Advanced Pharmaceutical Bulletin

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

Mini Review

How to cite this article:
Akbarzadeh-Khiavi M, Olfati AH, Safary A. Next-Generation Targeted Molecular Therapies in Immune-Mediated Inflammatory Diseases. Advanced Pharmaceutical Bulletin, doi: 10.34172/apb.46844

Next-Generation Targeted Molecular Therapies in Immune-Mediated Inflammatory Diseases

Mostafa Akbarzadeh-Khiavi[1], Amir-Hossein Olfati[2], Azam Safary[3*]

[1] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Research Center for Pharmaceutical Nanotechnology, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

ARTICLE INFO

Keywords:
Immune-mediated inflammatory diseases;
Targeted molecular therapies;
Precision medicine;
Immune tolerance

Article History:
Submitted: December 04, 2025
Revised: February 21, 2026
Accepted: March 23, 2026
ePublished: May 10, 2026

ABSTRACT

Immune-mediated inflammatory diseases (IMIDs) are chronic disorders characterized by dysregulated immunity and loss of self-tolerance. Although significant progress has been made in the management of IMIDs, challenges such as drug resistance, immunogenicity, and limited accessibility continue to impede clinical outcomes. Achieving sustained remission necessitates a transition toward precision medicine that addresses fundamental disease mechanisms. This study examines recent advances in molecular interventions, including cytokine inhibitors, kinase modulators, and B-cell therapies, and emphasizes how these approaches improve remission rates and reduce relapses. Additionally, emerging platforms such as RNA therapeutics, nanomedicine, and chimeric antigen receptor (CAR) cell therapies are discussed, with a focus on their potential to enhance efficacy and prolong clinical response duration. Integrating these innovations with artificial intelligence to identify therapeutic targets, predict patient responses, and optimize drug development is essential to realizing truly personalized, more successful treatments for IMIDs.

***Corresponding Author:**
Azam Safary, Email: azamsafary@gmail.com, ORCID: 0000-0002-8997-2003

1. Introduction

Immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), are chronic conditions characterized by dysregulated immune signaling and loss of self-tolerance. The activity of autoreactive immune cells leads to autoantibody production, proinflammatory cytokine release, tissue injury, organ dysfunction, and joint destruction, ultimately resulting in long-term disability and diminished quality of life.[1]

Conventional therapies for IMIDs, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and synthetic disease-modifying antirheumatic drugs (DMARDs), function primarily through broad immunosuppression or immunomodulation. While these agents offer symptomatic relief, their use is constrained by significant adverse effects, such as increased infection risk, cytopenias, organ toxicity, and other complications. Importantly, these treatments do not address the fundamental immune intolerance underlying IMIDs.[2,3]

Over the past two decades, significant advances in elucidating the molecular basis of immune dysregulation in IMIDs have driven the development of precision-targeted biological and small-molecule therapeutics. These innovations have transformed treatment paradigms by shifting the focus from symptomatic management to sustained clinical remission and the possibility of long-term drug-free remission. This review presents a focused analysis of current and emerging targeted molecular therapies, examining their mechanistic foundations, clinical efficacy, safety profiles, and limitations. Additionally, next-generation platforms are explored that may further redefine the therapeutic landscape of IMIDs.

2. Current Targeted Molecular Therapies in IMIDs

2.1. Cytokine Inhibition: Targeting the Inflammatory Cascade

Identifying key proinflammatory cytokines as central mediators of IMIDs enabled the development of biologic agents. Tumor necrosis factor-alpha (TNF-alpha) inhibitors, including adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol, were the first successful targeted therapies. [4] These agents are highly effective for achieving clinical remission, inhibiting radiographic progression, and improving functional outcomes in RA, AS, and PsA, as demonstrated by randomized trials and long-term studies. [5,6] Their mechanism is neutralizing soluble and membrane-bound TNF-alpha. Etanercept acts as a decoy receptor, preventing TNF-alpha from binding its receptors and interrupting downstream inflammation. [6,7]

Following the success of TNF-alpha inhibition, blocking the interleukin-6 (IL-6) pathway emerged as a major therapeutic advance. In this context, tocilizumab, a humanized monoclonal antibody targeting the IL-6 receptor, is more effective than methotrexate as monotherapy for moderate-to-severe RA. [8] Moreover, tocilizumab can be combined with methotrexate for patients who respond poorly to DMARDs or TNF-alpha inhibitors. [9,10] Supporting its clinical utility, long-term extension studies confirm disease control, less joint damage, and sustained physical function for five years, with a stable and manageable safety profile. [11-13]

Further refinement in targeting the cytokine network has led to selective inhibition of the interleukin-17/interleukin-23 (IL-17/IL-23) axis, transforming the therapeutic landscape for PsA and AS. Secukinumab and ixekizumab, monoclonal antibodies against IL-17A, have demonstrated rapid and significant improvements in the signs and symptoms of AS and PsA in large phase III trials. [14-16] Secukinumab has shown particular efficacy in

managing the axial manifestations of PsA, [17] while ixekizumab has also been shown to improve axial symptoms in patients with PsA. [18]

Expanding on these approaches, targeted therapies now include those directed at the upstream cytokine IL-23. Guselkumab, a monoclonal antibody that binds the p19 subunit of IL-23, has shown efficacy in phase III trials in biologic-naive patients with active PsA,[19] and in patients previously treated with TNF-alpha inhibitors. [20] Guselkumab reduces downstream T helper 17 (Th17) effector cytokines, including IL-17A and IL-17F. This provides sustained efficacy in PsA by suppressing the pathway. [21,22] Long-term data show that guselkumab's efficacy is maintained for at least 2 years. [23]

2.2. Small-Molecule Kinase Inhibitors as Oral Precision Medicine

The development of orally available small-molecule inhibitors represents a significant advancement in the management of IMIDs, providing an alternative to injectable biologic agents. These therapies are classified as Janus kinase (JAK) inhibitors and, more recently, as selective inhibitors of tyrosine kinase 2 (TYK2). JAK inhibitors, such as baricitinib, tofacitinib, upadacitinib, and filgotinib, enable broader inhibition of multiple cytokine signaling pathways, marking a paradigm shift in treatment strategies. [24] By targeting the JAK-STAT signaling cascade, these agents modulate responses from key inflammatory cytokines, including interleukins (ILs), interferons (IFNs), and growth factors. [25,26] In clinical trials, upadacitinib, a selective JAK1 inhibitor, produced higher clinical response and remission rates than the TNF inhibitor adalimumab in patients with RA who were unresponsive to methotrexate. [27,28] The five-year SELECT-COMPARE study confirmed that upadacitinib maintained higher response rates and remission over time, with a consistent safety profile. [29,30] Baricitinib, which inhibits JAK1 and JAK2, also showed sustained efficacy, with a manageable, unchanged long-term safety profile over a median of 4.6 years and up to 9.3 years. [31,32]

Recently, highly selective allosteric inhibition of TYK2 with deucravacitinib has emerged as a promising therapeutic approach. [33] Deucravacitinib binds to the TYK2 regulatory (JH2) domain, locking the enzyme in an inactive state. This selectivity for TYK2 over JAK1, JAK2, and JAK3 is associated with reduced adverse events commonly seen with less-selective JAK inhibitors, such as serious infections, thrombotic events, and hematologic issues. [34,35] In the phase 3 POETYK PSO-1 and PSO-2 trials, deucravacitinib achieved significantly higher efficacy than placebo and apremilast in moderate-to-severe plaque psoriasis, with sustained responses for up to three years. [36,37] In a phase 2 trial in active PsA, deucravacitinib led to greater improvements in the American College of Rheumatology-20 (ACR-20) response and other secondary measures compared with placebo. [38]

2.3. B-Cell-Directed Therapies for Humoral Autoimmunity

B lymphocytes play a central role in the pathogenesis of IMIDs by producing autoantibodies, presenting antigens, activating T cells, and secreting proinflammatory cytokines. Targeting B cells is a key therapeutic strategy for these conditions. Rituximab, a chimeric monoclonal antibody (mAb) directed against the CD20 antigen on B cells, induces profound and sustained B-cell depletion. [39] Foundational trials demonstrated its efficacy in combination with methotrexate for patients with RA, [40] and it is also used in severe, refractory SLE. [41] Although large randomized trials in SLE did not achieve their primary endpoints, multiple observational studies and meta-analyses indicate that rituximab may be effective for refractory lupus, including improved outcomes in lupus nephritis and reduced steroid requirements. [42,43] Incomplete B-cell depletion in some patients may contribute to suboptimal clinical responses in RA and SLE. [44] The safety profile is generally acceptable, although infusion-

related reactions and rare serious adverse events, such as progressive multifocal leukoencephalopathy, have been reported with long-term use. [45]

