineering two pools of T cells, each expressing different CARs, or by incorporating multiple antigen recognition domains into a single CAR construct, called a composite CAR (cCAR) [37]. An early phase 1 clinical trial has recently begun to evaluate the efficacy of CD19-BAFF CAR-T cell therapy in autoimmune diseases. However, several clinical trials have begun to investigate the safety and efficacy of CD19-BCMA CAR-T cell infusion in various autoimmune conditions.

3.4. Engineering of chimeric autoantibody receptors

The use of chimeric autoantibody receptors (CAAR) T cells to precisely target B cell subsets specific for an autoantigen and overcome complete B cell depletion is an emerging area of research. For autoimmune diseases caused by specific autoantibodies produced by individual B cell clones, these therapeutic T cells can be genetically engineered with a CAR targeting a specific autoantibody antigen on the autoreactive cells to suppress or modulate the immune response without affecting healthy tissue. CAAR-Ts provide a more targeted and personalized approach compared to traditional immunosuppressive therapy. Similar to CD19-specific CAR-T cells, CAAR-Ts function similarly by specifically targeting autoantigens, resulting in the destruction of pathological immune cells. Furthermore, natural killer (NK) cells expressing CAAR can also specifically remove pathological B cells in vitro and could potentially be investigated in future clinical trials [38]. Preclinical data have shown encouraging potential for CAAR-T cells in the treatment of a number of autoimmune diseases [39].

3.5. Engineered Tregs (CAR-Tregs)

Regulatory T lymphocytes (Tregs) are a small heterogeneous subset of T lymphocytes that play a vital role in maintaining immunological balance. Tregs suppress the immune response by limiting the ability of antigen-presenting cells to initiate an adaptive immune response, inducing apoptosis of effector T cells, disrupting metabolic pathways, and releasing anti-inflammatory cytokines [40]. Dysregulation of these processes can lead to Treg dysfunction, which can also manifest as activation defects. This creates an imbalance in the ratio between resting and activated Tregs, promoting autoimmunity. Moreover, Treg levels or functional changes are associated with many autoimmune disorders, and decreased Treg frequency has been identified in several autoimmune diseases, which may be associated with disease severity [41]. Modification of low frequency or dysfunction of Tregs is considered a new approach to the treatment of autoimmune diseases, with the main goal of reducing inflammation, facilitating tissue repair and restoring immune tolerance. Phase 1 clinical trials have shown that infusion of autologous ex vivo -expanded Tregs is safe and well tolerated, without significant side effects. Antigen-specific Tregs have demonstrated greater efficacy and reduced risk of general immunosuppression compared to polyclonal Tregs in preclinical trials, indicating a potential therapeutic strategy for the future [42]. Tregs have been found to have impaired function or numbers in RA patients and may therefore be used as a promising therapeutic target [43]. A phase I clinical trial is currently underway to evaluate the safety and efficacy of autologous CAR-Treg cell-based therapy for the treatment of RA. This therapy specifically targets citrullinated proteins accumulated in disease-related inflamed tissue to reduce inflammation and restore immune tolerance. Overall, further studies are needed to investigate the efficacy of CAR-Tregs, identify disease-specific targets, improve the manufacturing process by identifying suitable sources for Treg isolation, and improve marker selection and proliferative capacity [44].

4. Problems of the effectiveness and safety of current CAR - T therapy and ways to solve them

4.1. Immunosuppression

The duration of optimal CAR-T cell activity in the treatment of autoimmune diseases is a matter of debate. In

cancer treatment, long-term maintenance of CAR-T cells is beneficial to maintain ongoing immune monitoring. However, in autoimmune diseases, prolonged CAR-T cell activity may lead to immunosuppression or organ damage due to excessive elimination of normal immune cells. Therefore, it may be preferable to have limited or controlled expression of CAR-T cells in the treatment of autoimmune diseases to minimize potential long-term toxicity [45]. Future strategies should therefore introduce molecular switches or CAR constructs with shorter half-lives that are expressed transiently or degraded after a certain period to reduce long-term immune suppression. The introduction of molecular switches may help manage immune-mediated toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is the most common and potentially life-threatening inflammatory reaction caused by rapid activation and expansion of CAR-T cells. This can lead to excessive cytokine release, resulting in symptoms such as high fever, hypotension, and in rare cases, multiple organ failure. ICANS is related to CRS but presents with distinct symptoms such as confusion, seizures, and cerebral edema. CRS often precedes neurotoxic events, suggesting a temporal and mechanistic link [46]. Suicide switches provide a way to rapidly kill CAR-T cells in cases of severe toxicity, ensuring safety. On/off switches offer external control by activating CAR expression only in the presence of a specific drug, allowing precise titration of therapy based on patient response. Additionally, logic systems such as AND and NOT improve targeting specificity by activating CAR-T cells only when specific conditions are met, thereby minimizing damage to healthy tissue. These innovations improve safety and efficacy, making CAR-T therapy more adaptable to complex diseases such as autoimmunity [47].

