Advanced Therapies

JOURNAL

Medical Journal /8 years / No . 27 /50000 Rials / 2026 Spring / ISSN 3115-7394

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Advanced Therapies
JOURNAL

Journal Information

Name: Advanced Therapies Journal
Abbreviated Name: ATJ
Concessionaire: AmitisGen TECH Dev Group
Address: Unit 401, No. 2, Naderi Street, Tehran, Iran
Printing house: Saghar Printing House
Address: No. 12, Ahmadian Street, Sahel Street, 30 Meter Shora Street, Kalhor Boulevard, Shahr-e-Quds, Tehran, Iran

Editorial Board Information

Advanced Therapies
JOURNAL

Editorial Board Information

Advanced Therapies Journal

Spring 2026, Volume 8, Issue 27

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ATJ
Advanced Therapies Journal

VOL.8 / ISSUE 27 / SPRING 2026

Online ISSN: 2676-7236

DOI: 10.22034/atj.2026.250910

OPEN ACCESS

Pages: 1-7 / Review Article / Submit: 16 Feb 2026 / Accepted: 10 May 2026

Availablein: https://www.atjournal.ir

Advances in Immune Checkpoint Inhibitors and Their Combination with Novel Targeting Modalities

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Abstract:

Immune checkpoint inhibitors (ICIs) have significantly reshaped cancer therapy by reactivating antitumor immune mechanisms, leading to sustained clinical responses in a proportion of patients across various malignancies. Nevertheless, their overall therapeutic efficacy is still constrained by several factors, including intrinsic and acquired resistance, relatively low response rates, and the occurrence of immune-related adverse events, all of which limit their broader clinical benefit.. Recent research has therefore focused on integrating ICIs with emerging therapeutic modalities designed to enhance antitumor immunity, overcome resistance mechanisms, and improve patient stratification. This review provides a comprehensive overview of the biological principles underlying immune checkpoint blockade and summarizes current clinical evidence supporting combination strategies involving personalized mRNA neoantigen vaccines, bispecific antibodies, adoptive cellular therapies, Strategies involving microbiome-based interventions, artificial intelligence-assisted biomarker identification, and integrated multi-omics approaches have emerged as promising tools for advancing precision medicine and improving therapeutic decision-making. Particular attention is given to the evolving role of precision oncology approaches in identifying predictive biomarkers, distinguishing immunologically "hot" and "cold" tumors, and optimizing patient selection. In addition, the review discusses the management of immune-related toxicities, current clinical guidelines, and the challenges associated with translating innovative immunotherapy combinations into routine clinical practice. Collectively, the evidence suggests that the future of cancer immunotherapy lies in rationally designed, biomarker-guided combination strategies that integrate advanced technologies with immune checkpoint blockade to achieve more durable, personalized, and globally accessible cancer treatments.

Keywords: Antibody-Drug Conjugates, Cancer Immunotherapy, Combination Therapy, Immune Checkpoint Inhibitors, Monoclonal Antibodies

Introduction

The Evolution of Cancer Immunotherapy

The landscape of oncology has undergone a paradigm shift from non-specific cytotoxic treatments to highly precise immune-based interventions. Historically, cancer management relied on surgery and chemotherapy, but the discovery of immune surveillance mechanisms opened new therapeutic

How to Cite this Article:

N. Fallah Azad, M.S Mahmoudvand" Advanced Medical Personalized Treatment for Autoimmune Disorders: A review Article for in-depth Insight into Persoalized Autoimmune Medicine", Advanced Therapies Journal , vol. 6, no. 18, pp. 1-7, 2026.

doors. This evolution reflects a deeper improved insight into the ways the immune system can be utilized to recognize and eliminate malignant cells selectively (1).

In the late 20th century, the advent of cytokine therapies and early vaccines marked the first wave of modern immunotherapy efforts. Although these approaches showed limited clinical success, they laid the essential groundwork for targeting specific immune cell receptors. Researchers began to focus on the intricate the interplay of stimulatory and suppressive signals responsible for controlling T-cell activation and exhaustion (2).