Belimumab, a fully human mAb, provides an alternative B-cell-targeted therapy by neutralizing B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS). BAFF is essential for B cell survival, differentiation, and class-switch recombination. [46] By blocking BAFF, belimumab disrupts the formation of highly active BAFF 60-mers and impairs B-cell maturation, thereby reducing autoantibody production. [47] Large randomized controlled trials have confirmed the efficacy and safety of belimumab in active SLE, supporting its regulatory approval. [48,49] The BLISS-LN trial further demonstrated that the addition of belimumab to standard therapy significantly improves renal outcomes over 2 years in patients with active lupus nephritis, reducing the risk of renal-related events or death. [50] The safety profile remains favorable, with no significant increase in adverse events compared to placebo. [51]

2.4. Modulation of T-Cell Costimulation and Immune Checkpoints

Abatacept is a soluble fusion protein that combines the extracellular domain of cytotoxic T-lymphocyte antigen-4 (CTLA-4) with a modified Fc portion of human IgG1. It selectively modulates T-cell activation by blocking the critical costimulatory pathway involving CD28 on T cells and its ligands, CD80 and CD86, on antigen-presenting cells. [52,53] Without this second signal, T-cell activation is attenuated, leading to a downstream reduction in cytokine production such as IL-6, inhibition of B-cell autoantibody production, and reduced activation of other inflammatory cells. [54] Abatacept has proven effective for disease control in RA patients, including those with an inadequate response to methotrexate or TNF inhibitors. [55,56] Recent evidence also suggests that abatacept can downregulate FcγRI expression on monocytes, potentially suppressing inflammatory responses mediated by immune complexes. [57] It generally has a favorable safety profile, with a lower risk of serious infections than some other biologic agents. [54]

In addition to established therapies, recent research underscores the therapeutic potential of modulating alternative immune checkpoint pathways. The programmed cell death protein 1 (PD-1) pathway serves as a critical immune checkpoint that maintains self-tolerance by inhibiting T cell activity. [58,59] Dysregulation of this pathway is associated with several autoimmune diseases. [60] Although PD-1 blockade with checkpoint inhibitors has transformed cancer treatment, it may also induce or worsen autoimmune conditions. [61] Conversely, strategies to activate the PD-1 pathway are being investigated as therapies for autoimmunity. For example, an experimental immunotoxin targeting PD-1-expressing cells ameliorated disease in mouse models of type 1 diabetes and experimental autoimmune encephalomyelitis, while preserving normal immune function. [62] These findings indicate that selective targeting of autoreactive T cells via the PD-1 pathway may provide a promising strategy for modulating immune responses in autoimmune diseases. [63]

3. Next-Generation Therapeutic Platforms for IMIDs

While established molecular therapies have improved clinical outcomes, some IMIDs patients still experience treatment failure or adverse events, highlighting the need for next-generation therapeutic platforms. [64] To address these gaps, new approaches are emerging and include (i) chimeric antigen receptor (CAR) cell therapies; [65,66] (ii) RNA therapeutics, such as small interfering RNA (siRNA) technologies that selectively silence disease-associated genes; [67] (iii) nanotechnology-based targeted delivery systems for selective, inflammation-triggered drug administration; [37,68] and (iv) autologous hematopoietic stem cell transplantation (aHSCT), which seeks to reset the

immune system and achieve sustained, drug-free remission in severe, refractory cases. [69] An overview of the major therapeutic classes currently used or under investigation in IMIDs is summarized in Table 1. Advances in precision immunology and bioengineering may transform rheumatologic care by shifting the focus from symptomatic relief to deep disease modification and, for some patients, a functional cure.

Table 1. Overview of Key Therapeutic Classes in IMIDs.

Therapy Class	Examples	Targets	Diseases	Advantages	Limitations	References
Cytokine Inhibitors	Adalimumab, Tocilizumab	TNF-alpha, IL-6 receptor	RA, AS	Rapid symptom relief, established efficacy	Infection risk, injection-site reactions	[70,71]
Kinase Inhibitors	Baricitinib, Upadacitinib	JAK/STAT pathway	RA, PsA	Oral administration, broad cytokine suppression	Thrombotic events, laboratory monitoring required	[31,72]
Cell-Targeted	Rituximab, CD19 CAR-T Cells	B cells, autoreactive lymphocytes	SLE, RA	Sustained remission, immune reset	High costs, infusion-related risks	[3,41]
RNA/Nano-Based	siRNA liposomes, mRNA Tregs	Gene expression, inflamed tissues	SLE, RA	High precision, tolerance induction	Developmental stage, delivery hurdles	[73,74]

* TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin-6; JAK/STAT: Janus kinase/Signal transducer and activator of transcription; TYK2: Tyrosine kinase 2; BAFF: B-cell activating factor; CAR: Chimeric antigen receptor; CRS: Cytokine release syndrome; siRNA: Small interfering RNA; mRNA: Messenger RNA; Treg: Regulatory T cell; lncRNA: Long non-coding RNA; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; PsA: Psoriatic arthritis; SLE: Systemic lupus erythematosus.

3.1. Chimeric Antigen Receptor (CAR) Cell Therapies

CAR T-cell therapy represents a novel immunotherapeutic strategy originally developed in oncology and now applied to the treatment of severe, refractory IMIDs. [75] This approach involves the genetic modification of T cells, sourced either from patients (autologous) or healthy donors (allogeneic), to express synthetic chimeric antigen receptors (CARs). These engineered receptors specifically recognize and bind to antigens on the surface of target cells, facilitating their destruction independently of the major histocompatibility complex (MHC). [66] CD19-targeted CAR T-cell therapy has demonstrated remarkable efficacy in small cohorts of patients with severe, refractory SLE. [76] Case series have shown that a single infusion of CD19 CAR T-cells induces profound B-cell aplasia, eliminates autoantibodies, and results in drug-free remission in all treated individuals. [77,78] In these reports, disease activity scores reached zero within three months, and remissions persisted for over two years in some cases, significantly surpassing outcomes achieved with conventional therapies. [78,79]

Allogeneic, or "off-the-shelf," CAR cell products derived from healthy donors present several advantages over autologous approaches. [80] These products eliminate the need for individualized manufacturing, reduce associated costs, and mitigate production failures that may arise when using T cells from heavily pretreated patients. [80,81] Recent pilot studies of allogeneic anti-CD19 CAR T-cells in refractory SLE have demonstrated clinical remission rates comparable to those observed with autologous products. [81,82] Notably, these studies have reported favorable safety profiles, with only mild cytokine release syndrome (CRS) and no cases of graft-versus-host disease (GvHD), a significant concern in allogeneic therapies. [81,83]

CAR-engineered natural killer (NK) cells are being investigated as an alternative to T cells. These cells may provide safety advantages and can be produced from allogeneic donors for off-the-shelf application. [84] A phase 1 clinical trial is currently assessing an allogeneic anti-CD19 CAR-NK product (NKX019) in patients with refractory SLE. [85]

Despite its notable clinical efficacy, several significant barriers restrict the broader implementation of CAR-T cell therapy in IMIDs. These challenges include high manufacturing costs and complex logistics, the risk of toxicities and severe adverse effects such as CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), and long-term risks related to sustained B-cell aplasia, including increased susceptibility to infections and potential secondary malignancies. [80,86-88]

Current research aims to address these limitations by developing strategies such as dual-targeting CARs, for example, those targeting both CD19 and BCMA, to prevent relapse due to antigen escape. This approach has demonstrated success in achieving sustained remission in refractory SLE. [89,90] In addition to SLE, CAR T-cell therapy is under investigation for other refractory IMIDs, with case series and pilot studies reported in systemic sclerosis (SSc), [78,91] idiopathic inflammatory myopathies (IIM), including antisynthetase syndrome, [78,92] and ANCA-associated vasculitis (AAV). [93,94] These findings indicate that the profound immune "reset" induced by this therapy may have broad applicability across antibody-mediated autoimmune diseases. [95] Another emerging strategy involves engineering regulatory T cells (Tregs) to express CARs. Instead of depleting immune cells, CAR-Tregs are engineered to migrate to sites of inflammation and actively suppress autoimmune responses, which promotes immune tolerance. [96] This method combines the antigen specificity of CARs with the inherent immunosuppressive properties of Tregs and has shown promise in preclinical models of colitis and other autoimmune disorders. [97]

3.2. RNA Therapeutics: Precision Gene Silencing in IMIDs

RNA-based therapeutics, such as siRNA, antisense oligonucleotides (ASOs), and messenger RNA (mRNA), facilitate highly specific, sequence-directed modulation of disease-associated genes, thereby providing exceptional precision and reducing off-target effects. [98,99] This approach allows for intervention at the post-transcriptional level and represents a novel strategy for the management of IMIDs. [100]