Shorter half-life CAR constructs, such as messenger RNA (mRNA)-based CAR T cells, offer an alternative strategy to achieve transient and limited CAR expression, providing a more controlled treatment. Moreover, this also allows for in vivo reprogramming of T cells , which favors this approach due to faster production and lower cost [48].

4.2. Secondary malignancy

So far, CAR T cell therapy has shown encouraging results, demonstrating feasibility, tolerability, and efficacy in the treatment of autoimmune diseases. However, longer-term evaluations are needed before they are adopted for widespread clinical use. The FDA recently reported T cell malignancies in patients treated with autologous CAR T cell targeting BCMA or CD19. The risk of secondary malignancy is a concern for all approved products in this category. Although the benefits of these products still outweigh the potential drawbacks of their approved use, the FDA is investigating the potential for serious consequences such as hospitalization and death and is considering regulatory actions [49]. Therefore, the safety of autoimmune trials should be at a higher level. The choice of an adequate cell engineering strategy for the treatment of autoimmune diseases depends on the pathogenesis of the underlying disease, its severity and duration, and associated conditions. Furthermore, given the complex and heterogeneous nature of autoimmune diseases, further study of other targets as well as the efficacy and safety of multi-target interventions is needed [50].

4.3. Production and cost

One factor contributing to the high cost of CAR T cell therapy is the expense associated with its production and administration. The cost does not cover the costs associated with manufacturing the drug, managing potential long-term side effects, or continuing other lines of treatment after relapse. Leukapheresis is the first step in a multi-step process to create CAR T cells. T cells are then produced through genetic engineering, which involves the use of viral vectors or non-viral methods to add CAR expression. Finally, the transformed T cells are expanded in a controlled environment [51]. Each of these procedures may require specialized instruments, knowledgeable personnel, and rigorous quality assurance protocols. Local cell manufacturing facilities that produce experimental items face higher production costs due to the continuing high cost of reagents and lentiviral vectors that are often associated with individual items or product groups. This contrasts with commercial manufacturers that produce cell therapies on a large scale. The individualized nature of autologous CAR-T cell therapy increases manufacturing costs. Additional logistical costs for the apheresis procedure, cryopreservation, transportation of patient-derived cells to specialized manufacturing facilities, and return of the finished therapeutic product to the clinical site are also imposed by patient-specific characteristics [52]. Therefore, alternative strategies are being explored to address these issues. Decentralized or on-site manufacturing using a fully automated closed system can significantly shorten the manufacturing process and reduce the cost of therapy [53].

5. Discussion

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial inflammation, autoantibody production, and progressive joint destruction. While current therapies, such as DMARDs and biologics, aim to suppress inflammation, they often fail to restore immune tolerance or address the root molecular drivers of disease. CAR-T cell therapy, initially pioneered in oncology, has emerged as a groundbreaking strategy to recalibrate immune dysregulation in RA through precise targeting of pathogenic immune cells. This section explores the molecular mechanisms, clinical implications, and future directions of CAR-T therapy in RA, contextualized within the framework of cellular and molecular biology [54, 55].

RA is a gradually progressive disease and without proper treatment it can lead to irreversible joint damage, affecting physical and emotional well-being, and increased mortality due to complications and comorbidities [56]. Despite the availability of treatments, a significant number of RA patients still do not respond to current medications. Thus, the development of new treatments and the adoption of a more personalized treatment approach are becoming very important [57]. The concept of chimeric antigen receptor (CAR) T-cell therapy originated from cancer immunotherapy and was quickly adapted and developed for the treatment of autoimmune diseases, including RA. CAR T cell therapy offers significant advantages over traditional treatments because it targets the root cause of the disease: autoreactive immune cells. Unlike traditional treatments that suppress the immune system in general, CAR T cell therapy has the potential to specifically target and eliminate pathogenic immune cells that cause an autoimmune response. This precise approach helps preserve overall

immune function, reducing the risk of infections and other side effects. In addition, CAR T cells can be engineered with molecular switches that allow their activity to be controlled in real time, improving both safety and efficacy [31]. This strategy offers the potential for long-term remission by directly targeting the underlying drivers of autoimmunity rather than simply managing symptoms. Undoubtedly, CAR T cell therapy is a compelling therapeutic approach for a variety of autoimmune diseases, although there are still unsolved issues that need to be addressed for widespread clinical use.

