

บทความวิชาการ

Academic Articles

ความก้าวหน้าทางการพัฒนาเชิงเปลี่ยนแปลงในภูมิคุ้มกันบำบัดสังเคราะห์: การเข้าใจกลไกและนวัตกรรมการรักษาสำหรับโรคภูมิคุ้มกันทำลายตนเอง

นันทวรรณ วัฒนะโชติ

อิงค์ฟ้า ร่องเรืองกุล

พรกนก พุ่มพิสุทธิ์

กานต์พิชชา แก้วของแก้ว

สิริพร ชูเพชรสมบูรณ์

โรงเรียนนานาชาติเซนต์แอนดรูว์ส

โรงเรียนนานาชาติเฮดสตาาร์ท

โรงเรียนสามเสนวิทยาลัย

โรงเรียนนานาชาติเอ็กมัย

นักวิจัยอิสระ

DOI: 10.14456/jrpsi.2026.13

Received: September 21, 2025 | Revised: January 20, 2026 | Accepted: 3 February, 2026

บทคัดย่อ

ภูมิคุ้มกันบำบัดสังเคราะห์ (Synthetic immunotherapy) ถือเป็นความก้าวหน้าทางการแพทย์ที่ปฏิวัติการรักษาโรคภูมิคุ้มกันทำลายตนเอง โดยการบูรณาการชีววิทยาสังเคราะห์ การแก้ไขยีนส์เทคโนโลยีขั้นสูงนาโน และปัญญาประดิษฐ์ (AI) เพื่อพัฒนากลยุทธ์การรักษาที่มีความแม่นยำและมีประสิทธิภาพสูง โรคภูมิคุ้มกันทำลายตนเองมักเกิดจากความผิดปกติในการทนทานของระบบภูมิคุ้มกัน ส่งผลให้เกิดการอักเสบเรื้อรังและการทำลายเนื้อเยื่อจากการทำงานที่ผิดปกติของลิโฟไซด์ที่เกิดขึ้นจากตนเอง การควบคุมไซโตไคน์ที่ผิดปกติ และพันธุกรรมที่มีแนวโน้มทางโรค แม้ว่าการรักษาด้วยยาแบบดั้งเดิม เช่น สเตียรอยด์และยาชีวภาพจะช่วยพัฒนาการจัดการโรคได้ แต่ก็มีผลข้างเคียงและประสิทธิภาพระยะยาวที่จำกัด

บทความนี้สำรวจนวัตกรรมล่าสุดในภูมิคุ้มกันบำบัดสังเคราะห์ รวมถึงการแก้ไขจีโนมด้วยเทคนิค CRISPR/Cas9 การรักษาด้วยเซลล์ CAR-T เซลล์นำเสนอแอนติเจนสังเคราะห์ (Synthetic antigen-presenting cells หรือ APCs) และระบบการส่งยาแบบนาโนเทคโนโลยี การบูรณาการข้อมูลหลายมิติ (Multi-omics) และปัญญาประดิษฐ์ช่วยเพิ่มความแม่นยำและการปรับการรักษา โดยการระบุเครื่องหมายทางชีวภาพและเพิ่มประสิทธิภาพการตอบสนองการรักษา แม้จะมีความก้าวหน้าดังกล่าวแต่ยังคงมีอุปสรรคที่ท้าทาย เช่น ผลกระทบที่ไม่เจาะจง (off-target effects) ความเป็นพิษทางระบบ ความสามารถในการผลิตในปริมาณมาก และข้อกังวลทางจริยธรรม ซึ่งยังคงเป็นอุปสรรคสำคัญต่อการแปลผลทางคลินิก การพิจารณาตามกฎหมายระเบียบ และปัจจัยทางเศรษฐกิจยังทำให้การนำไปใช้ในวงกว้างและการเข้าถึงยากขึ้น

บทบทความนี้สรุปความก้าวหน้าของภูมิคุ้มกันบำบัดสังเคราะห์ในปัจจุบัน โดยเน้นถึงศักยภาพในการเปลี่ยนแปลง ในขณะที่คำนึงถึงอุปสรรคหลักที่ต้องดำเนินการเพื่อให้การนำไปใช้ทางคลินิกประสบความสำเร็จ แนวทางการวิจัยในอนาคตจะเน้นไปที่การปรับปรุงกลไกความปลอดภัย กรอบระเบียบข้อบังคับ และการทำงานร่วมกันระหว่างสาขาวิชาต่างๆ เพื่อให้ได้ผลทางการรักษาสูงสุด เมื่อชีววิทยาสังเคราะห์ยังคงพัฒนานวัตกรรมเหล่านี้มีศักยภาพในการพัฒนาการรักษาโรคภูมิคุ้มกันทำลายตนเองผ่านการออกแบบตามความถูกต้อง ซึ่งให้ทางเลือกการรักษาที่ปลอดภัยกว่ามีประสิทธิภาพมากขึ้น และสามารถปรับแต่งได้ตามผู้ป่วยแต่ละราย

ติดต่อผู้พิมพ์: สิริพร ชูเพชรสมบูรณ์

อีเมล: siriporn.shu@gmail.com

คำสำคัญ: ภูมิคุ้มกันบำบัดแบบสังเคราะห์, โรคภูมิคุ้มกันทำลายตนเอง, เซลล์ CAR-T, การตัดแต่งยีน, นาโนเวชกรรม, การแพทย์แม่นยำ

Transformative advances in synthetic immunotherapy: mechanistic insights and therapeutic innovations for autoimmune diseases