The breakthrough came with the identification Immune checkpoints function as physiological regulators that restrain immune activation, thereby preserving self-tolerance and preventing autoimmune reactions. Many tumors take advantage of these regulatory pathways to escape immune surveillance, prompting the development of monoclonal antibodies that inhibit checkpoint-mediated signaling and restore effective antitumor immune responses. This transition from general immune stimulation to specific pathway blockade has redefined survival expectations for many advanced-stage malignancies (3).

Currently, Immunotherapy is now widely recognized as the fourth major modality of cancer treatment, complementing conventional approaches such as surgery, radiotherapy, and systemic therapies. As we move into 2026, the focus has shifted toward refining these therapies through molecular targeting and personalized diagnostic tools. This section explores the historical trajectory and the fundamental principles that continue to drive innovation in the the area of immuno-oncology (4).

Mechanisms of Established Checkpoint Inhibitors: CTLA-4, PD-1, and PD-L1

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) represented the first immune checkpoint molecule to undergo clinical therapeutic targeting. It functions primarily by antagonizing CD28-mediated signaling during the early activation and priming of T cells in secondary lymphoid organs. By blocking CTLA-4, inhibitors like ipilimumab allow for a more robust and sustained proliferation of tumor-reactive T-cell clones (5).

Tumors evade immune surveillance by exploiting the PD-1/PD-L1 checkpoint, an essential peripheral regulatory pathway that drives T-cell exhaustion in the tumor microenvironment. Activated T cells express programmed cell death protein 1 (PD-1), while numerous cancer cells exhibit elevated levels of its ligand, PD-L1. Therapeutic disruption of this receptor–ligand interaction restores T-cell effector function, thereby strengthening antitumor immunity (6).

Beyond simple receptor-ligand interference, the blockade of these pathways triggers complex intracellular signaling changes that affect metabolic fitness. For instance, PD-1 inhibition has been shown to revitalize the glycolytic pathways necessary for T-cell migration and cytokine production. These metabolic shifts are essential for overcoming the immunosuppressive conditions typically found within the dense and nutrient-depleted tumor stroma (7).

Despite the success of these established inhibitors, primary and acquired resistance remain significant clinical hurdles for many patient populations. Understanding the structural biology and spatial distribution of these receptors is vital for predicting which patients will respond to therapy. Current research is focusing on the kinetics of receptor occupancy to optimize dosing and minimize the risk of immune-related toxicities (8).

Next-Generation Immune Checkpoints: Expanding the Horizon (LAG-3, TIM-3, and TIGIT)

As resistance to PD-1/CTLA-4 inhibitors becomes more prevalent, attention has turned to a new generation of inhibitory receptors. LAG-3 (lymphocyte-activation gene 3) functions as a key negative regulator of T-cell activation and immune homeostasis by engaging MHC class II molecules. The simultaneous blockade of LAG-3 and complementary immune checkpoint pathways has produced favorable results in clinical trials involving melanoma and several solid tumors (9).

T-cell immunoglobulin and mucin-domain protein 3 (TIM-3) is another critical regulator that marks highly exhausted or dysfunctional T-cells. Unlike other checkpoints, Beyond its expression on T cells, TIM-3 is found on a variety of innate immune cells, particularly dendritic cells and natural killer (NK) cells. Inhibiting TIM-3 not only boosts T-cell responses but also enhances the overall pro-inflammatory state of the tumor microenvironment (10).

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) has emerged as a high-potential target due to its role in both T-cell and NK cell suppression. It competes with the co-stimulatory receptor CD226 for binding to ligands like CD155, which are frequently overexpressed in various human cancers. Dual blockade of TIGIT and PD-1 is currently being evaluated as a strategy to achieve deeper and more durable clinical responses (11).

The exploration of these next-generation targets represents a shift toward addressing the multifaceted nature of immune exhaustion. Each of these molecules occupies a unique niche in the immune regulatory network, suggesting that their simultaneous inhibition could provide synergistic benefits. Ongoing studies are characterizing the specific expression patterns of

these markers to develop more precise and effective therapeutic combinations (12).

Synergy in Combination: Rationales for Multi-modal Approaches

The heterogeneity of the tumor microenvironment often necessitates the use of multiple therapeutic modalities to achieve a complete clinical response. Combining different classes of immunotherapy aims to target various stages of the cancer-immunity cycle, from antigen release to T-cell infiltration. This multi-modal strategy is designed to overcome the limitations of monotherapy by addressing diverse escape mechanisms simultaneously (13).