Long non-coding RNAs (lncRNAs) have been identified as essential regulators of immune homeostasis and are frequently dysregulated in IMIDs. Molecules such as NEAT1, GAS5, and HOTAIR modulate key inflammatory signaling pathways, including IL-6/STAT3 and TNF-alpha/NF-κB, and influence the differentiation of T and B cells. [101-103] Expression profiles of lncRNAs often correlate with disease activity in RA and SLE, suggesting their potential as biomarkers and therapeutic targets. [104,105] For instance, upregulation of HOTAIR and THRIL has been observed in patients with RA and was associated with elevated TNF-alpha levels, while altered GAS5 levels have

been reported in both SLE and RA. [105] Preclinical studies have demonstrated the therapeutic potential of targeting these pathogenic molecules. A cationic liposome formulation has been developed for systemic delivery of siRNA to silence the proinflammatory cytokine TNF-alpha in experimental arthritis models. [106] Lipid nanoparticles designed for minimal burst release of TNF-alpha siRNA have demonstrated significant activity against RA, even in methotrexate-unresponsive models, by reducing bone loss and improving histopathological scores. [107]

Beyond silencing pathogenic genes, mRNA lipid nanoparticle platforms are being developed to engineer immune cells for adoptive cell therapy. This strategy enables the generation of immunosuppressive Tregs by delivering mRNA encoding key transcription factors, such as Foxp3, and antigen-specific T-cell receptors. [73] These ex vivo engineered Tregs show enhanced suppressive function and can be directed to specific tissues. [73,108] Compared to viral transduction, this method reduces the risk of insertional mutagenesis due to the transient nature of mRNA expression and allows for faster manufacturing. [109] In addition to engineering immune cells, another approach uses non-inflammatory mRNA-LNP constructs encoding disease-relevant autoantigens to induce antigen-specific tolerance. In mouse models of multiple sclerosis (MS), this method suppressed disease by expanding antigen-specific Tregs, highlighting its potential to restore self-tolerance without systemic immunosuppression. [110,111] Despite these advances, the clinical translation of RNA therapeutics remains challenging. Key issues include optimizing delivery vehicles for targeted biodistribution, protecting RNA from nuclease degradation, ensuring efficient cellular uptake and endosomal escape, and confirming long-term safety by minimizing off-target effects and unwanted immune activation. [112,113]

3.3. Nanotechnology-Based Targeted Delivery Systems in IMIDs

Nanotechnology platforms include biodegradable polymeric nanoparticles, liposomes, micelles, dendrimers, and stimuli-responsive hydrogels. These advanced systems provide targeted drug delivery to inflammatory sites, which reduces systemic exposure and toxicity. [68,114] They can be designed to release drugs in response to specific features of inflamed tissues, including acidic pH, high levels of reactive oxygen species (ROS), unique enzyme activities such as matrix metalloproteinases and cathepsins, or increased temperature. [115,116]

For example, folate receptor-targeted, pH-responsive nanocarriers encapsulating methotrexate or glucocorticoids have demonstrated increased therapeutic efficacy and reduced systemic adverse effects in preclinical models of arthritis. [117] The folate receptor, which is overexpressed on activated macrophages within inflamed synovium, facilitates selective nanoparticle uptake through receptor-mediated endocytosis. [118] In adjuvant-induced arthritis rat models, folate-conjugated polymeric nanoparticles containing methotrexate resulted in greater drug accumulation in arthritic joints compared to healthy joints, leading to improved arthritis score reduction and cartilage preservation relative to free methotrexate at equivalent doses. [119] Similarly, folate-targeted liposomes delivering dexamethasone, combined with ultrasound-targeted microbubble destruction, have enhanced drug release and significantly decreased joint swelling and inflammation in RA models. [120] In addition, nanoparticles responsive to ROS and loaded with anti-inflammatory agents also enable triggered drug release specifically within oxidatively stressed arthritic joints [121-123]. For instance, celastrol-loaded bilirubin nanoparticles target ROS at pathological sites, thereby improving anti-arthritic efficacy and reducing toxicity in RA models. [124] Furthermore, pH-responsive multifunctional manganese dioxide nanoparticles enhance methotrexate delivery. They ameliorate the RA microenvironment by eliminating ROS and generating oxygen, thereby regulating inflammation and promoting macrophage polarization. [125]

Advanced multifunctional theranostic nanomedicine facilitates real-time monitoring of drug biodistribution, therapeutic efficacy, and disease progression through non-invasive imaging modalities, including magnetic resonance imaging (MRI), positron emission tomography (PET), and optical imaging. [126,127] For instance, ceria-based nanotheranostic agents for RA combine ROS scavenging with imaging capabilities. [128] Additionally, a theranostic nanoprobe that integrates activatable near-infrared (NIR-II) fluorescence imaging with synergistic immunotherapy, by releasing carbon monoxide and inhibiting IL-6 signaling, enables precise diagnosis and treatment of rheumatoid arthritis. [129]

Tolerogenic nanoparticles conjugated with disease-relevant autoantigens and immunomodulatory molecules can induce antigen-specific immune tolerance by promoting Tregs expansion and DCs tolerization without causing broad immunosuppression. [130] For example, lignin-based tolerogenic nanoparticles loaded with autoantigens have demonstrated the capacity to scavenge ROS and induce robust antigen-specific immune tolerance through Treg induction in experimental autoimmune encephalomyelitis (EAE) models. [131] Similarly, biomaterial-based therapeutic vaccines that carry self-antigens and tolerance-inducing inorganic nanoparticles, such as cerium oxide nanoparticles, can suppress activation of antigen-presenting cells (APCs). This approach enhances antigen-specific immune tolerance, resulting in recovery in EAE models. [132]

Recent advancements include biomimetic nanoparticles coated with Treg cell membranes, which retain native targeting ligands and immune-evasive characteristics. [3] Nanoparticles coated with Treg membranes and loaded with immunosuppressive agents exhibit extended circulation times and preferentially accumulate in inflamed lymph nodes in experimental autoimmune encephalomyelitis models, resulting in improved therapeutic efficacy compared to uncoated counterparts. [133,134] Furthermore, self-assembled peptide-based nanofibers displaying multiple autoantigenic epitopes can interact with B-cell receptors on autoreactive B cells, leading to anergy or apoptosis without inducing systemic immunosuppression. [135] These peptide-based self-assembling systems are under investigation as vaccine platforms and for oral immunization, offering controlled epitope presentation and enhanced stability. [136-138]

3.4. Autologous Hematopoietic Stem Cell Transplantation (aHSCT) for IMIDs

The aHSCT constitutes an intensive immunoablative strategy that induces a profound reset of the immune system, facilitating long-term drug-free remission in certain patients with severe, refractory IMIDs. [139] The procedure involves administration of high-dose immunosuppressive or myeloablative conditioning regimens, followed by reinfusion of previously collected autologous CD34+ hematopoietic stem cells. [139] The conditioning phase aims to eliminate pathogenic immune cell clones. Subsequent immune reconstitution from stem cells restores self-tolerance by promoting thymic re-education and diversification of the T-cell receptor repertoire. [140] Regarding immune cell recovery, evidence indicates that B-cell numbers recover within 3 months post-transplantation and may exceed baseline levels after 1 year, resulting in a predominantly naive immune phenotype. However, memory B cell populations recover more slowly, remaining below normal levels and exhibiting reduced repertoire diversity for up to a year. [140] In clinical practice, aHSCT is increasingly employed in aggressive MS and, compared to immune-reconstitution therapies such as cladribine and alemtuzumab, has demonstrated greater efficacy in suppressing relapses and promoting neurological function recovery in patients with active relapsing-remitting MS and moderate disability. [139] The therapeutic benefit of aHSCT likely results from a complex interplay between immune suppression and subsequent immune reconstitution. [139] Furthermore, beyond MS, aHSCT is also considered for patients with AL amyloidosis who are unresponsive to induction therapy; these patients may benefit

from high-dose chemotherapy and aHSCT, with significant responses observed in those achieving a very good partial response or better following transplantation. [141] Despite these therapeutic advantages, aHSCT carries a substantial risk of treatment-related mortality, necessitating careful patient selection and specialized transplantation expertise. Notably, delayed complications, primarily infections, have been reported in 34% of MS patients treated with aHSCT in one study, although no treatment-associated deaths occurred in that cohort. [139]

4. Future Directions, Challenges, and Barriers to Clinical Implementation

Despite remarkable progress, considerable challenges persist in the clinical implementation of therapeutics for IMIDs. High costs associated with biologics and advanced therapies restrict accessibility, especially in low- and middle-income countries, thereby exacerbating global health disparities. [66,142] For instance, advanced therapies such as CAR T-cell therapy, despite their promise for IMIDs, present significant financial obstacles. [143]