Nuntawan Watanachote

St Andrews International School Bangkok

Ingfah Rongrueangkul

Headstart International School Phuket

Pronkanok Pootpisut

Samsenwittayalai School

Kanpitcha Kaewkongkaew

Ekamai International School

Siriporn Shupetchsomboon

Independent Researcher

Abstract

Synthetic immunotherapy represents a transformative advancement in the treatment of autoimmune diseases, by integrating synthetic biology, gene editing, nanotechnology, and artificial intelligence to develop highly targeted and effective therapeutic strategies. Autoimmune diseases are characterized by a breakdown in immune tolerance, resulting in chronic inflammation and progressive tissue damage driven by autoreactive lymphocytes, cytokine dysregulation, and genetic predispositions. Although conventional therapies such as corticosteroids and biologics have improved disease management, they are frequently associated with adverse effects and limited long-term efficacy.

This review explores the latest innovations in synthetic immunotherapy, including CRISPR/Cas9-mediated genome editing, chimeric antigen receptor (CAR) T-cell therapies, synthetic antigen-presenting cells (APCs), and nanotechnology-based drug delivery systems. The integration of multi-omics technologies and artificial intelligence further enhances the precision and personalization of these therapies by identifying biomarker and optimizing therapeutic responses. Despite these advances, challenges such as off-target effects, systemic toxicity, manufacturing scalability, and ethical concerns remain significant barriers to clinical translation. Regulatory considerations and economic factors further complicate widespread adoption and accessibility.

We critically assess the current landscape of synthetic immunotherapy, highlighting its transformative potential while addressing key obstacles that must be overcome for successful clinical implementation. Future research directions emphasize the need for improved safety mechanisms, regulatory frameworks, and interdisciplinary collaboration to maximize therapeutic impact. As synthetic biology continues to evolve, these innovations hold the promise of revolutionizing autoimmune disease treatment through precision-engineered interventions, that enable safer, more effective, and personalized therapeutic solutions.

Corresponding Author: Siriporn Shupetchsomboon **E-mail:** siriporn.shu@gmail.com

Keywords: Synthetic immunotherapy, Autoimmune diseases, CAR-T cells, Gene editing, Nanomedicine, Precision medicine

Introduction

Autoimmune diseases comprise a heterogeneous group of chronic conditions characterized by a breakdown of immune tolerance, leading to persistent inflammation and progressive tissue damage. These disorders including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease impose a substantial global health burden due to lifelong disease courses, reduced quality of life, and significant healthcare costs⁽¹⁾. Despite advances in immunology, the complex and multifactorial nature of autoimmune disease pathogenesis continues to pose major challenges to effective and durable disease management.

Conventional therapeutic strategies for autoimmune diseases have traditionally relied on broad immunosuppression using corticosteroids, non-steroidal anti-inflammatory drugs, and conventional disease-modifying antirheumatic drugs. While these approaches can alleviate symptoms and control inflammation, their lack of specificity frequently results in systemic adverse effects, increased risk of infection, and incomplete disease control⁽¹⁾. The introduction of biologic therapies targeting specific cytokines or immune cell populations has improved clinical outcomes for many patients; however, therapeutic resistance, long-term safety concerns, high costs, and interindividual variability in treatment responses remain significant limitations⁽²⁾.

In recent years, the convergence of synthetic biology, immune engineering, and computational technologies has given rise to synthetic immunotherapy as a transformative therapeutic paradigm aimed at reprogramming immune responses with high precision. Rather than broadly suppressing immune activity, synthetic immunotherapy seeks to selectively modulate pathogenic pathways, restore immune tolerance, and achieve durable disease control. Advances in genome editing, cellular engineering, biomaterials, and data-driven therapeutic design have accelerated the development of innovative immunomodulatory strategies with the potential to overcome the limitations of existing treatments⁽³⁻⁶⁾.

Despite its promise, the rapidly expanding field of synthetic immunotherapy remains fragmented across diverse preclinical and early-stage clinical studies. Critical questions persist regarding safety, scalability, regulatory oversight, ethical considerations, and long-term efficacy. A comprehensive synthesis of the current evidence is therefore essential to clarify the therapeutic potential, limitations, and translational readiness of synthetic immunotherapy approaches for the management of autoimmune diseases.

Accordingly, this review aims to synthesize and critically evaluate recent advances in synthetic immunotherapy for autoimmune diseases. Specifically, it examines (i) the evolution of immunotherapeutic strategies, (ii) emerging synthetic biology-based interventions, (iii) technological innovations enabling precision immune modulation, and (iv) key challenges and future research directions necessary for successful clinical translation.

Literature Review

Evolution of immunotherapy in autoimmune diseases

The therapeutic management of autoimmune diseases has evolved substantially over the past several decades. Early treatment paradigms were dominated by nonspecific immunosuppressive agents, including corticosteroids and NSAIDs, which effectively reduced

inflammation but failed to address the underlying immune dysregulation driving disease progression⁽¹⁾. Conventional synthetic disease-modifying antirheumatic drugs further improved disease control; however, their delayed onset of action and systemic toxicity limited long-term clinical utility.

The development of biologic therapies marked a pivotal shift toward targeted immunomodulation. Monoclonal antibodies and fusion proteins targeting tumor necrosis factor, interleukin-6, interleukin-17, interleukin-23, and B-cell surface antigens demonstrated improved efficacy and specificity across multiple autoimmune conditions^(2,7). Nevertheless, accumulating evidence revealed persistent challenges, including immunogenicity, secondary loss of response, increased risk of infection, and financial burden, underscoring the need for more adaptable and durable therapeutic approaches.