One primary rationale for combination therapy is the induction of "immunogenic cell death" through traditional or targeted agents. When tumor cells die in a manner that releases danger signals and neoantigens, they prime the immune system for a more effective response. This "vaccinal effect" can turn a "cold" tumor—one with few immune cells—into a "hot" tumor that is susceptible to checkpoint inhibitors (14).

Spatial and temporal coordination of combined treatments is critical for maximizing efficacy while minimizing cumulative toxicity to healthy tissues. For example, sequencing chemotherapy before immunotherapy may deplete suppressive immune cell subsets, particularly regulatory T cells and myeloid-derived suppressor cells. Such strategic timing ensures that the immune system is primed and unencumbered before the administration of checkpoint blockade agents (15).

The complexity of these interactions requires sophisticated mathematical modeling and preclinical validation to identify the most potent drug pairings. Emerging data suggest that low-dose combinations may offer better safety profiles without compromising the synergistic anti-tumor activity observed in high-dose regimens. This section reviews the biological logic and clinical evidence supporting the move toward integrated, multi-agent therapeutic protocols (16).

Combining ICIs with Targeted Therapies (Small Molecules and Tyrosine Kinase Inhibitors)

Treatment paradigms have been significantly reshaped by targeted therapies, with tyrosine kinase inhibitors (TKIs) playing a central role. These small molecules interfere with signaling cascades that drive cellular proliferation, survival, and angiogenesis, such as the VEGF or EGFR pathways. Combining TKIs with immune checkpoint blockade has demonstrated considerable potential in enhancing the overall therapeutic index (17).

TKIs can exert profound effects on the the tumor-associated microenvironment by modulating the recruitment and function of various immune cell subsets. For instance, VEGF inhibitors not only normalize tumor vasculature but also reduce the infiltration of immunosuppressive cells like M2 macrophages. This creates a more hospitable environment for effector T-cells to penetrate the tumor and perform their cytotoxic functions (18).

Synergy between small molecules and ICIs is also observed at the level of intracellular signaling and cytokine expression. Certain targeted agents can upregulate the expression of MHC molecules or PD-L1 on tumor cells, making them more visible to the immune system. This "priming" effect ensures that the subsequent checkpoint blockade can act more efficiently against the targeted malignant population (19).

Clinical studies involving patients with renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC) have already led to the approval of several TKI-ICI combinations. However, managing the overlapping toxicities, such as hepatotoxicity or skin rashes, remains a significant challenge for clinicians and researchers. Future efforts are focused on developing selective small molecules that specifically enhance immune functions without inducing systemic adverse effects (20).

Antibody-Drug Conjugates (ADCs) and Checkpoint Inhibition: A Double-Edged Sword

Antibody-drug conjugates (ADCs) are an advanced therapeutic platform that integrates the high target specificity of monoclonal antibodies with the potent cytotoxic activity of anticancer agents.. By delivering a lethal payload directly to cells expressing a specific antigen, ADCs minimize damage to healthy surrounding tissues. Their integration with checkpoint inhibitors is a rapidly growing area of research aimed at maximizing tumor destruction (21).

The primary benefit of combining ADCs with ICIs lies in the ADC's ability to promote an inflammatory tumor milieu. Upon delivery of the cytotoxic payload, the resulting tumor cell lysis releases a plethora of tumor-associated antigens and pro-inflammatory cytokines. This process effectively recruits T-cells to the tumor site, where checkpoint inhibitors can then maintain their long-term activation (22).

However, this approach is often described as a "double-edged sword" due to the potential for increased systemic toxicity and off-target effects. The cytotoxic components of ADCs can sometimes negatively impact the very immune cells required for the checkpoint inhibitor to function. Finding the optimal balance between potent tumor killing and preservation of immune cell viability is crucial for the success of these regimens (23).

Recent clinical data have shown that ADCs can overcome resistance to PD-1/PD-L1 inhibition in

patients who have previously failed immunotherapy. This suggests that the targeted delivery of chemotherapy can "reset" the immune landscape and provide a second window of opportunity for treatment. Advanced linker technologies and more stable payloads are being developed to further enhance both the safety and therapeutic efficacy of these combinations (24).