The development of anti-drug antibodies against biologics represents another significant challenge, as it can lead to secondary treatment failure. [144] While biosimilars have shown immunogenicity profiles similar to their reference biologics, immune responses to a range of immunomodulatory agents continue to influence treatment outcomes. [66,145]

Inter-individual molecular heterogeneity, influenced by genetic background, microbiome composition, and environmental exposures, as well as pathway redundancy, results in variable treatment responses among patients with similar clinical disease phenotypes. [146,147] This variability underscores the need for more precise treatment strategies. Addressing these challenges requires biomarker-driven clinical trials that utilize predictive enrichment strategies to identify patient subgroups most likely to benefit from specific interventions. [148] The introduction of biosimilar and generic versions of established biologics can enhance affordability and access, as studies have shown substantial cost savings without compromising efficacy or safety. [66] Global collaboration through international consortia, harmonized clinical trial protocols, and equitable distribution mechanisms, together with health policy initiatives such as value-based pricing models and expanded insurance coverage, is crucial for ensuring equitable access to these therapies worldwide. [142]

The future of IMID therapeutics is advancing toward multimodal precision medicine approaches that integrate next-generation platforms with advanced computational methodologies. Artificial intelligence (AI) and machine learning (ML) algorithms, when applied to multi-omics datasets such as genomics, transcriptomics, proteomics, and metabolomics, accelerate target identification, biomarker discovery, and patient stratification. These AI-driven approaches facilitate a deeper mechanistic understanding of disease processes and enable the prediction of drug safety and efficacy. [149,150]

AI is also used to optimize drug and dose parameters in combinatorial nanomedicine, addressing the time-, dose-, and patient-specific aspects of drug synergy. [151] In addition, AI-optimized CAR designs that incorporate predictive models of antigen binding affinity, T-cell activation kinetics, and toxicity risk scores, together with CRISPR-based gene-editing strategies to enhance CAR T-cell persistence and reduce exhaustion, have the potential to improve the efficacy, safety, and durability of cellular therapies. [152-155] However, challenges such as off-target effects, immune responses, and delivery methods must still be addressed to further improve the efficacy and safety of CRISPR-based therapies.

6. Conclusion

Targeted molecular therapies have transformed IMID management by shifting from broad immunosuppression to precise immunomodulation. Biologics and small-molecule inhibitors have improved disease control, clinical outcomes, and patient quality of life. CAR T-cell therapy, RNA therapeutics, nanotechnology-based drug delivery, and aHSCT offer the potential for sustained remission and, in some cases, functional cures. Advances in precision immunology, bioengineering, and AI are creating personalized, mechanism-based treatments that address the root immunological causes. AI and machine learning with multi-omics data accelerate target identification, biomarker discovery, patient stratification, and drug repurposing, thereby reducing development timelines and costs. High costs, immunogenicity, and variable treatment responses due to molecular heterogeneity remain major barriers. Continued translational research, robust clinical validation, and global collaboration are essential to overcome these challenges.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was conducted as part of a research project funded by the Connective Tissue Diseases Research Center at Tabriz University of Medical Sciences (Grant No. 69327).

References

1. Song Y, Li J, Wu Y. Evolving understanding of autoimmune mechanisms and new therapeutic strategies of autoimmune disorders. *Signal Transduct Target Ther* 2024;9(1):263. doi: 10.1038/s41392-024-01952-8

2. Song X, Liang H, Nan F, Chen W, Li J, He L, et al. Autoimmune Diseases: Molecular Pathogenesis and Therapeutic Targets. *MedComm* 2025;6(7):e70262. doi: 10.1002/mco2.70262.

3. Chen Y, Huang H, Wang X, Yu X, Huang Z, Jin Z, et al. Regulatory T Cells and Nanomaterials: Dual Perspectives in Therapeutics and Immunomodulation. *Small Sci* 2026;6(1):e202500481. doi: 10.1002/smsc.202500481

4. Wiedmann MW, Mossner J, Baerwald C, Pierer M. TNF alpha inhibition as treatment modality for certain rheumatologic and gastrointestinal diseases. *Endocr Metab Immune Disord Drug Targets* 2009;9(3):295-314. doi: 10.2174/187153009789044347

5. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Expert Opin Drug Saf* 2011;10(4):655-73. doi: 10.1517/14740338.2011.581661

6. Murdaca G, Spanò F, Contatore M, Guastalla A, Magnani O, Puppo F. Efficacy and safety of etanercept in chronic immune-mediated disease. *Expert Opin Drug Saf* 2014;13(5):649-61. doi: 10.1517/14740338.2014.899579

7. Murdaca G, Spano F, Miglino M, Puppo F. Effects of TNF-α inhibitors upon the mechanisms of action of VEGF. Taylor & Francis; 2013. p. 113-5.

8. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;69(1):88-96. doi: 10.1136/ard.2008.105197

9. Emery P, Keystone E, Tony H, Cantagrel A, Van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67(11):1516-23. doi: 10.1136/ard.2008.092932

10. Maini R, Taylor P, Szechinski J, Pavelka K, Bröll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006;54(9):2817-29. doi: 10.1002/art.22033

11. Kremer JM, Blanco R, Halland A-M, Brzosko M, Burgos-Vargas R, Mela CM, et al. Clinical efficacy and safety maintained up to 5 years in patients with rheumatoid arthritis treated with tocilizumab in a randomised trial. *Clin Exp Rheumatol* 2016;34(4):625-33.

12. Jones G, Wallace T, McIntosh MJ, Brockwell L, Gómez-Reino JJ, Sebba A. Five-year efficacy and safety of tocilizumab monotherapy in patients with rheumatoid arthritis who were methotrexate-and biologic-naive or free of methotrexate for 6 months: the AMBITION study. *J Rheumatol* 2017;44(2):142-6. doi: 10.3899/jrheum.160287

13. Jones G, Panova E. New insights and long-term safety of tocilizumab in rheumatoid arthritis. *Ther Adv Musculoskelet Dis* 2018;10(10):195-9. doi: 10.1177/1759720X18798462

14. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med* 2015;373(26):2534-48. doi: 10.1056/NEJMoa1505066

15. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, Van Der Heijde D, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med* 2015;373(14):1329-39. doi: 10.1056/NEJMoa1412679

16. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386(9999):1137-46. doi: 10.1016/S0140-6736(15)61134-5

17. Baraliakos X, Gossec L, Pournara E, Jeka S, Mera-Varela A, d'Angelo S, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial. *Ann Rheum Dis* 2021;80(5):582-90. doi: 10.1136/annrheumdis-2020-218808

18. Deodhar A, Gladman D, Bolce R, Sandoval D, Park SY, Leage SL, et al. The effect of ixekizumab on axial manifestations in patients with psoriatic arthritis from two phase III clinical trials: SPIRIT-P1 and SPIRIT-P2. *Ther Adv Musculoskelet Dis* 2023;15:1759720X231189005. doi: 10.1177/1759720X231189005

19. Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2020;395(10230):1126-36. doi: 10.1016/S0140-6736(20)30263-4

20. Deodhar A, Helliwell PS, Boehncke W-H, Kollmeier AP, Hsia EC, Subramanian RA, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2020;395(10230):1115-25. doi: 10.1016/S0140-6736(20)30265-8

21. Sweet K, Song Q, Loza MJ, McInnes IB, Ma K, Leander K, et al. Guselkumab induces robust reduction in acute phase proteins and type 17 effector cytokines in active psoriatic arthritis: results from phase 3 trials. *RMD open* 2021;7(2):e001679. doi: 10.1136/rmdopen-2021-001679

22. Schett G, Chen W, Gao S, Chakravarty SD, Shawi M, Lavie F, et al. Effect of guselkumab on serum biomarkers in patients with active psoriatic arthritis and inadequate response to tumor necrosis factor inhibitors: results from the COSMOS phase 3b study. *Arthritis Res Ther* 2023;25(1):150. doi: 10.1186/s13075-023-03125-4

23. Mcinnes I, Tesser J, Schiopu E, Merola J, Chakravarty S, Rampakakis E, et al. POS0072 CONSISTENT LONG-TERM GUSELKUMAB EFFICACY ACROSS PSORIATIC ARTHRITIS DOMAINS IRRESPECTIVE OF BASELINE PATIENT CHARACTERISTICS. *Ann Rheum Dis* 2022;81:253-4. doi: 10.1136/annrheumdis-2022-eular.47

24. Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022;18(3):133-45. doi: 10.1038/s41584-021-00726-8

25. Raychaudhuri SP, Raychaudhuri SK. JAK inhibitor: Introduction. *Indian J Dermatol Venereol Leprol* 2023;89(5):688-90. doi: 10.25259/IJDVL_8_2023

26. Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez J-B, Dowty ME, et al. The mechanism of action of tofacitinib-an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016;34(2):318-28.