Targeted synthetic DMARDs, particularly Janus kinase and tyrosine kinase 2 inhibitors, further expanded therapeutic options by modulating intracellular cytokine signaling pathways^(8,9). While these agents offer oral administration and rapid efficacy, post-marketing data have raised concerns regarding cardiovascular risk, malignancy, and long-term safety, highlighting persistent limitations within current immunotherapeutic frameworks.

Emergence of synthetic immunotherapy

Synthetic immunotherapy has emerged as a novel paradigm that integrates synthetic biology, immune engineering, and systems-level design to actively reprogram immune responses rather than merely inhibiting inflammatory mediators. This approach leverages advances in genome editing, cellular engineering, and synthetic gene circuits to achieve precise, programmable, and context-dependent immune modulation⁽³⁾.

Genome-editing technologies, particularly CRISPR/Cas9, have enabled targeted modification of immune cell genomes with unprecedented precision. Studies demonstrate the feasibility of disrupting autoreactive signaling pathways, enhancing regulatory immune functions, and improving therapeutic specificity through controlled genetic interventions^(3,10). Compared with earlier genome-editing platforms such as TALENs and zinc finger nucleases, CRISPR-based systems offer improved efficiency and scalability, thereby accelerating translational research in autoimmune immunotherapy.

Cellular engineering and synthetic immune modulation

Adoptive cellular therapies represent a central component of synthetic immunotherapy. Chimeric antigen receptor T-cell therapies, originally developed for oncology, have been repurposed for autoimmune diseases with promising early results. Preclinical and early clinical studies in systemic lupus erythematosus indicate that CD19-targeted CAR-T cells can effectively eliminate autoreactive B-cell populations and induce sustained remission in selected patients^(4,5).

Beyond CAR-T cells, recent advances in synthetic suppressor T cells and engineered regulatory T cells have expanded the scope of immune tolerance induction. Synthetic gene circuits enable immune cells to sense inflammatory cues and respond dynamically through controlled cytokine release or immunosuppressive signaling, thereby minimizing systemic

toxicity while preserving protective immunity^(6,11). These approaches represent a shift toward programmable and self-regulating immunotherapies.

Synthetic antigen presentation and Tolerance Induction

Antigen-specific tolerance remains a critical goal in autoimmune disease treatment. Synthetic antigen-presenting cells have been developed to mimic dendritic cell functions using engineered biomaterials and major histocompatibility complex molecules. By delivering defined antigenic signals and costimulatory cues, synthetic APCs selectively engage autoreactive T cells and promote regulatory immune responses⁽¹²⁾. Experimental models suggest that this strategy reduces off-target immune activation and may enable long-term immune tolerance without chronic immunosuppression.

Nanotechnology-enabled immunotherapy

Nanotechnology has emerged as a key enabling platform for synthetic immunotherapy by enhancing drug delivery precision, bioavailability, and safety. Polymeric nanoparticles, liposomes, and hydrogel-based systems have demonstrated improved targeting of inflamed tissues, controlled drug release, and reduced systemic exposure in autoimmune disease models⁽¹³⁻¹⁵⁾. These delivery platforms are particularly advantageous for localized autoimmune pathologies and for protecting sensitive biologic or nucleic-acid-based therapeutics.

Multi-omics integration and computational advances

The integration of multi-omics technologies has significantly advanced the understanding of autoimmune disease heterogeneity and therapeutic responsiveness. Single-cell RNA sequencing and spatial transcriptomics have revealed previously unrecognized immune cell subsets and pathogenic signaling networks, thereby facilitating the identification of novel therapeutic targets⁽¹⁶⁾. Artificial intelligence and machine learning approaches are increasingly employed to analyze complex biological datasets, optimize synthetic construct design, and predict patient-specific therapeutic responses, supporting the development of precision immunotherapy strategies^(17,18).

Gaps and limitations in current literature

Despite rapid progress, the literature consistently identifies unresolved challenges that limit clinical translation. These include off-target genetic effects, the durability of immune reprogramming, manufacturing scalability, regulatory uncertainty, and ethical considerations related to permanent immune modification^(8,19,20). Moreover, most evidence remains confined to preclinical or early-phase clinical studies, emphasizing the need for long-term safety data, standardized evaluation frameworks, and cost-effective production strategies to ensure equitable global access⁽²¹⁾.

Findings

This study employed a systematic literature review to evaluate the integration of synthetic biology in advancing immunotherapy for autoimmune diseases. Searches were conducted across major electronic databases, including MEDLINE®, Springer, ACS Publications, Google Scholar, and ScienceDirect, without restrictions on publication dates but limited to

English-language articles. Specific keywords and Medical Subject Headings (MeSH) terms were used, including "synthetic biology," "immunotherapy," "autoimmune diseases," "gene therapy," "immune engineering," "synthetic circuits," "immune modulation," "biotherapeutics," and "genome editing."

The inclusion criteria emphasized studies that explored the molecular mechanisms of synthetic constructs in immune modulation, investigated preclinical and clinical outcomes of synthetic immunotherapies, and addressed the safety and scalability of these approaches. In addition to primary research articles, the bibliographies of key studies were manually reviewed to capture broader insights. Abstracts from international conferences on synthetic biology and immunotherapy were incorporated to ensure coverage of cutting-edge research. This comprehensive methodology provided a robust framework for analyzing how synthetic biology can revolutionize the treatment of autoimmune disease.