Nanotechnology-Based Delivery Systems for Co-Targeted Immunotherapy

Nanotechnology offers a transformative platform for the simultaneous delivery of multiple therapeutic agents to the tumor site with high precision. Nano-carriers, including liposomal formulations and polymer-based nanoparticles, and gold clusters, can be engineered to encapsulate both checkpoint inhibitors and targeted drugs. This co-delivery ensures that the agents reach the target tissue at the same time and in the optimal ratio (25).

The "enhanced permeability and retention" The enhanced permeability and retention (EPR) effect promotes the preferential accumulation of nanoparticles within tumor tissues as a result of their highly permeable and defective vasculature. Furthermore, the surface of these nanocarriers can be modified with specific ligands capable of recognizing receptors that are highly expressed on cancer cells or immune cell populations. This active targeting significantly reduces the systemic exposure of the drugs, thereby decreasing the incidence of immune-related adverse events (26).

Smart nano-systems are now being developed to respond to distinct stimuli present in the tumor microenvironment, including acidic pH conditions or elevated levels of specific factors. These "responsive" nanoparticles release their cargo only upon reaching the acidic environment of the tumor stroma or the interior of a cancer cell. Such controlled release mechanisms provide an additional layer of safety and improve the bioavailability of the therapeutic agents (27).

Despite their promise, the translation of nano-immunotherapies The transition from laboratory research to clinical application remains challenging due to obstacles associated with large-scale production and regulatory authorization. Researchers are currently focusing on improving the the biocompatibility and degradation characteristics of these materials to guarantee. As the field matures, nanotechnology is expected to become a cornerstone of personalized and highly effective cancer immunotherapy (28).

The Role of Personalized Medicine: Predictive Biomarkers for Combination Therapy

The success of combination immunotherapies depends heavily on the ability to determine which patient populations are most likely to derive benefit from specific regimens. Personalized medicine utilizes molecular profiling and bioinformatics to tailor treatments based on the unique genetic landscape of an individual's tumor. This approach aims to maximize clinical efficacy while avoiding the administration of unnecessary and potentially toxic treatments (29).

Predictive biomarkers, including the expression level of Programmed Death-Ligand 1 (PD-L1) levels, remain the standard for selecting candidates for checkpoint blockade. However, PD-L1 alone is often insufficient for predicting responses in complex combination settings where multiple pathways are being targeted. Emerging biomarkers, such as Tumor Mutational Burden (TMB) and Microsatellite Instability (MSI), are providing more comprehensive insights into tumor immunogenicity (30).

Advances in liquid biopsy and single-cell sequencing are allowing for the real-time monitoring of immune responses during the course of treatment. By analyzing circulating tumor DNA (ctDNA) or peripheral immune cell populations, clinicians can detect early signs of resistance or therapy-induced toxicity. This dynamic assessment enables timely adjustments to the therapeutic strategy, ensuring that the treatment remains aligned with the tumor's evolution (31).

The incorporation of artificial intelligence and machine learning approaches into biomarker discovery is set to revolutionize the field of personalized oncology by 2026. These tools can analyze vast datasets from genomic, proteomic, and imaging sources to identify subtle patterns that human observers might miss. The ultimate goal is to develop a "precision immunotherapy" framework that guarantees the best possible outcome for every patient (32).

Management of Immune-Related Adverse Events (irAEs) in Combination Regimens

The therapeutic utility of combination immunotherapy is often counterbalanced by an increased frequency and severity associated with immune-related adverse events (irAEs). These toxicities, arising from the uncoupling of self-tolerance mechanisms, can affect nearly every organ system, with dual checkpoint blockade consistently showing higher toxicity profiles than monotherapy. Effective clinical management relies on the early identification of symptoms and the prompt initiation of immunosuppressive protocols (33).

Organ-specific irAEs, such as colitis, hepatitis, pneumonitis, and endocrinopathies, require distinct management algorithms tailored to the severity of the reaction. While low-grade events may be managed

with supportive care or temporary treatment interruption, high-grade toxicities necessitate the immediate cessation of immunotherapy and the administration of systemic corticosteroids. The clinical challenge lies in mitigating toxicity without completely neutralizing the anti-tumor immune response generated by the therapy (34).