27. Fleischmann RM, Genovese MC, Enejosa JV, Mysler E, Bessette L, Peterfy C, et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis* 2019;78(11):1454-62. doi: 10.1136/annrheumdis-2019-215764

28. Fleischmann R, Mysler E, Bessette L, Peterfy CG, Durez P, Tanaka Y, et al. Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study. *RMD open* 2022;8(1):e002012. doi: 10.1136/rmdopen-2021-002012corr1

29. Fleischmann R, Swierkot J, Penn SK, Durez P, Bessette L, Bu X, et al. Long-term safety and efficacy of upadacitinib versus adalimumab in patients with rheumatoid arthritis: 5-year data from the phase 3, randomised SELECT-COMPARE study. *RMD open* 2024;10(2). doi: 10.1136/rmdopen-2023-004007

30. Burmester GR, Mysler E, Taylor P, Hall S, Wick-Urban B, Garrison A, et al. Benefit–risk analysis of upadacitinib versus adalimumab in patients with rheumatoid arthritis and higher or lower risk of cardiovascular disease. *RMD open* 2025;11(2):e005371. doi: https://doi.org/10.1136/rmdopen-2024-005371

31. Caporali R, Taylor PC, Aletaha D, Sanmartí R, Takeuchi T, Mo D, et al. Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis up to 6.5 years of treatment: results of a long-term study. *Rheumatology* 2024;63(10):2799-809. doi: 10.1093/rheumatology/keae012

32. Taylor PC, Takeuchi T, Burmester GR, Durez P, Smolen JS, Deberdt W, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. *Ann Rheum Dis* 2022;81(3):335-43. doi: 10.1136/annrheumdis-2021-221276

33. Rusiñol L, Puig L. Tyk2 targeting in immune-mediated inflammatory diseases. *Int J Mol Sci* 2023;24(4):3391. doi: 10.3390/ijms24043391

34. Chimalakonda A, Burke J, Cheng L, Catlett I, Tagen M, Zhao Q, et al. Selectivity profile of the tyrosine kinase 2 inhibitor deucravacitinib compared with Janus kinase 1/2/3 inhibitors. *Dermatol Ther* 2021;11(5):1763-76. doi: 10.1007/s13555-021-00596-

35. Bang C-H, Park C-J, Kim Y-S. The Expanding Therapeutic Potential of Deucravacitinib Beyond Psoriasis: A Narrative Review. *J Clin Med* 2025;14(5):1745. doi: 10.3390/jcm14051745

36. Armstrong A, Gooderham M, Warren R, Papp K, Strober B, Thaçi D, et al. POS1042 efficacy and safety of deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, compared with placebo and apremilast in moderate to severe plaque psoriasis: results from the phase 3 poetyk PSO-1 study. *Ann Rheum Dis* 2021;80:795-6. doi: 10.1136/annrheumdis-2021-eular.1002

37. Armstrong AW, Lebwohl M, Warren RB, Sofen H, Imafuku S, Ohtsuki M, et al. Safety and efficacy of deucravacitinib in moderate to severe plaque psoriasis for up to 3 years: an open-label extension of randomized clinical trials. *JAMA Dermatol* 2025;161(1):56-66. doi: 10.1001/jamadermatol.2024.4688

38. Mease PJ, Deodhar AA, Van Der Heijde D, Behrens F, Kivitz AJ, Neal J, et al. Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis. *Ann Rheum Dis* 2022;81(6):815-22. doi: 10.1136/annrheumdis-2021-221664

39. Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 2006;6(5):859-66. doi: 10.1111/j.1600-6143.2006.01288.x

40. Edwards JC, Szczepański L, Szechiński J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350(25):2572-81. doi: 10.1056/NEJMoa032534

41. Staveri C, Lykoura C, Melissaropoulos K, Liossis S-NC. Favorable outcomes for patients with refractory systemic lupus erythematosus treated with rituximab as evidenced with a follow-up of ≥ 10 years: a real-world evidence study. *Rheumatol Int* 2025;45(5):127. doi: 10.1007/s00296-025-05879-3

42. Lan L, Han F, Chen J-h. Efficacy and safety of rituximab therapy for systemic lupus erythematosus: a systematic review and meta-analysis. *J Zhejiang Univ Sci B* 2012;13(9):731-44. doi: 10.1631/jzus.B1200057

43. Kalashnikova E, Raupov R, Lyubimova N, Kuchinskaya E, Masalova V, Isupova E, et al. The experience of rituximab therapy in patients with juvenile systemic lupus erythematosus: the preliminary results of two-center cohort study. *Ross Vestn Perinatol Pediatr* 2023;68:74-84. doi: 10.21508/1027-4065-2023-68-1-74-84

44. Reddy V, Cambridge G, Isenberg DA, Glennie MJ, Cragg MS, Leandro M. Internalization of rituximab and the efficiency of B cell depletion in rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Rheumatol* 2015;67(8):2046-55. doi: 10.1002/art.39167

45. Wang K-Y, Lu C-H, Cheng C-F, Hsieh S-C, Ko-Jen L. FRI0126 THE INFUSION-RELATED REACTIONS OF RITUXIMAB IN RHEUMATIC DISEASES: SINGLE-CENTER EXPERIENCE OF 1893 INFUSIONS OVER 5 YEARS. *Ann Rheum Dis* 2019;78:731-2. doi: 10.1136/annrheumdis-2019-eular.2326

46. Fujio K, Ushijima T, Abe T, Okamura T, Bae SC, Tsuchida Y. Treatment strategy for systemic lupus erythematosus using belimumab as indicated by multi-omics analysis. *Rheumatol Autoimmun* 2025;5(2):81-7. doi: 10.1002/rai2.70001

47. Shin W, Lee HT, Lim H, Lee SH, Son JY, Lee JU, et al. BAFF-neutralizing interaction of belimumab related to its therapeutic efficacy for treating systemic lupus erythematosus. *Nat Commun* 2018;9(1):1200. doi: 10.1038/s41467-018-03620-2

48. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377(9767):721-31. doi: 10.1016/S0140-6736(10)61354-2

49. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63(12):3918-30. doi: 10.1002/art.30613

50. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YO, Contreras G, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020;383(12):1117-28. doi: 10.1056/NEJMoa2001180

51. Shrestha S, Budhathoki P, Adhikari Y, Marasini A, Bhandari S, Mir WAY, Shrestha DB. Belimumab in lupus nephritis: A systematic review and meta-analysis. *Cureus* 2021;13(12). doi: 10.7759/cureus.20440

52. Bonelli M, Scheinecker C. How does abatacept really work in rheumatoid arthritis? *Curr Opin Rheumatol* 2018;30(3):295-300. doi: 10.1097/BOR.0000000000000491

53. Korhonen R, Moilanen E. Abatacept, a novel CD80/86–CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. *Basic Clin Pharmacol Toxicol* 2009;104(4):276-84. doi: 10.1111/j.1742-7843.2009.00375.x

54. Su Q-Y, Zhang J-T, Gao H-J, Zhang Y, Luo J, Cao T-Y, et al. Mechanism and clinical utility of abatacept in the treatment of rheumatoid arthritis. *Expert Opin Drug Saf* 2025:1-12. doi: 10.1080/14740338.2025.2505542

55. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;144(12):865-76. doi: 10.7326/0003-4819-144-12-200606200-00003

56. Genovese MC, Becker J-C, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N Engl J Med* 2005;353(11):1114-23. doi: 10.1056/NEJMoa050524

57. Fukue R, Okazaki Y, Gono T, Kuwana M. Abatacept downregulates Fcγ receptor I on circulating monocytes: a potential therapeutic mechanism in patients with rheumatoid arthritis. *Arthritis Res Ther* 2022;24(1):194. doi: 10.1186/s13075-022-02886-8

58. Lin X, Kang K, Chen P, Zeng Z, Li G, Xiong W, et al. Regulatory mechanisms of PD-1/PD-L1 in cancers. *Mol Cancer* 2024;23(1):108. doi: 10.1186/s12943-024-02023-w

59. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol* 2008;26:677-704. doi: 10.1146/annurev.immunol.26.021607.090331

60. Xiang G, Cui Y, Wang P, Feng Y, Zhang C, Lou J, Zhou X. Nanomedicine targeting the PD-1/PD-L1 axis in autoimmune diseases: breaking conventional barriers to restore immune tolerance. *J Nanobiotechnol* 2025;23(1):1-26. doi: 10.1186/s12951-025-03766-4

61. Nabel CS, Severgnini M, Hung YP, Cunningham-Bussel A, Gjini E, Kleinsteuber K, et al. Anti-PD-1 immunotherapy-induced flare of a known underlying relapsing vasculitis mimicking recurrent cancer. *Oncologist* 2019;24(8):1013-21. doi: 10.1634/theoncologist.2018-0633