5.1. Molecular mechanisms of CAR-T action in RA

CAR-T cells are engineered to recognize specific antigens on autoreactive immune cells, bypassing MHC restrictions and enabling direct elimination of pathogenic B cells, plasma cells, or cytokine-producing T cells. Key molecular components include:

- **Antigen-binding domains:** Single-chain variable fragments (scFvs) derived from monoclonal antibodies enable CAR-T cells to bind surface antigens such as CD19 (B cells), CD138 (plasma cells), or citrullinated peptides (RA-specific neoepitopes).
- **Costimulatory signaling domains:** Incorporation of CD28 or 4-1BB enhances T cell activation, proliferation, and persistence. For instance, CD28 promotes rapid cytotoxic activity, while 4-1BB supports long-term survival via NF-κB and PI3K-AKT pathways.
- **Regulatory CAR-T cells (CAR-Tregs):** Engineered to express immunosuppressive cytokines (e.g., IL-10, TGF-β) or Fas-ligand, CAR-Tregs modulate inflammatory microenvironments and restore immune tolerance.

In preclinical RA models, CD19-targeted CAR-T cells deplete autoreactive B cells, reducing autoantibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). Similarly, chimeric autoantibody receptor T cells (CAAR-T) targeting autoantigens such as citrullinated vimentin or collagen demonstrate selective elimination of autoantibody-producing B cells without broad immunosuppression [29, 58].

5.2. Engineering innovations and clinical translation

Recent advances in CAR-T engineering address RA-specific challenges:

- **Dual-targeting CARs:** Simultaneous targeting of CD19 and BCMA enhances efficacy against both B cells and long-lived plasma cells, critical drivers of RA pathogenesis.
- **Inducible safety switches:** Caspase-9 or HSV-TK "suicide genes" enable controlled CAR-T cell depletion to mitigate cytokine release syndrome (CRS) or off-target effects.
- **Armored CAR-T cells:** Secretion of anti-inflammatory cytokines (e.g., IL-4, IL-35) counteracts synovial inflammation while preserving tissue homeostasis.

Clinical trials in refractory RA patients highlight sustained remission and reduced Disease Activity Score-28 (DAS-28) following CAR-T therapy. For example, early-phase studies report >50% reduction in serum autoantibody titers and synovial inflammation within 3–6 months post-infusion. However, challenges persist, including CAR-T cell exhaustion due to chronic antigen exposure and limited trafficking to joint tissues [59].

5.3. Challenges in cellular persistence and safety

While CAR-T therapy offers durable responses, molecular hurdles remain:

- **Tumor microenvironment (TME) resistance:** Synovial hypoxia, TGF-β, and PD-L1 expression impair CAR-T cell infiltration and function. Strategies like engineering hypoxia-resistant CAR-T cells or co-administering checkpoint inhibitors are under investigation.
- **CRS and neurotoxicity:** Excessive IFN-γ and IL-6 release can trigger systemic inflammation. Tocilizumab (IL-6R antagonist) and anakinra (IL-1 blocker) are used prophylactically, while next-gen CARs incorporate self-limiting cytokine circuits.

Manufacturing complexity: Autologous CAR-T production faces scalability issues. Allogeneic "off-the-shelf" CAR-T cells, generated via CRISPR-Cas9 editing to eliminate TCR and HLA expression, aim to reduce costs and delays [60].

5.4. Future directions in CAR-T cell biology

Emerging molecular strategies aim to optimize CAR-T therapy for RA:

1. **CAR-Tregs for immune tolerance:** Engineering Tregs to express CARs targeting synovial dendritic cells or citrullinated antigens could suppress localized inflammation while preserving systemic immunity.
2. **Gene-editing synergies:** Combining CAR-T cells with CRISPR-mediated knockout of autoimmune-associated genes (e.g., PTPN22, HLA-DRB1) may enhance therapeutic precision.

Biomaterial-assisted delivery: Hydrogel-based CAR-T cell carriers improve retention in joint tissues, enabling localized action and reducing systemic toxicity [61].