This review adhered to stringent criteria for evaluating study quality, including reproducibility of experimental designs, the robustness of reported outcomes, and comprehensive reporting of safety and efficacy data. By synthesizing these insights, the review delivers an in-depth understanding of the potential of synthetic medicine to address the unmet needs in the management of autoimmune disease.

Detailed mechanistic insights into autoimmune pathogenesis

Autoimmune diseases result from a fundamental breakdown in immune tolerance, whereby the immune system erroneously recognizes self-tissues as foreign invaders, leading to chronic inflammation, progressive tissue damage, and impaired organ function⁽²⁾. Central to autoimmune pathology are autoreactive T and B lymphocytes that escape mechanisms of immune tolerance, persistently targeting self-tissues. Genetic factors significantly influence autoimmune susceptibility, particularly polymorphisms in immune-regulatory genes such as *HLA*, *CTLA4*, and *PTPN22*, strongly associated with rheumatoid arthritis and multiple sclerosis⁽²²⁾. Environmental triggers, including infections, dietary factors, and toxins, further modulate disease risk and may precipitate autoimmune conditions through mechanisms such as molecular mimicry, where microbial antigens resemble self-antigens, leading to immune cross-reactivity and autoimmunity.

A critical aspect of autoimmune pathogenesis involves cytokine dysregulation, characterized by an imbalance between pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-17 (IL-17), and regulatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β). This imbalance promotes chronic inflammation and tissue destruction, exemplified by IL-17-driven pathology in multiple sclerosis, which disrupts the blood-brain barrier and leads to neuronal damage⁽²²⁾. In addition, abnormal antigen presentation by dendritic cells exacerbates autoimmune responses, significantly enhancing T-cell activation against self-antigens⁽²³⁾.

Emerging insights into autoimmune mechanisms have highlighted aberrant signaling pathways as critical contributors to inflammatory processes. These include the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, nuclear factor-kappa B

(NF-**KB**) signaling, and Toll-like receptor (TLR) pathways, all of which significantly amplify autoimmune responses. Furthermore, autoantibodies, such as anti-citrullinated protein antibodies (ACPAs) in rheumatoid arthritis and anti-nuclear antibodies (ANAs) in systemic lupus erythematosus, produced by dysregulated B cells, actively target specific self-antigens, thereby perpetuating inflammation and tissue damage⁽²⁾.

A detailed understanding of these molecular mechanisms provides critical targets for the development of innovative therapeutic strategies aimed at restoring immune homeostasis and promoting sustained immune tolerance⁽²⁴⁾.

Discussion

Table 1 Chronological timeline of immunotherapy strategies in autoimmune diseases

Year	Development	Details
1950-2015	Traditional immunosuppressive therapies	Corticosteroids (e.g., prednisone) and NSAIDs (e.g., ibuprofen) remain first-line treatments despite adverse effects like osteoporosis and gastrointestinal complications. Corticosteroids will suppress inflammatory genes that are found to be active, causing it to be effective in reducing inflammation. It is, however, limited by their lack of specificity and side effects, both mentally and physically. NSAIDs, similarly, also work by inhibiting the synthesis of prostaglandins, substances that cause inflammation. However, while useful for pain relief, do not address the underlying autoimmune pathology ⁽¹⁾ .
2015-2018	Biologics and monoclonal antibodies	TNF inhibitors (e.g., infliximab, adalimumab), IL-6 inhibitors (e.g., tocilizumab), and B-cell depleting therapies (e.g., rituximab) are experiencing rapid growth and is gaining prominence. They are more complicated in structure than the previous small molecule drugs and target specific immune pathways, offering improved efficacy and reduced off-target effects compared to traditional therapies. From observation, they also showed that it is well tolerated with lower risk in patients. However, there are still drawbacks and adverse effects including immunogenicity ⁽²⁾ .
2015	First JAK Inhibitor Approval	Tofacitinib, a selective Janus kinase (JAK) inhibitor, showed signs of effectiveness in most of its preclinical trials in diseases, both as a monotherapy and in conjunction with another drug. This led to it being the first JAK to be tested and approved by FDA for rheumatoid arthritis, marking a shift towards targeted small-molecule therapies. JAK inhibitors modulate cytokine signaling which is crucial in inflammation and autoimmune diseases, offering a new avenue for autoimmune disease management ⁽⁹⁾ .

Table 1 Chronological timeline of immunotherapy strategies in autoimmune diseases (continued)