62. Zhao P, Wang P, Dong S, Zhou Z, Cao Y, Yagita H, et al. Depletion of PD-1-positive cells ameliorates autoimmune disease. *Nat Biomed Eng* 2019;3(4):292-305. doi: 10.1038/s41551-019-0360-0

63. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010;236(1):219-42. doi: 10.1111/j.1600-065X.2010.00923.x

64. McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol* 2021;21(10):680-6. doi: 10.1038/s41577-021-00603-1

65. Lee B-W, Kwon E-J, Ju JH. Chimeric Antigen Receptor T-cell therapy in systemic autoimmune rheumatic diseases: current insights and future prospects. *J Rheum Dis* 2025;32(3):154. doi: 10.4078/jrd.2024.0122

66. Du X, Luo X, Guo Q, Jiang X, Su Z, Zhou W, et al. Assessment of clinical benefit, cost and uptake of biosimilars versus reference biologics in immune-mediated inflammatory diseases in China. *Front Public Health* 2024;12:1476213. doi: 10.3389/fpubh.2024.1476213

67. Sawan S, Kumari A, Majie A, Ghosh A, Karmakar V, Kumari N, et al. siRNA-based nanotherapeutic approaches for targeted delivery in rheumatoid arthritis. *Biomater Adv* 2025;168:214120. doi: 10.1016/j.bioadv.2024.214120

68. Parvin N, Joo SW, Mandal TK. Biodegradable and Stimuli-Responsive Nanomaterials for Targeted Drug Delivery in Autoimmune Diseases. *J Funct Biomater* 2025;16(1):24. doi: 10.3390/jfb16010024

69. Felten R, Mertz P, Sebbag E, Scherlinger M, Arnaud L. Novel therapeutic strategies for autoimmune and inflammatory rheumatic diseases. *Drug Discov Today* 2023;28(7):103612. doi: 10.1016/j.drudis.2023.103612

70. Parisi S, Ditto MC, Ghellere F, Panaro S, Piccione F, Borrelli R, Fusaro E. Update on tocilizumab in rheumatoid arthritis: a narrative review. *Front Immunol* 2025;Volume 16 - 2025. doi: 10.3389/fimmu.2025.1470488

71. Mounach A, El Maghraoui A. Efficacy and safety of adalimumab in ankylosing spondylitis. *Open Access Rheumatol Res Rev* 2014;6(null):83-90. doi: 10.2147/OARRR.S44550

72. Burmester GR, Van den Bosch F, Tesser J, Shmagel A, Liu Y, Khan N, et al. Upadacitinib in rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs: efficacy and safety through 5 years (SELECT-NEXT). *J Rheumatol* 2024;51(7):663-72. doi: 10.3899/jrheum.2023-1062

73. Thatte AS, Hamilton AG, Nachod BE, Mukalel AJ, Billingsley MM, Palanki R, et al. mRNA Lipid Nanoparticles for Ex Vivo Engineering of Immunosuppressive T Cells for Autoimmunity Therapies. *Nano Lett* 2023;23(22):10179-88. doi: 10.1021/acs.nanolett.3c02573

74. Razavi R, Kegel M, Muscat-Rivera J, Weissman D, Melamed JR. Harnessing mRNA-lipid nanoparticles as innovative therapies for autoimmune diseases. *Mol Ther Methods Clin Dev* 2025;33(3). doi: 10.1016/j.omtm.2025.101566

75. Yang Z, Ha B, Wu Q, Ren F, Yin Z, Zhang H. Expanding the horizon of CAR T cell therapy: from cancer treatment to autoimmune diseases and beyond. *Front Immunol* 2025;16:1544532. doi: 10.3389/fimmu.2025.1544532

76. Mougiakakos D, Krönke G, Völkl S, Kretschmann S, Aigner M, Kharboutli S, et al. CD19-targeted CAR T cells in refractory systemic lupus erythematosus. *N Engl J Med* 2021;385(6):567-9. doi: 10.1056/NEJMc2107725

77. Mackensen A, Müller F, Mougiakakos D, Böltz S, Wilhelm A, Aigner M, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med* 2022;28(10):2124-32. doi: 10.1038/s41591-022-02017-5

78. Müller F, Taubmann J, Bucci L, Wilhelm A, Bergmann C, Völkl S, et al. CD19 CAR T-cell therapy in autoimmune disease—a case series with follow-up. *N Engl J Med* 2024;390(8):687-700. doi: 10.1056/NEJMoa2308917

79. Johnson NM, Koumpouras F. Chimeric antigen receptors:"CARs" in the fast lane for rheumatology. *Curr Opin Rheumatol* 2024;36(3):176-83. doi: 10.1097/BOR.0000000000001012

80. Ma Y, Qin J, Liu M, Du B. Allogeneic CAR-T cell therapy in autoimmune diseases. *Immunotherapy* 2025;17(15):1129-43. doi: 10.1080/1750743X.2025.2572963

81. Yang C, Sun C, Tan B, Hu C, Wan L, Wang C, et al. Allogeneic anti-CD19 CAR-T cells induce remission in refractory systemic lupus erythematosus. *Cell Res* 2025:1-3. doi: 10.1038/s41422-025-01128-1

82. Wang D, Wang X, Tan B, Wen X, Ye S, Wu Y, et al. Allogeneic CD19-targeted CAR-T therapy in refractory systemic lupus erythematosus achieved durable remission. *Med* 2025. doi: 10.1016/j.medj.2025.100749

83. Orofino G, Greco R. Allogeneic CAR-T cells in lupus: Bridging the gap for a new therapeutic era? *Med* 2025;6(10).

84. Gao J, Li M, Sun M, Yu Y, Kong R, Xu X, et al. Efficacy and safety of allogeneic CD19 CAR NK-cell therapy in systemic lupus erythematosus: a case series in China. *Lancet* 2025;406(10522):2968-79. doi: 10.1016/S0140-6736(25)01671-X

85. Askanase A, Khalili L, Chang C, Blaus A, Gip P, Karis E, Shook D. A Phase 1 Study of NKX019, an Allogeneic Chimeric Antigen Receptor Natural Killer (CAR-NK) Cell Therapy in Patients with Systemic Lupus Erythematosus. *Blood* 2024;144:4846.1.

86. Müller F, Schwingen NR, Hagen M, Scholz JK, Aigner M, Wirsching A, et al. Comparison of the safety profiles of CD19-targeting CAR T-cell therapy in patients with SLE and B-cell lymphoma. *Blood* 2025;146(9):1088-95. doi: 10.1182/blood.2025028375

87. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J* 2021;11(4):69. doi: 10.1038/s41408-021-00459-7

88. Bailey SR, Berger TR, Graham C, Larson RC, Maus MV. Four challenges to CAR T cells breaking the glass ceiling. *Eur J Immunol* 2023;53(11):e2250039. doi: 10.1002/eji.202250039

89. Feng J, HU Y, Chang AH, Huang H. CD19/BCMA CAR-T Cell Therapy for Refractory Systemic Lupus Erythematosus - Safety and Preliminary Efficacy Data from a Phase I Clinical Study. *Blood* 2023;142(Supplement 1):4835-. doi: 10.1182/blood-2023-186669

90. Wang W, He S, Zhang W, Zhang H, DeStefano VM, Wada M, et al. BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: a phase 1 open-label clinical trial. *Ann Rheum Dis* 2024;83(10):1304-14. doi: 10.1136/ard-2024-225785

91. Bergmann C, Müller F, Distler JHW, Györfi AH, Völkl S, Aigner M, et al. Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells. *Ann Rheum Dis* 2023;82(8):1117-20. doi: 10.1136/ard-2023-223952

92. Pecher AC, Hensen L, Klein R, Schairer R, Lutz K, Atar D, et al. CD19-Targeting CAR T Cells for Myositis and Interstitial Lung Disease Associated With Antisynthetase Syndrome. *Jama* 2023;329(24):2154-62. doi: 10.1001/jama.2023.8753

93. Lodka D, Zschummel M, Bunse M, Rousselle A, Sonnemann J, Kettritz R, et al. CD19-targeting CAR T cells protect from ANCA-induced acute kidney injury. *Ann Rheum Dis* 2024;83(4):499-507. doi: 10.1136/ard-2023-224875

94. Minopoulou I, Wilhelm A, Albach F, Kleyer A, Wiebe E, Schallenberg S, et al. Anti-CD19 CAR T cell therapy induces antibody seroconversion and complete B cell depletion in the bone marrow of a therapy-refractory patient with ANCA-associated vasculitis. *Ann Rheum Dis* 2025;84(3):e4-e7. doi: 10.1016/j.ard.2025.01.008