5.4.1. Manufacturing process of CAR-T cells

The clinical application of CAR-T cell therapy involves a complex manufacturing process. As detailed in Table 3, this process begins with leukapheresis to collect peripheral blood mononuclear cells (PBMCs), followed by T cell isolation and activation. Gene transfer using viral vectors introduces the CAR construct into T cells, which are then expanded in bioreactors. Quality control measures ensure the viability, potency, and CAR expression of the final product before reinfusion into patients [62].

Table 3. Manufacturing process of CAR-T cells [62].

Step	Description	Techniques Used
1. Leukapheresis	Collection of PBMCs	Centrifugation, cell separation
2. T Cell Isolation	Enrichment of T cells	Magnetic bead separation, flow cytometry
3. Gene Transfer	Introduction of CAR gene	Viral vectors (lentivirus, retrovirus), electroporation
4. Expansion	Cultivation and growth of CAR-T cells	Bioreactors, IL-2 supplementation
5. Quality Control	Testing for CAR expression, viability, and potency	Flow cytometry, PCR, functional assays

Table 4. CAR-T therapy in autoimmune diseases [63].

Disease	Target Antigen	CAR-T Strategy	Clinical Outcomes
Rheumatoid Arthritis (RA)	CD19, autoantigens	Depletion of autoreactive B cells	Reduced autoantibody production, improved joint function
Multiple Sclerosis (MS)	CD4+ T cells	Suppression of autoreactive T cells	Reduced disease activity, improved neurological function
Type 1 Diabetes (T1D)	CD8+ T cells targeting islet cells	Prevention of β-cell destruction	Preservation of insulin production

5.4.2. CAR-T therapy in autoimmune diseases

CAR-T cell therapy is being explored for various autoimmune diseases, offering a promising approach to selectively target pathogenic immune cells. Table 4 highlights the application of CAR-T therapy in diseases such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes. For RA, targeting CD19-positive B cells has shown potential in reducing autoantibody production. In MS, suppressing autoreactive T cells aims to reduce disease activity. Similarly, in T1D, CAR-T cells are designed to prevent β-cell destruction, preserving insulin production [63].

6. Conclusion

In conclusion, CAR-T cell therapy offers a transformative approach for treating autoimmune diseases like rheumatoid arthritis by precisely targeting pathogenic immune cells and autoantigens. This strategy leverages the molecular engineering of T cells to restore immune balance, potentially overcoming the limitations of conventional therapies. While preliminary studies demonstrate promising outcomes, further research is essential to elucidate the clinical efficacy, safety, and long-term effects of CAR-T therapy. Key challenges include optimizing CAR design, dosing regimens, and delivery methods, as well as addressing technical and economic barriers. By integrating insights from cellular and molecular biology, CAR-T therapy holds significant potential to revolutionize the management of autoimmune diseases, providing patients with targeted, durable, and safe therapeutic options.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal roles in study design, work, statistical analysis and manuscript writing.

Funding

This study was supported by the Russian Science Foundation, Grant#25-25-00364.