Year	Development	Details
2016-2020	Expansion of Biologics	IL-17 inhibitors (e.g., secukinumab) and IL-23 inhibitors (e.g., guselkumab), which work by disrupting the inflammatory cascade, are introduced for psoriasis and psoriatic arthritis, providing more targeted treatment options. These therapies demonstrate significant efficacy in clinical trials, showing notable signs of remission of the disease in most patients. However, there are still adverse effects present during the trials including nasopharyngitis, infections, headaches, and depression ⁽⁷⁾ .
2018	Targeted Synthetic DMARDs (tsDMARDs)	Baricitinib, a JAK1/JAK2 inhibitor, is approved for moderate-to-severe rheumatoid arthritis. tsDMARDs represent a new class of drugs that target intracellular signaling pathways with high specificity and when tested, it appears superior to csDMARDs in reducing mortality. This then improves the clinical symptoms and increases the patients quality of life ⁽⁸⁾ .
2020	Small molecule inhibitors	PDE4 inhibitors (e.g., apremilast) and TYK2 inhibitors (e.g., deucravacitinib), both of which suppress the function of inflammatory cells, are approved or under investigation for psoriatic arthritis and psoriasis, respectively. These inhibitors target specific enzymes involved in immune signaling. They, however, still have side effects including nausea, diarrhea, and headaches which can limit its utility ⁽¹⁹⁾ .
2020	CAR T-Cell therapy enters autoimmune research	Preclinical studies explore CD19-targeted CAR T cells for lupus treatment, showing promising early results which will then counter the problems of efficiency and patients not responding to previous treatments. CAR T-cell therapy, originally developed for cancer, is repurposed for autoimmune diseases after it appears to be safe and efficient in trials ⁽⁴⁾ .
2021	First clinical success of CAR T-cell Therapy in autoimmune disease	A breakthrough study demonstrates effective and sustained remission in systemic lupus erythematosus (SLE) patients treated with CAR T-cell therapy, marking a significant milestone in autoimmune disease treatment since there have been problems of patients not responding to the treatments ⁽⁵⁾ .
2022-2025	CRISPR/Cas9 in Autoimmune Disease Research	Advances in gene editing enable precision modifications in immune cells, targeting autoreactive pathways. CRISPR/Cas9 technology is used to engineer immune cells for enhanced specificity and reduced off-target effects ⁽³⁾ .
2023	Synthetic Immunology and Engineered T Cells	Development of synthetic receptors and engineered T cells to modulate autoimmune responses with high specificity. These therapies are designed to reprogram immune cells to recognize and suppress autoreactive immune responses ⁽⁶⁾ .

Table 1 Chronological timeline of immunotherapy strategies in autoimmune diseases (continued)

Year	Development	Details
2023	Next-Generation JAK and TYK Inhibitors	FDA approves deucravacitinib, a first-in-class TYK2 inhibitor, for psoriasis. These next-generation inhibitors offer enhanced precision in targeting immune signaling pathways ⁽¹⁷⁾ .
2024-2025	Gene Therapy and Cellular Reprogramming	Research into regulatory T cell (Treg) reprogramming and engineered immune tolerance for treating autoimmunity. Gene therapy approaches aim to restore immune balance by reprogramming autoreactive T cells ⁽¹³⁾ .

Advanced synthetic biology tools for autoimmune diseases

Recent advancements in synthetic biology have significantly impacted the treatment landscape of autoimmune diseases by integrating sophisticated genetic engineering and molecular tools to enable for precise modulation of immune responses.

CRISPR/Cas9, TALEN, and ZFN systems

Gene-editing technologies such as CRISPR/Cas9, TALEN, and Zinc finger nucleases (ZFNs) offer unprecedented precision in modifying immune cell functions. The CRISPR/Cas9 system enables highly specific genetic edits by creating double-strand breaks at targeted DNA sequences, which are repaired through Homology-Directed Repair (HDR) or Non-Homologous End Joining (NHEJ). This technology facilitates targeted disruptions of genes involved in autoreactive pathways, significantly advancing therapeutic strategies for autoimmune diseases by reducing off-target effects and improving specificity^(3,10).

TALENs and ZFNs, employing DNA-binding domains combined with nuclease domains, further enhance genome-editing capabilities. These nucleases have demonstrated effectiveness in modifying T-cell receptors (TCRs), enabling the reprogramming of T cells to specifically recognize and suppress pathogenic immune responses, thereby promoting immune tolerance in autoimmune diseases⁽¹⁰⁾.

Synthetic gene circuits and engineered receptors

Synthetic gene circuits represent an innovative approach for precise immune modulation. Recent developments include synthetic T-cell receptors engineered to selectively recognize and regulate pathogenic immune responses while preserving normal immune functions. These engineered T-cells mediate targeted immunosuppression through the secretion of anti-inflammatory cytokines such as IL-10 and TGF- β as well as through the neutralization of pro-inflammatory cytokines at sites of inflammation. This programmable and targeted immunosuppression significantly reduces systemic side effects compared to conventional immunosuppressive therapies⁽⁶⁾.

Synthetic Antigen-Presenting Cells (APCs)

Advances in biomaterials and genome-editing technologies have enabled the development of synthetic antigen-presenting cells (APCs) that recapitulate key functions of natural dendritic cells. These synthetic APCs are engineered to present tailored antigenic

peptides via modified major histocompatibility complex (MHC) molecules, optimizing their interaction with autoreactive T cells and promoting immune tolerance. Clinical trials investigating synthetic APCs in rheumatoid arthritis and multiple sclerosis have demonstrated improved therapeutic outcomes, reduced inflammation, and minimized systemic toxicity⁽¹²⁾.

Nanotechnology-Based Delivery Systems

Nanoparticle-based drug delivery platforms have transformed synthetic immunotherapy, by enabling the precise targeting of immunosuppressive agents to localized sites of inflammation. Polymeric and liposomal nanoparticles effectively encapsulate therapeutic agents, facilitating controlled and sustained release while significantly reducing systemic adverse effects. Clinical studies in psoriasis, rheumatoid arthritis, and inflammatory bowel diseases have demonstrated improved efficacy and safety profiles of nanoparticle-mediated delivery systems^(14,15).

Synthetic Regulatory T-Cells (Tregs)

Synthetic Tregs have been engineered to exhibit enhanced stability and suppressive functions, enabling the selective targeting of autoreactive immune responses. Advances in CRISPR-Cas9 technology have facilitated precise modifications of Treg receptors, thereby significantly enhancing their therapeutic potential and specificity. Clinical applications in autoimmune diseases, including type 1 diabetes and inflammatory bowel disease, have demonstrated improved outcomes, reduced inflammation, and prolonged remission⁽¹¹⁾.