95. Anyfanti P, Evangelidis P, Kotsiou N, Papakonstantinou A, Eftychidis I, Sakellari I, et al. Chimeric antigen receptor T cell immunotherapy for autoimmune rheumatic disorders: Where are we now? *Cells* 2025;14(16):1242. doi: 10.3390/cells14161242

96. Riet T, Chmielewski M. Regulatory CAR-T cells in autoimmune diseases: Progress and current challenges. *Front Immunol* 2022;13:934343. doi: 10.3389/fimmu.2022.934343

97. Bulliard Y, Freeborn R, Uyeda MJ, Humes D, Bjordahl R, de Vries D, Roncarolo MG. From promise to practice: CAR T and Treg cell therapies in autoimmunity and other immune-mediated diseases. *Front Immunol* 2024;15:1509956. doi: 10.3389/fimmu.2024.1509956

98. Holm A, Hansen SN, Klitgaard H, Kauppinen S. Clinical advances of RNA therapeutics for treatment of neurological and neuromuscular diseases. *RNA Biol* 2022;19(1):594-608. doi: 10.1080/15476286.2022.2066334

99. Kim Y. Drug Discovery Perspectives of Antisense Oligonucleotides. *Biomol Ther (Seoul)* 2023;31(3):241-52. doi: 10.4062/biomolther.2023.001

100. Zhang Y, Zang C, Mao M, Zhang M, Tang Z, Chen W, Zhu W. Advances in RNA therapy for the treatment of autoimmune diseases. *Autoimmun Rev* 2025:103753.

101. Javidi-Aghdam K, Faghfouri A, Jafarpour M, Akbarzadeh-Khiavi M, Safary A, Pourbagherian O, Khabbazi A. Role of NEAT1 and HOTAIR long non-coding RNAs in Behcet's Disease pathogenesis and their correlation with target inflammatory cytokines. *Mol Biol Rep* 2025;52(1):111. doi: 10.1007/s11033-025-10218-7

102. Wu H, Chen S, Li A, Shen K, Wang S, Wang S, et al. LncRNA Expression Profiles in Systemic Lupus Erythematosus and Rheumatoid Arthritis: Emerging Biomarkers and Therapeutic Targets. *Front Immunol* 2021;12:792884. doi: 10.3389/fimmu.2021.792884

103. Li Z, Li X, Jiang C, Qian W, Tse G, Chan MTV, Wu WKK. Long non-coding RNAs in rheumatoid arthritis. *Cell Prolif* 2018;51(1). doi: 10.1111/cpr.12404

104. Wu GC, Hu Y, Guan SY, Ye DQ, Pan HF. Differential Plasma Expression Profiles of Long Non-Coding RNAs Reveal Potential Biomarkers for Systemic Lupus Erythematosus. *Biomolecules* 2019;9(6). doi: 10.3390/biom9060206

105. Cieśla M, Darmochwał-Kolarz D, Pałka A, Łagowska K, Tabarkiewicz J, Kolarz B. Expression of NEAT1, PACERR, and GAS5 circulating long noncoding RNAs can be associated with disease activity in rheumatoid arthritis patients. *Pol Arch Intern Med* 2024;134(12). doi: 10.20452/pamw.16866

106. Khoury M, Louis-Plence P, Escriou V, Noel D, Largeau C, Cantos C, et al. Efficient new cationic liposome formulation for systemic delivery of small interfering RNA silencing tumor necrosis factor alpha in experimental arthritis. *Arthritis Rheum* 2006;54(6):1867-77. doi: 10.1002/art.21876

107. Aldayel AM, O'Mary HL, Valdes SA, Li X, Thakkar SG, Mustafa BE, Cui Z. Lipid nanoparticles with minimum burst release of TNF-α siRNA show strong activity against rheumatoid arthritis unresponsive to methotrexate. *J Control Release* 2018;283:280-9. doi: 10.1016/j.jconrel.2018.05.035

108. Yim EY, Zhou AC, Yim YC, Wang X, Xia T. Antigen-specific mRNA lipid nanoparticle platforms for the prevention and treatment of allergy and autoimmune diseases. *BMEMat* 2024;2(2):e12060.

109. Billingsley MM, Singh N, Ravikumar P, Zhang R, June CH, Mitchell MJ. Ionizable Lipid Nanoparticle-Mediated mRNA Delivery for Human CAR T Cell Engineering. *Nano Lett* 2020;20(3):1578-89. doi: 10.1021/acs.nanolett.9b04246

110. Krienke C, Kolb L, Diken E, Streuber M, Kirchhoff S, Bukur T, et al. A noninflammatory mRNA vaccine for treatment of experimental autoimmune encephalomyelitis. *Science* 2021;371(6525):145-53. doi: https://doi.org/10.1126/science.aay3638

111. Kenison-White J, Saunders L, Danko A, Quintana FJ. Antigen-specific tolerogenic mRNA-LNPs for the treatment of autoimmunity 4721. *J Immunol* 2025;214(Supplement_1). doi: 10.1093/jimmun/vkaf283.2357

112. Ertural B, Çiçek BN, Kurnaz IA. RNA Therapeutics: Focus on Antisense Oligonucleotides in the Nervous System. *Biomol Ther (Seoul)* 2025;33(4):572-81. doi: 10.4062/biomolther.2025.022

113. Kaczmarek JC, Kowalski PS, Anderson DG. Advances in the delivery of RNA therapeutics: from concept to clinical reality. *Genome Med* 2017;9(1):60. doi: 10.1186/s13073-017-0450-0

114. Fathi M, Safary A, Barar J. Therapeutic impacts of enzyme-responsive smart nanobiosystems. *BioImpacts: BI* 2019;10(1):1. doi: 10.15171/bi.2020.01

115. Delgado-Pujol EJ, Martínez G, Casado-Jurado D, Vázquez J, León-Barberena J, Rodríguez-Lucena D, et al. Hydrogels and Nanogels: Pioneering the Future of Advanced Drug Delivery Systems. *Pharmaceutics* 2025;17(2). doi: 10.3390/pharmaceutics17020215

116. Das BC, Chokkalingam P, Masilamani P, Shukla S, Das S. Stimuli-Responsive Boron-Based Materials in Drug Delivery. *Int J Mol Sci* 2023;24(3). doi: 10.3390/ijms24032757

117. Zhao J, Zhao M, Yu C, Zhang X, Liu J, Cheng X, et al. Multifunctional folate receptor-targeting and pH-responsive nanocarriers loaded with methotrexate for treatment of rheumatoid arthritis. *Int J Nanomedicine* 2017;12:6735-46. doi: 10.2147/ijn.S140992

118. Martín-Sabroso C, Torres-Suárez AI, Alonso-González M, Fernández-Carballido A, Fraguas-Sánchez AI. Active Targeted Nanoformulations via Folate Receptors: State of the Art and Future Perspectives. *Pharmaceutics* 2021;14(1). doi: 10.3390/pharmaceutics14010014

119. Wu Z, Xu K, Min J, Chen M, Shen L, Xu J, et al. Folate-conjugated hydrophobicity modified glycol chitosan nanoparticles for targeted delivery of methotrexate in rheumatoid arthritis. *J Appl Biomater Funct Mater* 2020;18:2280800020962629. doi: 10.1177/2280800020962629

120. Wang L, Zhu B, Huang J, Xiang X, Tang Y, Ma L, et al. Ultrasound-targeted microbubble destruction augmented synergistic therapy of rheumatoid arthritis via targeted liposomes. *J Mater Chem B* 2020;8(24):5245-56. doi: 10.1039/d0tb00430h

121. Ma B, Xu H, Zhuang W, Wang Y, Li G, Wang Y. Reactive Oxygen Species Responsive Theranostic Nanoplatform for Two-Photon Aggregation-Induced Emission Imaging and Therapy of Acute and Chronic Inflammation. *ACS Nano* 2020;14(5):5862-73. doi: 10.1021/acsnano.0c01012

122. Fan XX, Xu MZ, Leung EL, Jun C, Yuan Z, Liu L. ROS-Responsive Berberine Polymeric Micelles Effectively Suppressed the Inflammation of Rheumatoid Arthritis by Targeting Mitochondria. *Nanomicro Lett* 2020;12(1):76. doi: 10.1007/s40820-020-0410-x

123. Zhang Y, Liu L, Wang T, Mao C, Shan P, Lau CS, et al. Reactive Oxygen Species-Responsive Polymeric Prodrug Nanoparticles for Selective and Effective Treatment of Inflammatory Diseases. *Adv Healthc Mater* 2023;12(29):e2301394. doi: 10.1002/adhm.202301394

124. Zhao X, Huang C, Su M, Ran Y, Wang Y, Yin Z. Reactive Oxygen Species-Responsive Celastrol-Loaded : Bilirubin Nanoparticles for the Treatment of Rheumatoid Arthritis. *AAPS J* 2021;24(1):14. doi: 10.1208/s12248-021-00636-3

125. Jia J, Liu M, Yang H, Li X, Liu S, Li K, et al. Manganese Dioxide-Based pH-Responsive Multifunctional Nanoparticles Deliver Methotrexate for Targeted Rheumatoid Arthritis Treatment. *Biomater Res* 2025;29:0187. doi: 10.34133/bmr.0187

126. Goyal AK, Ramchandani M, Basak T. Recent advancements, challenges, and future prospects in usage of nanoformulation as theranostics in inflammatory diseases. *J Nanotheranostics* 2023;4(1):106-26.