References

1. Klareskog L, Rönnelid J, Saevarsdottir S, Padyukov L, Alfredsson L (2020) The importance of differences; On environment and its interactions with genes and immunity in the causation of rheumatoid arthritis. J Intern Med 287 (5): 514-533. doi: 10.1111/joim.13058
2. Batsalova T, Dzhambazov B (2023) Significance of Type II Collagen Posttranslational Modifications: From Autoantigenesis to Improved Diagnosis and Treatment of Rheumatoid Arthritis. Int J Mol Sci 24 (12). doi: 10.3390/ijms24129884
3. Zhao W, Shi S, Jian A, Wang Y, Zhao Q (2023) Evaluating the expression level of genes related to autophagy in rheumatoid arthritis patients. Cell Mol Biol (Noisy-le-grand) 69 (9): 229-233. doi: 10.14715/cmb/2023.69.9.35
4. Kim ES, Keam SJ (2021) Filgotinib in Rheumatoid Arthritis: A Profile of Its Use. Clin Drug Investig 41 (8): 741-749. doi: 10.1007/s40261-021-01055-0
5. Levin-Piaeda O, Levin N, Pozner S, Danieli A, Weinstein-Marom H, Gross G (2021) The Intracellular Domain of CD40 is a Potent Costimulatory Element in Chimeric Antigen Receptors. J Immunother 44 (6): 209-213. doi: 10.1097/cji.0000000000000373
6. Amatya C, Pegues MA, Lam N, Vanasse D, Geldres C, Choi S, Hewitt SM, Feldman SA, Kochenderfer JN (2021) Development of CAR T Cells Expressing a Suicide Gene Plus a Chimeric Antigen Receptor Targeting Signaling Lymphocytic-Activation Molecule F7. Mol Ther 29 (2): 702-717. doi: 10.1016/j.ymthe.2020.10.008
7. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J (2018) Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract 27 (6): 501-507. doi: 10.1159/000493390
8. Zhao Z, Ma X, Dong S, Yin H, Yang Y, Xiong G (2023) Regulatory effect of zinc finger protein A20 on rheumatoid arthritis through NLRP3/Caspase-1 signaling axis mediating pyroptosis of HFLS- RA cells. Cell Mol Biol (Noisy-le-grand) 69 (8): 179-184. doi: 10.14715/cmb/2023.69.8.27
9. Sparks JA (2019) Rheumatoid Arthritis. Ann Intern Med 170 (1): ITC1-ITC16. doi: 10.7326/aitc201901010
10. Abdulameer NA (2025) Relationships between genetic polymorphisms of IL-1β and rheumatoid arthritis. Cell Mol Biol (Noisy-le-grand) 70 (12): 95-98. doi: 10.14715/cmb/2024.70.12.13
11. Qais Ahmed M, Razak Al-Sharifi ZA, Gorial F (2023) Association of soluble triggering receptor expressed on myeloid cells-1 with rheumatoid arthritis in Iraqi patients: A case-control study. Cell Mol Biol (Noisy-le-grand) 69 (13): 142-148. doi: 10.14715/cmb/2023.69.13.22
12. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compán MV, Oliver S, Schoels

M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, Kouloumas M, Landewe R, Martin-Mola E, Nash P, Ostergaard M, Östör A, Richards P, Sokka-Isler T, Thorne C, Tzioufas AG, van Vollenhoven R, de Wit M, van der Heijde D (2016) Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 75 (1): 3-15. doi: 10.1136/annrheumdis-2015-207524