Collectively, these advanced synthetic biology tools represent a paradigm shift in the treatment of autoimmune diseases, providing highly targeted and effective interventions with reduced adverse effects. Continued research and development in these areas are expected to further enhance therapeutic precision, patient safety, and clinical outcomes.

Innovations in nanotechnology and drug delivery

Nanotechnology-based drug delivery systems have significantly improved synthetic immunotherapy by enabling highly precise targeting, enhanced pharmacokinetics, and reduced systemic toxicity^(13,14). Polymeric nanoparticles, especially those derived from poly (lactic-co-glycolic acid) (PLGA), provide biocompatible platforms tailored for the targeted delivery of immunosuppressive agents directly to inflammatory sites, thereby minimizing off-target effects and systemic adverse reactions⁽¹⁵⁾. Liposomal nanoparticles further enhance the stability and bioavailability of encapsulated therapeutics, optimizing their controlled release and therapeutic efficacy⁽¹³⁾. In addition, advances in hydrogel and scaffold-based delivery systems facilitate the sustained release of tolerance-inducing molecules, significantly improving patient outcomes in autoimmune diseases⁽¹⁴⁾.

Multi-omics integration and computational advances

The integration of multi-omics technologies including genomics, transcriptomics, proteomics, and metabolomics has dramatically enhanced our understanding of autoimmune diseases⁽¹⁷⁾. Techniques such as single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have revealed distinct cellular states and interactions within disease microenvironments,

enabling more precise therapeutic targeting⁽¹⁶⁾. High-resolution mass spectrometry-based proteomic and metabolomic analyses have identified novel biomarkers for early disease detection and treatment monitoring. Additionally, advanced computational tools, notably machine learning and artificial intelligence (AI), have revolutionized therapeutic design by facilitating the rapid development and optimization of synthetic immunotherapies through accurate prediction of immune responses and therapeutic efficacy.

Comprehensive ethical and regulatory considerations

Synthetic immunotherapies pose significant ethical and regulatory challenges, including patient safety, informed consent, and long-term monitoring. Ensuring patient autonomy through transparent communication regarding potential genetic modifications and associated risks is paramount. Regulatory frameworks must evolve to address the unique challenges posed by synthetic biology, incorporating rigorous safety assessments, iterative testing protocols, and transparent reporting practices⁽²⁰⁾. Global regulatory authorities, including the FDA and EMA, continue refining guidelines to balance innovation with patient protection, emphasizing harmonized standards across jurisdictions. Public engagement and education remain essential for fostering societal trust and acceptance of these advanced therapies.

Economic challenges and accessibility issues

Despite substantial clinical promise, synthetic immunotherapies face significant economic challenges, primarily due to high manufacturing costs, limitations in production scalability, and disparities in global healthcare accessibility⁽²¹⁾. Overcoming these barriers requires strategic partnerships among academia, industry, healthcare providers, and governmental agencies. Innovations focused on reducing production costs through technological advancements, standardization, and robust public-private partnerships are critical to improving the affordability and accessibility of these cutting-edge treatments.

Clinical translation: current challenges and opportunities

The clinical translation of synthetic immunotherapies involves navigating complex challenges, including the inherent heterogeneity of autoimmune disease presentations, the scalability of therapeutic manufacturing, and the need to ensure patient-specific immune compatibility⁽²⁰⁾. Significant challenges include mitigating off-target effects, effectively managing the risks of cytokine release syndrome associated with cellular therapies, and maintaining the durability of therapeutic responses^(8,19). Rigorous clinical trials, standardized manufacturing protocols, and comprehensive regulatory oversight are critical to addressing these issues. Moreover, interdisciplinary collaboration among scientific, clinical, and regulatory stakeholders is essential for streamlining the translational pipeline, enhancing therapeutic efficacy, and ensuring patient safety.

Despite their promising potential, synthetic immunotherapies face significant obstacles that hinder their widespread clinical adoption. These challenges include severe adverse effects, limited efficacy in certain indications, such as solid tumors and complex autoimmune diseases, and substantial complexities associated with therapeutic manufacturing^(25,26). Systemic toxicity and immune tolerance represent major hurdles, particularly for small

molecule-based therapies like Toll-like receptor agonists. Furthermore, variability in the quality of autologous cell products and the requirement for specialized manufacturing facilities add layers of complexity to broad clinical implementation⁽²⁷⁾.

Innovative strategies and solutions

To overcome these clinical translation challenges, researchers are developing cutting-edge strategies, including the use of synthetic molecules and engineered cells to precisely regulate immune functions, thereby enhancing therapeutic outcomes while minimizing adverse effects. Dynamic immunomodulation strategies, including prodrug-like molecules and nanoliposome delivery systems, have been specifically designed to reduce systemic toxicity and significantly improve the targeted efficacy of synthetic immunotherapies^(28,29). Additionally, innovative constructs such as synthetic dendritic cells and multifunctional polymers are being explored to effectively recapitulate natural immune cell functions, offering potential off-the-shelf therapeutic solutions while substantially simplifying manufacturing and scalability challenges⁽²⁷⁾. These advances highlight the transformative potential of synthetic immunotherapies to achieve safer, more effective, and broadly accessible clinical applications.