127. Johnson SL, Gibbons SR, Nielsen CJ. Theranostics Beyond Oncology: Emerging Applications. *J Nucl Med Technol* 2025;53(Suppl 1):141s-3s. doi: 10.2967/jnmt.125.271192

128. Kalashnikova I, Chung SJ, Nafiujjaman M, Hill ML, Siziba ME, Contag CH, Kim T. Ceria-based nanotheranostic agent for rheumatoid arthritis. *Theranostics* 2020;10(26):11863-80. doi: 10.7150/thno.49069

129. Zhang Y, Liu D, Chen W, Tao Y, Li W, Qi J. Microenvironment-Activatable Probe for Precise NIR-II Monitoring and Synergistic Immunotherapy in Rheumatoid Arthritis. *Adv Mater* 2024;36(48):e2409661. doi: 10.1002/adma.202409661

130. LaMothe RA, Kolte PN, Vo T, Ferrari JD, Gelsinger TC, Wong J, et al. Tolerogenic Nanoparticles Induce Antigen-Specific Regulatory T Cells and Provide Therapeutic Efficacy and Transferrable Tolerance against Experimental Autoimmune Encephalomyelitis. *Front Immunol* 2018;9:281. doi: 10.3389/fimmu.2018.00281

131. Phan NM, Nguyen TL, Shin H, Trinh TA, Kim J. ROS-Scavenging Lignin-Based Tolerogenic Nanoparticle Vaccine for Treatment of Multiple Sclerosis. *ACS Nano* 2023;17(24):24696-709. doi: 10.1021/acsnano.3c04497

132. Nguyen TL, Choi Y, Im J, Shin H, Phan NM, Kim MK, et al. Immunosuppressive biomaterial-based therapeutic vaccine to treat multiple sclerosis via re-establishing immune tolerance. *Nat Commun* 2022;13(1):7449. doi: 10.1038/s41467-022-35263-9

133. Yang Y, Zhao Y, Liu H, Wu X, Guo M, Xie L, et al. Inflammation-Targeted Biomimetic Nano-Decoys via Inhibiting the Infiltration of Immune Cells and Effectively Delivering Glucocorticoids for Enhanced Multiple Sclerosis Treatment. *Adv Healthc Mater* 2025;14(2):e2402965. doi: 10.1002/adhm.202402965

134. Rhodes KR, Tzeng SY, Iglesias M, Lee D, Storm K, Neshat SY, et al. Bioengineered particles expand myelin-specific regulatory T cells and reverse autoreactivity in a mouse model of multiple sclerosis. *Sci Adv* 2023;9(22):eadd8693. doi: 10.1126/sciadv.add8693

135. Shetty S, Wu Y, Lloyd CZ, Mehta N, Liu Y, Woodruff ME, et al. Anti-Cytokine Active Immunotherapy Based on Supramolecular Peptides for Alleviating IL-1β-Mediated Inflammation. *Adv Healthc Mater* 2025;14(5):e2401444. doi: 10.1002/adhm.202401444

136. Curvino EJ, Woodruff ME, Roe EF, Freire Haddad H, Cordero Alvarado P, Collier JH. Supramolecular Peptide Self-Assemblies Facilitate Oral Immunization. *ACS Biomater Sci Eng* 2024;10(5):3041-56. doi: 10.1021/acsbiomaterials.4c00525

137. Wu Y, Kelly SH, Sanchez-Perez L, Sampson JH, Collier JH. Comparative study of α-helical and β-sheet self-assembled peptide nanofiber vaccine platforms: influence of integrated T-cell epitopes. *Biomater Sci* 2020;8(12):3522-35. doi: 10.1039/d0bm00521e

138. Abdullah T, Bhatt K, Eggermont LJ, O'Hare N, Memic A, Bencherif SA. Supramolecular Self-Assembled Peptide-Based Vaccines: Current State and Future Perspectives. *Front Chem* 2020;8:598160. doi: 10.3389/fchem.2020.598160

139. Kalincik T, Sharmin S, Roos I, Freedman MS, Atkins H, Massey J, et al. Haematopoietic stem cell transplant versus immune-reconstitution therapy in relapsing multiple sclerosis. *Brain* 2025. doi: 10.1093/brain/awaf286

140. von Niederhäusern V, Ruder J, Ghraichy M, Jelcic I, Müller AM, Schanz U, et al. B-Cell Reconstitution After Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2022;9(6). doi: 10.1212/nxi.0000000000200027

141. Nelson BE, Ramdial JL, Bashir Q, Saini N, Hosing C, Popat UR, et al. Autologous hematopoietic stem cell transplantation for AL Amyloidosis refractory to induction therapy. *Blood* 2021;138:482.

142. Zhu X, Yue M, Zhang X, Han Y, Xia R, Zhang Q, et al. Global Disease Burden of Immune-Mediated Inflammatory Diseases (IMIDs), 1990–2021. *Med Res* 2025;1(2):285-96.

143. Liang Z, Xie H, Wu D. Immune mediated inflammatory diseases: moving from targeted biologic therapy, stem cell therapy to targeted cell therapy. *Front Immunol* 2025;16:1520063. doi: 10.3389/fimmu.2025.1520063

144. Opdam M, Vriezekolk J, Den Broeder A, Verhoef L. POS1561-HPR HEALTH CARE PROVIDERS'PERSPECTIVE ON CONTINUATION VERSUS TEMPORARY INTERRUPTION OF IMMUNOMODULATORY AGENTS IN CASE OF AN INFECTION: AN INTERVIEW STUDY. *Ann Rheum Dis* 2022;81:1126-7.

145. Cheon JH, Duk Ye B, Armuzzi A, Rieder F, Girolomoni G, Puig L, et al. The 'totality of evidence' and 'extrapolation' of SB17, a ustekinumab biosimilar. *Expert Opin Biol Ther* 2025;25(6):615-32. doi: 10.1080/14712598.2025.2508838

146. Forbes JD, Van Domselaar G, Bernstein CN. The Gut Microbiota in Immune-Mediated Inflammatory Diseases. *Front Microbiol* 2016;7:1081. doi: 10.3389/fmicb.2016.01081

147. Guilliams TG, Weintraub J. Implementing Personalized Dietary Interventions for Immune-Mediated Inflammatory Diseases. *Integr Med (Encinitas)* 2023;22(5):18-26.

148. Gaetz J, Wall TR, Stylianou ES, Khalil E, Levy O, Selinger DW. Abstract A019: A fully transparent and automatable form of AI for biomarker and new target discovery using diverse multi-omics data. *Clin Cancer Res* 2025;31(13_Supplement):A019-A.

149. Upadhyay AK, Kumari N, Gupta N, Kumar S. AI Convergence in Drug Development and Recent Applications: A Review. *Res J Pharm Dosage Forms Technol* 2025;17(2):107-14.

150. Husnain A, Rasool S, Saeed A, Hussain HK. Revolutionizing pharmaceutical research: Harnessing machine learning for a paradigm shift in drug discovery. *Int J Multidiscip Sci Arts* 2023;2(4):149-57.

151. Ho D, Wang P, Kee T. Artificial intelligence in nanomedicine. *Nanoscale Horiz* 2019;4(2):365-77. doi: 10.1039/c8nh00233a

152. Zou J. The Application Progress, Challenges, and Future Directions of Gene Editing Technology in Immunotherapy. *Highl Sci Eng Technol* 2025;129:115-21.

153. Far BF, Akbari M, Habibi MA, Katavand M, Nasseri S. CRISPR technology in disease management: An updated review of clinical translation and therapeutic potential. *Cell Proliferation* 2025;58(11):e70099. doi: 10.1111/cpr.70099

154. Zang S-s, Zhang R, Zhang J-r, Zhang X, Li J. Progress, Applications and Prospects of CRISPR-Based Genome Editing Technology in Gene Therapy for Cancer and Sickle Cell Disease. *Hum Gene Ther* 2025;36(11-12):858-69.

155. Hu Y, Zhou Y, Zhang M, Ge W, Li Y, Yang L, et al. CRISPR/Cas9-engineered universal CD19/CD22 dual-targeted CAR-T cell therapy for relapsed/refractory B-cell acute lymphoblastic leukemia. *Clin Cancer Res* 2021;27(10):2764-72.