For patients who are refractory to standard corticosteroid therapy, the integration of secondary immunosuppressive agents has become the clinical standard. Agents such as infliximab for refractory colitis or mycophenolate mofetil for hepatitis and pneumonitis are critical components of modern safety protocols. Continuous clinical vigilance and the implementation of multidisciplinary teams are essential to ensure patient safety during intensive combination regimens (35).

Future approaches to irAE management are increasingly moving toward predictive and personalized strategies. Research into biological markers, such as circulating cytokine profiles, autoantibody signatures, and gut microbiome composition, aims to identify high-risk patients before the onset of symptomatic toxicity. As combination therapies become more complex, shifting from reactive treatment to proactive risk-stratified monitoring will be vital to sustaining long-term clinical benefits (36)(Table1).

Future Perspectives and Clinical Challenges: Beyond the Current Success

Despite the transformative success of immunotherapy, primary and acquired resistance mechanisms remain significant hurdles. Tumors frequently evolve to bypass immune recognition through the loss of antigen-presenting machinery or the activation of alternative inhibitory pathways. Addressing these resistance patterns requires a transition from one-size-fits-all strategies to dynamic, combination-based therapeutic approaches that target multiple facets of the tumor microenvironment (41).

Precision medicine is evolving beyond simple PD-L1 immunohistochemistry. The integration of high-dimensional data, including spatial transcriptomics and multi-omic profiling, is enabling a more granular understanding of the tumor-immune interactome. By mapping the specific immune landscape of an individual tumor, clinicians can move toward rational combinations, selecting therapies that specifically address the unique immunological bottlenecks present in each patient's malignancy (42).

The rapid pace of innovation introduces significant logistical and economic challenges for global healthcare systems. As combination regimens increase in complexity and cost, ensuring equitable access remains a critical priority. Streamlining clinical trial designs and leveraging artificial intelligence for patient stratification are essential steps to accelerate the translation of promising innovations into accessible, standard-of-care treatments (43).

The next decade of immuno-oncology will likely be defined by the convergence of checkpoint inhibition with emerging modalities such as mRNA neoantigen vaccines and bispecific antibodies. These approaches offer the potential to reinvigorate the immune response and overcome resistance in tumors that are currently non-responsive. By orchestrating these therapies in synergistic sequences, the field aims to push beyond existing survival benchmarks and improve long-term outcomes for patients with advanced disease (44)(Table2).

Conclusion

Immune checkpoint blockade therapies have established a new paradigm in cancer therapy; however, therapeutic resistance, tumor heterogeneity, and treatment-related toxicities continue to limit their effectiveness across many patient populations. Emerging combination approaches, including personalized neoantigen vaccines, bispecific antibodies, engineered cellular therapies, microbiome-based interventions, and AI-enabled precision medicine, offer promising solutions to these limitations. Growing evidence indicates that integrating these modalities with checkpoint blockade can enhance immune activation, broaden response rates, and support more individualized treatment strategies. Simultaneously, advances in biomarker discovery and multi-omics technologies are improving patient stratification and facilitating the transition toward precision immuno-oncology. Effective toxicity monitoring and evidence-

Table1. Key Management Strategies for irAEs in Combination Therapy

Strategy	Clinical Focus	Expected Outcome	Ref
Guideline-Directed Care	**ASCO/SITC protocols**	**Standardization of grade-based steroid dosing.**	**(37)**
Toxicity Monitoring	**Dual ICI analysis**	**Early detection of grade ≥3 systemic inflammatory events.**	**(38)**
Refractory Protocols	**Infliximab / Vedolizumab**	**Resolution of steroid-resistant colitis and hepatitis.**	**(39)**
Personalized Risk	**Predictive biomarkers**	**Pre-treatment stratification for high-risk patients.**	**(40)**

Table2. Emerging Technologies and Future Directions

Technology	Therapeutic Approach	Strategic Goal	Ref
mRNA Vaccines	Neoantigen targeting	Overcoming adaptive resistance to ICIs.	(45)
Bispecific Abs	Dual-targeting	Simultaneous blockade of multiple checkpoints.	(46)
AI / Multi-omics	Precision stratification	Identification of "cold" vs "hot" tumor profiles.	(47)
Global Access	Economic modeling	Sustainable deployment of combination regimens.	(48)

based management protocols remain essential for maximizing clinical benefit while minimizing adverse events. Looking forward, the successful implementation of biomarker-driven combination regimens, supported by robust clinical validation and sustainable healthcare models, is expected to further expand the impact of immunotherapy and contribute to improved long-term outcomes for patients with cancer worldwide.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable.