13. Solomon DH, Husni ME, Wolski KE, Wisniewski LM, Borer JS, Graham DY, Libby P, Lincoff AM, Lüscher TF, Menon V, Yeomans ND, Wang Q, Bao W, Berger MF, Nissen SE (2018) Differences in Safety of Nonsteroidal Antiinflammatory Drugs in Patients With Osteoarthritis and Patients With Rheumatoid Arthritis: A Randomized Clinical Trial. Arthritis Rheumatol 70 (4): 537-546. doi: 10.1002/art.40400
14. Halim L, Maher J (2020) CAR T-cell immunotherapy of B-cell malignancy: the story so far. Ther Adv Vaccines Immunother 8: 2515135520927164. doi: 10.1177/2515135520927164
15. June CH, Sadelain M (2018) Chimeric Antigen Receptor Therapy. N Engl J Med 379 (1): 64-73. doi: 10.1056/NEJMra1706169
16. Jayaraman J, Mellody MP, Hou AJ, Desai RP, Fung AW, Pham AHT, Chen YY, Zhao W (2020) CAR-T design: Elements and their synergistic function. EBioMedicine 58: 102931. doi: 10.1016/j.ebiom.2020.102931
17. Műzes G, Sipos F (2023) CAR-Based Therapy for Autoimmune Diseases: A Novel Powerful Option. Cells 12 (11). doi: 10.3390/cells12111534
18. He C, Zhou Y, Li Z, Farooq MA, Ajmal I, Zhang H, Zhang L, Tao L, Yao J, Du B, Liu M, Jiang W (2020) Co-Expression of IL-7 Improves NKG2D-Based CAR T Cell Therapy on Prostate Cancer by Enhancing the Expansion and Inhibiting the Apoptosis and Exhaustion. Cancers (Basel) 12 (7). doi: 10.3390/cancers12071969
19. Weinkove R, George P, Dasyam N, McLellan AD (2019) Selecting costimulatory domains for chimeric antigen receptors: functional and clinical considerations. Clin Transl Immunology 8 (5): e1049. doi: 10.1002/cti2.1049
20. Ma G, Wang Y, Li Y, Cui L, Zhao Y, Zhao B, Li K (2015) MiR-206, a key modulator of skeletal muscle development and disease. Int J Biol Sci 11 (3): 345-352. doi: 10.7150/ijbs.10921
21. Dana H, Chalbatani GM, Jalali SA, Mirzaei HR, Grupp SA, Suarez ER, Rapôso C, Webster TJ (2021) CAR-T cells: Early successes in blood cancer and challenges in solid tumors. Acta Pharm Sin B 11 (5): 1129-1147. doi: 10.1016/j.apsb.2020.10.020
22. Zhang Q, Zhang Z, Peng M, Fu S, Xue Z, Zhang R (2016) CAR-T cell therapy in gastrointestinal tumors and hepatic carcinoma: From bench to bedside. Oncoimmunology 5 (12): e1251539. doi: 10.1080/2162402x.2016.1251539
23. Gomes-Silva D, Ramos CA (2018) Cancer Immunotherapy Using CAR-T Cells: From the Research Bench to the Assembly Line. Biotechnol J 13 (2). doi: 10.1002/biot.201700097
24. Weiss R, Gerdes W, Berthold R, Sack U, Koehl U, Hauschildt S, Grahnert A (2021) Comparison of Three CD3-Specific Separation Methods Leading to Labeled and Label-Free T Cells. Cells 10 (11). doi: 10.3390/cells10112824
25. Coppola C, Hopkins B, Huhn S, Du Z, Huang Z, Kelly WJ (2020) Investigation of the Impact from IL-2, IL-7, and IL-15 on the Growth and Signaling of Activated CD4(+) T Cells. Int J Mol Sci 21 (21). doi: 10.3390/ijms21217814
26. Krug C, Wiesinger M, Abken H, Schuler-Thurner B, Schuler G, Dörrie J, Schaft N (2014) A GMP-compliant protocol to expand and transfect cancer patient T cells with mRNA encoding a tumor-specific chimeric antigen receptor. Cancer Immunol Immunother 63 (10): 999-1008. doi: 10.1007/s00262-014-1572-5
27. Harrison RP, Zylberberg E, Ellison S, Levine BL (2019) Chimeric antigen receptor-T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. Cytotherapy 21 (2): 224-233. doi: 10.1016/j.jcyt.2019.01.003