Future research directions

Future advancements in synthetic immunotherapy are expected to further leverage precision medicine by integrating patient-specific genetic profiling with synthetic therapeutic design⁽¹⁸⁾. Innovations such as engineered synthetic regulatory T-cells (Tregs) and the development of synthetic immunological memory represent promising strategies for achieving sustained immune tolerance⁽¹¹⁾. Artificial intelligence-driven synthetic therapeutic design is anticipated to accelerate drug development and enhance personalized medicine approaches. Continued collaboration among interdisciplinary research teams, regulatory authorities, and clinical practitioners will be critical for realizing the full potential of synthetic immunotherapy, ultimately transforming treatment paradigms for autoimmune disease management.

Conclusion

Synthetic immunotherapy presents a transformative advancement in the treatment of autoimmune diseases integrating mechanistic precision, personalized therapeutic design, and innovative drug delivery systems. Prioritizing safety, efficacy, ethical responsibility, and global accessibility will be essential to fully realize the clinical and societal benefits of synthetic immunotherapy.

References

1. Elkoshi Z. Autoimmune Diseases Refractory to Corticosteroids and Immunosuppressants. *Frontiers in Immunology* [Internet]. 2024 [cited 2025 Mar 25];15:1447337. Available from: <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1447337/full>
2. Adytia GJ, Sutanto H, Pratiwi L, Fetarayani D. Advances in Synthetic Immunology for Targeted Treatment of Systemic Autoimmune Diseases: Opportunities, Challenges, and Future

- Directions. Immuno [Internet]. 2025 [cited 2025 Mar 25];5(1):6. Available from: <https://www.mdpi.com/2673-5601/5/1/6>
3. Lee MH, Shin JI, Yang JW, Lee KH, Cha DH, Hong JB, et al. Genome Editing Using CRISPR-Cas9 and Autoimmune Diseases: a Comprehensive Review. International Journal of Molecular Sciences [Internet]. 2022 [cited 2025 Mar 25];23(3):1337. Available from: <https://www.mdpi.com/1422-0067/23/3/1337>
 4. Park H, Mugundu GM, Singh AP. Mechanistic Evaluation of Anti-CD19 CAR-T Cell Therapy Repurposed in Systemic Lupus Erythematosus Using a Quantitative Systems Pharmacology Model. Clinical and Translational Science [Internet]. 2025 [cited 2025 Mar 25];18(2):e70146. Available from: <https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.70146>
 5. Zhou J, Lei B, Shi F, Luo X, Wu K, Xu Y, et al. CAR T-cell Therapy for Systemic Lupus erythematosus: Current Status and Future Perspectives. Frontiers in Immunology [Internet]. 2024 [cited 2025 Mar 25];15:1476859. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11694027/>
 6. Reddy NR, Maachi H, Xiao Y, Simic MS, Yu W, Tonai Y, et al. Engineering Synthetic Suppressor T Cells That Execute Locally Targeted Immunoprotective Programs. Science [Internet]. 2024 [cited 2025 Mar 25];386(6726):eadl4793. Available from: <https://www.science.org/doi/10.1126/science.adl4793>
 7. Menter A, Krueger GG, Paek SY, Kivelevitch D, Adamopoulos IE, Langley RG. Interleukin-17 and Interleukin-23: a Narrative Review of Mechanisms of Action in Psoriasis and Associated Comorbidities. Dermatology and Therapy [Internet]. 2021 [cited 2025 Mar 25];11(2):385–400. Available from: <https://link.springer.com/article/10.1007/s13555-021-00483-2>
 8. Maeyama A, Kondo M, Harada H, Shono E, Nagamine R, Tsuru T, et al. Efficacy and Safety of Baricitinib in Rheumatoid Arthritis Patients with Moderate Renal impairment: a Multicenter Propensity Score Matching Study. BMC Rheumatology [Internet]. 2024 [cited 2025 Mar 25];8(1):69. Available from: <https://doi.org/10.1186/s41927-024-00446-y>
 9. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus Kinase Inhibitors in Autoimmune Diseases. Annals of the Rheumatic Diseases [Internet]. 2013 [cited 2025 Mar 25];72(02):111-5. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3616338/>
 10. Xu Y, Chen C, Guo Y, Hu S, Sun Z. Effect of CRISPR/Cas9-Edited PD-1/PD-L1 on Tumor Immunity and Immunotherapy. Frontiers in Immunology [Internet]. 2022 [cited 2025 Mar 25];13:848327. Available from: <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.848327/full>
 11. Tang X, Zhang Y, Zhang H, Zhang N, Dai Z, Cheng Q, et al. Single-Cell Sequencing: High-Resolution Analysis of Cellular Heterogeneity in Autoimmune Diseases. Clinical Reviews in Allergy & Immunology [Internet]. 2024 [cited 2025 Mar 25];66(3):376-400. Available from: <https://link.springer.com/article/10.1007/s12016-024-09001-6>
 12. Turtle CJ, Riddell SR. Artificial Antigen-Presenting Cells for Use in Adoptive Immunotherapy. The Cancer Journal [Internet]. 2010 [cited 2025 Mar 25];16(4):374–81. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2929753/>
 13. Ferreira LMR, Muller YD, Bluestone JA, Tang Q. Next-generation Regulatory T Cell Therapy. Nature Reviews Drug Discovery [Internet]. 2019 [cited 2025 Mar 25];18(10):749–69. Available from: <https://www.nature.com/articles/s41573-019-0041-4>