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ATJ
Advanced Therapies Journal

VOL.8 / ISSUE 27 / SPRING 2026

Online ISSN: 2676-7236

DOI:

OPEN ACCESS

Pages: 8-16/ Review Article / Submit: 16 Dec 2025 / Accepted: 10 Mar 2026

Availablein: https://www.atjournal.ir

Neural Stem Cell-Based Strategies for Repairing Injured Neural Circuits: Recent Advances and Future Perspectives

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Abstract:
Neural stem cells (NSCs) represent a promising therapeutic strategy for repairing damaged neural circuits in the central nervous system (CNS). The therapeutic promise of NSCs stems from their dual capacity for sustained self-renewal and differentiation into neurons, astrocytes, and oligodendrocytes, which collectively support the regeneration of injured neural tissue and the recovery of neurological function. Beyond direct cell replacement, NSCs exert powerful paracrine effects through the secretion of neurotrophic factors, cytokines, and extracellular vesicles that modulate inflammation, enhance neuronal survival, and promote axonal regeneration. Increasing evidence indicates that NSC-mediated immunomodulation plays a central role in shifting the post-injury microenvironment from a neurotoxic to a regenerative state, primarily through regulation of microglial polarization and suppression of pro-inflammatory signaling pathways.
In addition, NSCs contribute to neural repair by enhancing synaptic plasticity, supporting remyelination, stabilizing the blood–brain barrier, and facilitating angiogenesis. Accumulating preclinical evidence suggests that both NSC transplantation and the therapeutic application of NSC-derived secretomes lead to significant functional improvement in animal models of spinal cord injury, stroke, and traumatic brain injury. However, clinical translation remains limited by challenges such as poor cell survival, immune rejection, tumorigenic risk, and lack of standardized delivery protocols. Emerging strategies, including gene-edited NSCs, biomaterial scaffolds, and exosome-based cell-free therapies, are being developed to overcome these limitations. Overall, NSCs provide a multifaceted regenerative platform with strong potential for future clinical applications in neurological disorders, although further large-scale clinical studies are essential to validate the long-term safety and efficacy of these therapies.

Keywords: Neural stem cells, CNS regeneration; Neuroplasticity, Immunomodulation; Axonal regeneration; neurodegenerative diseases

Introduction

Damage to neural pathways resulting from spinal cord injury, traumatic brain injury, stroke, and neurodegenerative disorders remains one of the greatest challenges in modern neuroscience. Unlike the peripheral nervous system, the adult central

How to Cite this Article:
Z. Azami. M. Piri-Gharaghie" Advanced Medical Personalized Treatment for Autoimmune Disorders: A review Article for in-depth Insight into Persoalized Autoimmune Medicine, vol. 6, no. 18, pp. 8-16, 2024.

nervous system (CNS) exhibits limited regenerative capacity due to inhibitory microenvironments, glial scar formation, chronic inflammation, and reduced intrinsic neuronal growth potential (1, 2). Consequently, the restoration of functional neural circuits following injury is often incomplete, leading to persistent neurological deficits and disability. Recent advances in regenerative medicine have highlighted neural stem cells (NSCs) as promising therapeutic candidates because of their ability to self-renew, differentiate into neurons and glial cells, modulate immune responses, and secrete neurotrophic factors that support tissue repair (3, 4). Experimental studies have demonstrated that endogenous and transplanted NSCs can promote axonal regeneration, remyelination, synaptic plasticity, and reconstruction of disrupted neural networks after CNS injury (5, 6). Furthermore, emerging biomaterial-based approaches, including hydrogel-supported NSC transplantation, have shown enhanced cell survival and integration within injured tissues, thereby improving functional outcomes in preclinical models (7). These findings have generated significant interest in NSC-based therapies as a potential strategy for restoring damaged neural pathways and improving neurological recovery.