28. Li G, Boucher JC, Kotani H, Park K, Zhang Y, Shrestha B, Wang X, Guan L, Beatty N, Abate-Daga D, Davila ML (2018) 4-1BB enhancement of CAR T function requires NF-κB and TRAFs. JCI Insight 3 (18). doi: 10.1172/jci.insight.121322
29. Zhang B, Wang Y, Yuan Y, Sun J, Liu L, Huang D, Hu J, Wang M, Li S, Song W, Chen H, Zhou D, Zhang X (2021) In vitro elimination of autoreactive B cells from rheumatoid arthritis patients by universal chimeric antigen receptor T cells. Ann Rheum Dis 80 (2): 176-184. doi: 10.1136/annrheumdis-2020-217844
30. Whittington KB, Prislovsky A, Beaty J, Albritton L, Radic M, Rosloniec EF (2022) CD8(+) T Cells Expressing an HLA-DR1 Chimeric Antigen Receptor Target Autoimmune CD4(+) T Cells in an Antigen-Specific Manner and Inhibit the Development of Autoimmune Arthritis. J Immunol 208 (1): 16-26. doi: 10.4049/jimmunol.2100643
31. Bhandari S, Bhandari S, Bhandari S (2023) Chimeric antigen receptor T cell therapy for the treatment of systemic rheumatic diseases: a comprehensive review of recent literature. Ann Med Surg (Lond) 85 (7): 3512-3518. doi: 10.1097/ms9.0000000000000891
32. Zhang W, Feng J, Cinquina A, Wang Q, Xu H, Zhang Q, Sun L, Chen Q, Xu L, Pinz K, Wada M, Jiang X, Ma Y, Zhang H (2021) Treatment of Systemic Lupus Erythematosus using BCMA-CD19 Compound CAR. Stem Cell Rev Rep 17 (6): 2120-2123. doi: 10.1007/s12015-021-10251-6
33. Landsverk OJ, Snir O, Casado RB, Richter L, Mold JE, Réu P, Horneland R, Paulsen V, Yaqub S, Aandahl EM, Øyen OM, Thorarensen HS, Salehpour M, Possnert G, Frisén J, Sollid LM, Baekkevold ES, Jahnsen FL (2017) Antibody-secreting plasma cells persist for decades in human intestine. J Exp Med 214 (2): 309-317. doi: 10.1084/jem.20161590
34. Smulski CR, Eibel H (2018) BAFF and BAFF-Receptor in B Cell Selection and Survival. Front Immunol 9: 2285. doi: 10.3389/fimmu.2018.02285
35. Carrillo-Ballesteros FJ, Oregon-Romero E, Franco-Topete RA, Govea-Camacho LH, Cruz A, Muñoz-Valle JF, Bustos-Rodríguez FJ, Pereira-Suárez AL, Palafox-Sánchez CA (2019) B-cell activating factor receptor expression is associated with germinal center B-cell maintenance. Exp Ther Med 17 (3): 2053-2060. doi: 10.3892/etm.2019.7172
36. Vincent FB, Kandane-Rathnayake R, Koelmeyer R, Hoi AY, Harris J, Mackay F, Morand EF (2019) Analysis of serum B cell-activating factor from the tumor necrosis factor family (BAFF) and its soluble receptors in systemic lupus erythematosus. Clin Transl Immunology 8 (4): e01047. doi: 10.1002/cti2.1047
37. van der Schans JJ, van de Donk N, Mutis T (2020) Dual Targeting to Overcome Current Challenges in Multiple Myeloma CAR T-Cell Treatment. Front Oncol 10: 1362. doi: 10.3389/fonc.2020.01362
38. Seifert L, Riecken K, Zahner G, Hambach J, Hagenstein J, Dubberke G, Huber TB, Koch-Nolte F, Fehse B, Tomas NM (2024) An antigen-specific chimeric autoantibody receptor (CAAR) NK cell strategy for the elimination of anti-PLA2R1 and anti-THSD7A antibody-secreting cells. Kidney Int 105 (4): 886-889. doi: 10.1016/j.kint.2024.01.021
39. Oh S, Mao X, Manfredo-Vieira S, Lee J, Patel D, Choi EJ, Alvarado A, Cottman-Thomas E, Maseda D, Tsao PY, Ellebrecht CT, Khella SL, Richman DP, O'Connor KC, Herzberg U, Binder GK, Milone MC, Basu S, Payne AS (2023) Precision targeting of autoantigen-specific B cells in muscle-specific tyrosine kinase