14. Lim S, Park J, Shim MK, Um W, Yoon HY, Ryu JH, et al. Recent advances and challenges of repurposing nanoparticle-based drug delivery systems to enhance cancer immunotherapy. *Theranostics*. 2019;9(25):7906–23.
15. Sriwidodo, Umar AbdK, Wathoni N, Zothantluanga JH, Das S, Luckanagul JA. Liposome-polymer Complex for Drug Delivery System and Vaccine Stabilization. *Heliyon* [Internet]. 2022 [cited 2025 Mar 25];8(2):e08934. Available from: <https://doi.org/10.1016/j.heliyon.2022.e08934>
16. Peng L, Jin X, Li B, Zeng X, Liao B, Jin T, et al. Integrating single-cell RNA Sequencing with Spatial Transcriptomics Reveals Immune Landscape for Interstitial Cystitis. *Signal Transduction and Targeted Therapy* [Internet]. 2022 [cited 2025 Mar 25];7(1):161. Available from: <https://www.nature.com/articles/s41392-022-00962-8.pdf>
17. Galluzzo M, Vellucci L, Marcelli L, Paganini C, Bianchi L, Talamonti M. Deucravacitinib, a Selective Tyrosine Kinase 2 inhibitor, for the Treatment of moderate-to-severe Plaque Psoriasis. *Expert Opinion on Pharmacotherapy* [Internet]. 2023 [cited 2025 Mar 25];24(9):981–8. Available from: <https://www.tandfonline.com/doi/full/10.1080/14656566.2023.2211764>
18. Topol EJ. High-performance medicine: the Convergence of Human and Artificial Intelligence. *Nature Medicine* [Internet]. 2019 [cited 2025 Mar 25];25(1):44–56. Available from: <https://www.nature.com/articles/s41591-018-0300-7>
19. Wittmann M, Helliwell PS. Phosphodiesterase 4 Inhibition in the Treatment of Psoriasis, Psoriatic Arthritis and Other Chronic Inflammatory Diseases. *Dermatology and Therapy* [Internet]. 2013 [cited 2025 Mar 25];3(1):1–15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680635/>
20. Suhag D. Regulatory and Ethical Considerations. In: *Handbook of Biomaterials for Medical Applications, Volume 2* [Internet]. Singapore. Springer Nature Singapore; 2024 [cited 2025 Mar 25]. 355–72 p. Available from: https://link.springer.com/chapter/10.1007/978-981-97-5906-4_11
21. Li J, Chen P, Ma W. The next Frontier in immunotherapy: Potential and Challenges of CAR-macrophages. *Experimental Hematology and Oncology* [Internet]. 2024 [cited 2025 Mar 25];13(1):76. Available from: <https://ehoonline.biomedcentral.com/articles/10.1186/s40164-024-00549-9>
22. Chang ZL, Chen YY. CARs: Synthetic Immunoreceptors for Cancer Therapy and beyond. *Trends in Molecular Medicine* [Internet]. 2017 [cited 2025 Mar 25];23(5):430–50. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5423782/>
23. Goswami TK, Singh M, Dhawan M, Mitra S, Emran TB, Rabaan AA, et al. Regulatory T Cells (Tregs) and Their Therapeutic Potential against Autoimmune Disorders - Advances and Challenges. *Human Vaccines & Immunotherapeutics* [Internet]. 2022 [cited 2025 Mar 25];18(1):2035117. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9009914/>
24. Gaj T, Gersbach CA, Barbas CF. ZFN, TALEN, and CRISPR/Cas-based Methods for Genome Engineering. *Trends in Biotechnology* [Internet]. 2013 [cited 2025 Mar 25];31(7):397–405. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3694601/>
25. Garcia JM, Burnett CE, Roybal KT. Toward the Clinical Development of Synthetic Immunity to Cancer. *Immunological Reviews* [Internet]. 2023 [cited 2025 Mar 25];20(1):83–99. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/imr.13245>

26. Lin H, Li C, Zhang W, Wu B, Wang Y, Wang S, et al. Synthetic Cells and Molecules in Cellular Immunotherapy. *International Journal of Biological Sciences* [Internet]. 2024 [cited 2025 Apr 2];20(8):2833–59. Available from: <https://www.ijbs.com/v20p2833.htm>
27. Figdor CG, Mandal S, Hammink R, Eggermont L, Weiden J, Voerman D, et al. Abstract IA29: Towards Synthetic Immune Cells for Cancer Immunotherapy. *Cancer Immunology Research* [Internet]. 2016 [cited 2025 Mar 25];4(1_Supplement):IA29. Available from: https://aacrjournals.org/cancerimmunolres/article/4/1_Supplement/IA29/468245/Abstract-IA29-Towards-synthetic-immune-cells-for
28. Shin HS, Kim S, Jin SM, Yoo YJ, Heo JH, Lim YT. Molecular Masking of Synthetic Immunomodulator Evokes Antitumor Immunity with Reduced Immune Tolerance and Systemic Toxicity by Temporal Activity Recovery and Sustained Stimulation. *Advanced Materials* [Internet]. 2023 [cited 2025 Mar 25];36(9):e2309039. Available from: <https://advanced.onlinelibrary.wiley.com/doi/abs/10.1002/adma.202309039>
29. Shim MK, Yang S, Sun IC, Kim K. Tumor-activated carrier-free Prodrug Nanoparticles for Targeted Cancer Immunotherapy: Preclinical Evidence for Safe and Effective Drug Delivery. *Advanced Drug Delivery Reviews* [Internet]. 2022 [cited 2025 Mar 25];183:114177. Available from: <https://pubmed.ncbi.nlm.nih.gov/35245568/>