In recent years, substantial progress has been made in understanding the mechanisms through which NSCs contribute to neural regeneration and circuit reconstruction. Beyond direct cell replacement, NSCs exert paracrine effects by releasing extracellular vesicles, cytokines, and growth factors that attenuate neuroinflammation and stimulate endogenous repair processes (8). Advances in stem cell engineering, gene editing technologies, and the manipulation of endogenous neural stem/progenitor cell populations have further expanded the therapeutic potential of NSCs in spinal cord injury and other CNS disorders (5, 9). Preliminary clinical evidence supports the safety and feasibility of neural stem cell transplantation in chronic spinal cord injury and stroke (10, 11). Nevertheless, several challenges remain, including limited cell survival, insufficient functional integration, tumorigenic risk, immune rejection, and ethical considerations associated with stem cell sources (3, 7). Therefore, a comprehensive evaluation of current evidence is essential to determine the translational potential of NSC-based therapies. This review aims to summarize recent advances in neural stem cell biology, explore their role in regenerating damaged neural pathways, and discuss future directions for clinical application.

Biology and Characteristics of Neural Stem Cells

NSCs are characterized by their self-renewal capacity and multilineage differentiation potential, allowing them to generate the principal neural cell types that support central nervous system development and regeneration (13, 14). The adult mammalian brain contains two principal neurogenic niches that harbor NSCs: the SVZ and the SGZ of the hippocampal dentate gyrus (15, 16). These specialized microenvironments consist of endothelial cells, astrocytes, microglia, and extracellular matrix components that tightly regulate NSC fate decisions (15). Recent single-cell transcriptomic analyses have demonstrated that NSCs are highly heterogeneous, comprising multiple subpopulations with distinct transcriptional signatures and regenerative capacities (16). This heterogeneity enables adaptive neurogenic responses under both physiological and pathological conditions. NSCs maintain a dynamic equilibrium between quiescence and activation, which is essential for preserving long-term regenerative potential (17). Disruption of this balance contributes to impaired neurogenesis and reduced neural repair capacity.

NSC function is tightly regulated by a network of conserved signaling pathways, including Notch, Wnt/β-catenin, Sonic Hedgehog (Shh), and BMP signaling, which collectively coordinate stem cell maintenance and differentiation (13, 17). Notch signaling is primarily responsible for maintaining NSC quiescence, whereas Wnt signaling promotes activation and neuronal differentiation (17, 18). Beyond classical signaling pathways, epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs—serve as critical regulators of gene expression that influence NSC fate decisions (18). In addition, metabolic regulation and mitochondrial dynamics significantly influence NSC proliferation and differentiation capacity (19). Age-associated alterations in these molecular pathways result in a progressive decline in neurogenic potential (17). Therefore, targeting these regulatory networks represents a promising strategy for enhancing endogenous neural repair mechanisms.

Beyond intrinsic properties, NSCs actively interact with their microenvironment through paracrine signaling and cell-cell communication (14, 16). They secrete cytokines, neurotrophic factors, and extracellular vesicles that regulate inflammation, support enhance synaptic plasticity and neuronal survival (16). NSCs also respond to neurotransmitters such as GABA and glutamate, which influence their proliferation and differentiation dynamics (13). Bidirectional communication between NSCs, neurons, and immune cells forms a complex regulatory network within neurogenic niches (15). This network is essential for maintaining CNS homeostasis and facilitating repair processes following injury. Collectively, these features highlight NSCs as key

regulators of neural plasticity and regeneration.

Sources and Classification of Neural Stem Cells

The adult CNS contains two principal neurogenic niches that serve as the primary reservoirs of NSCs: the SVZ along the lateral ventricles and the SGZ located in the dentate gyrus of the hippocampus (15, 20). Neurogenesis in the SVZ involves the formation of intermediate progenitor cells from NSCs, followed by the differentiation of these progenitors into neuroblasts that migrate through the rostral migratory stream to the olfactory bulb (20). Conversely, NSCs in the SGZ generate granule neurons that integrate into hippocampal neural circuits, thereby supporting cognitive functions, particularly learning and memory (16). These region-specific neurogenic processes reflect functional specialization within the CNS. Developmentally, adult NSCs originate from embryonic radial glial cells that persist as quiescent stem cells after birth (21). This lineage relationship underlies the lifelong, albeit limited, regenerative capacity of the brain.