myasthenia gravis with chimeric autoantibody receptor T cells. Nat Biotechnol 41 (9): 1229-1238. doi: 10.1038/s41587-022-01637-z

40. Grant CR, Liberal R, Mieli-Vergani G, Vergani D, Longhi MS (2015) Regulatory T-cells in autoimmune diseases: challenges, controversies and--yet--unanswered questions. Autoimmun Rev 14 (2): 105-116. doi: 10.1016/j.autrev.2014.10.012
41. Li M, Luo L, Wu Y, Song Z, Ni B, Hao F, Luo N (2022) Elevated apoptosis and abnormal apoptosis signaling of regulatory T cells in patients with systemic lupus erythematosus. Lupus 31 (12): 1441-1455. doi: 10.1177/09612033221119455
42. Li W, Deng C, Yang H, Wang G (2019) The Regulatory T Cell in Active Systemic Lupus Erythematosus Patients: A Systemic Review and Meta-Analysis. Front Immunol 10: 159. doi: 10.3389/fimmu.2019.00159
43. Jiang Q, Yang G, Liu Q, Wang S, Cui D (2021) Function and Role of Regulatory T Cells in Rheumatoid Arthritis. Front Immunol 12: 626193. doi: 10.3389/fimmu.2021.626193
44. Ferreira LMR, Muller YD, Bluestone JA, Tang Q (2019) Next-generation regulatory T cell therapy. Nat Rev Drug Discov 18 (10): 749-769. doi: 10.1038/s41573-019-0041-4
45. Sheth VS, Gauthier J (2021) Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL. Bone Marrow Transplant 56 (3): 552-566. doi: 10.1038/s41409-020-01134-4
46. Dholaria BR, Bachmeier CA, Locke F (2019) Mechanisms and Management of Chimeric Antigen Receptor T-Cell Therapy-Related Toxicities. BioDrugs 33 (1): 45-60. doi: 10.1007/s40259-018-0324-z
47. Jan M, Scarfò I, Larson RC, Walker A, Schmidts A, Guirguis AA, Gasser JA, Słabicki M, Bouffard AA, Castano AP, Kann MC, Cabral ML, Tepper A, Grinshpun DE, Sperling AS, Kyung T, Sievers QL, Birnbaum ME, Maus MV, Ebert BL (2021) Reversible ON- and OFF-switch chimeric antigen receptors controlled by lenalidomide. Sci Transl Med 13 (575). doi: 10.1126/scitranslmed.abb6295
48. Parayath NN, Stephan SB, Koehne AL, Nelson PS, Stephan MT (2020) In vitro-transcribed antigen receptor mRNA nanocarriers for transient expression in circulating T cells in vivo. Nat Commun 11 (1): 6080. doi: 10.1038/s41467-020-19486-2
49. Nelson R (2023) FDA investigating safety risks in CAR T-cell recipients. Lancet 402 (10418): 2181. doi: 10.1016/s0140-6736(23)02747-2
50. Vukovic J, Abazovic D, Vucetic D, Medenica S (2024) CAR-engineered T cell therapy as an emerging strategy for treating autoimmune diseases. Front Med (Lausanne) 11: 1447147. doi: 10.3389/fmed.2024.1447147
51. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC (2018) CAR T cell immunotherapy for human cancer. Science 359 (6382): 1361-1365. doi: 10.1126/science.aar6711
52. Moore TJ, Zhang H, Anderson G, Alexander GC (2018) Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. JAMA Intern Med 178 (11): 1451-1457. doi: 10.1001/jamainternmed.2018.3931
53. Palani HK, Arunachalam AK, Yasar M, Venkatraman A, Kulkarni U, Lionel SA, Selvarajan S, Korula A, Abraham A, George B, Adair JE, Orentas R, Dropulic B, Mathews V (2023) Decentralized manufacturing of anti CD19 CAR-T cells using CliniMACS Prodigy®: real-world experience and cost analysis in India. Bone Marrow Transplant 58 (2): 160-167. doi: 10.1038/s41409-022-01866-5
54. Kaur J, Cairns E, Barra L (2023) Restoring Balance: Immune Tolerance in Rheumatoid Arthritis. J Rheumatol 50 (8): 991-1001. doi: 10.3899/jrheum.220881
55. Song S, Wang Y, Fang Y, Teng F, Yue T, Chen L, Wan X, Hong R, Xue M (2024) Glucocorticoids promote joint microenvironment alteration of GABBR1 expression associated with mitigating rheumatoid arthritis. Cell Mol Biol (Noisy-le-grand) 70 (6): 73-77. doi: 10.14715/cmb/2024.70.6.12
56. Chaurasia N, Singh A, Singh IL, Singh T, Tiwari T (2020) Cognitive dysfunction in patients of rheumatoid arthritis. J Family Med Prim Care 9 (5): 2219-2225. doi: 10.4103/jfmpc.jfmpc_307_20
57. Köhler BM, Günther J, Kaudewitz D, Lorenz HM (2019) Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. J Clin Med 8 (7). doi: 10.3390/jcm8070938
58. Zhou J, Xu Y, Shu J, Jiang H, Huang L, Xu M, Liu J, Hu Y, Mei H (2024) GPIbα CAAR T cells function like a Trojan horse to eliminate autoreactive B cells to treat immune thrombocytopenia. Haematologica 109 (7): 2256-2270. doi: 10.3324/haematol.2023.283874
59. Khan SH, Choi Y, Veena M, Lee JK, Shin DS (2024) Advances in CAR T cell therapy: antigen selection, modifications, and current trials for solid tumors. Front Immunol 15: 1489827. doi: 10.3389/fimmu.2024.1489827
60. Sterner RM, Sakemura R, Cox MJ, Yang N, Khadka RH, Forsman CL, Hansen MJ, Jin F, Ayasoufi K, Hefazi M, Schick KJ, Walters DK, Ahmed O, Chappell D, Sahmoud T, Durrant C, Nevala WK, Patnaik MM, Pease LR, Hedin KE, Kay NE, Johnson AJ, Kenderian SS (2019) GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. Blood 133 (7): 697-709. doi: 10.1182/blood-2018-10-881722
61. Raslan HM, Attia HR, Salama I, Ibrahim MH, Hassan EM, El Hussieny MS, El Menyawi MM, Amr KS (2016) Association of PTPN22 1858C→T polymorphism, HLA-DRB1 shared epitope and autoantibodies with rheumatoid arthritis. Rheumatol Int 36 (8): 1167-1175. doi: 10.1007/s00296-016-3511-6
62. Pandit S, Smith BE, Birnbaum ME, Brudno Y (2024) A biomaterial platform for T cell-specific gene delivery. Acta Biomater 177: 157-164. doi: 10.1016/j.actbio.2024.02.013
63. Schett G, Mackensen A, Mougiakakos D (2023) CAR T-cell therapy in autoimmune diseases. Lancet 402 (10416): 2034-2044. doi: 10.1016/s0140-6736(23)01126-1