In addition to classical neurogenic niches, emerging evidence suggests the presence of NSC-like populations in non-canonical regions such as the hypothalamus, striatum, and spinal cord (20). These cells exhibit restricted neurogenic activity under specific physiological or injury conditions. Moreover, cellular reprogramming studies have demonstrated that astrocytes and pericytes can be converted into induced neural stem cells (iNSCs) using defined transcription factors (19). This finding expands the concept of NSC origin beyond traditional developmental pathways. Furthermore, induced pluripotent stem cell (iPSC)-derived neural progenitors provide an exogenous and scalable source for regenerative applications (18). However, challenges such as incomplete maturation and functional heterogeneity remain.

NSCs can also be classified based on their functional states, including quiescent NSCs (qNSCs) and activated NSCs (aNSCs) (17, 21). Quiescent NSCs serve as a long-term reservoir, preserving stem cell pools and preventing depletion (21). Activated NSCs, in contrast, enter the cell cycle in response to injury or physiological demands and contribute to tissue regeneration (17). Recent single-cell sequencing studies suggest that NSC states exist along a dynamic continuum rather than discrete categories (16). This plasticity is regulated by both intrinsic genetic programs and extrinsic niche-derived signals. Understanding these functional states is critical for optimizing therapeutic strategies aimed at enhancing neurodegeneration.

Mechanisms of Neural Pathway Damage in the Central Nervous System

Neural pathway damage in the CNS occurs due to traumatic, ischemic, inflammatory, and neurodegenerative processes, including traumatic brain injury, spinal cord injury, stroke, and diseases such as multiple sclerosis (22, 23). These conditions lead to axonal disruption, neuronal apoptosis, demyelination, and synaptic loss, ultimately impairing neural circuit connectivity. A major barrier to regeneration is forming of a glial scar composed of reactive astrocytes and extracellular matrix molecules (22). This scar physically and chemically inhibits axonal regrowth. Additionally, inhibitory molecules such as Nogo-A, MAG, and chondroitin sulfate proteoglycans further restrict neural regeneration (23). Together, these factors create a non-permissive environment for repair.

Neuroinflammation is recognized as a major driver of secondary injury progression after CNS damage (22). Following CNS injury, inflammatory cytokines released by activated microglia and infiltrating immune cells, including TNF-α, IL-1β, and IL-6, contribute to neuronal degeneration. This process is further intensified by oxidative stress and mitochondrial dysfunction, which impair cellular energy production and increase tissue damage (22). Glutamate-induced excitotoxicity promotes excessive intracellular calcium accumulation, thereby triggering neuronal degeneration and cell death (23). Chronic inflammation also suppresses endogenous NSC activation and migration, limiting intrinsic repair capacity. Therefore, modulation of inflammatory pathways is a critical therapeutic target in CNS injury.

At the network level, disruption of long-range axonal connections leads to severe functional deficits, including motor impairment, cognitive dysfunction, and sensory loss (22). Although compensatory plasticity mechanisms exist, they are often insufficient for full functional recovery (23). Aging further worsens outcomes by reducing NSC activity and regenerative responsiveness (21). The severity of functional impairment is influenced not only by primary injury but also by failure of endogenous repair signaling (20). Enhancing intrinsic regenerative capacity, particularly through NSC-based strategies, represents a promising therapeutic approach for restoring damaged neural pathways.

Molecular Mechanisms of Neural Stem Cell–Mediated Neural Regeneration

Neural stem cells (NSCs) promote regeneration of damaged neural pathways through highly coordinated molecular signaling networks that regulate proliferation, differentiation, and neuronal integration (24, 25, 26). Among these, the Wnt/β-catenin pathway plays a central role in promoting neuronal lineage commitment and enhancing

neurogenic activity following CNS injury (24). The Notch signaling pathway, in contrast, maintains NSC quiescence under physiological conditions but becomes dynamically regulated after injury to balance self-renewal and differentiation (25). Sonic Hedgehog (Shh) signaling also contributes significantly by enhancing NSC proliferation and guiding neural patterning during regeneration (26). These pathways interact in a tightly regulated manner, ensuring controlled neurogenesis without depletion of the stem cell pool. Dysregulation of these mechanisms leads to impaired regenerative responses and incomplete neural repair (Table 1).

Epigenetic regulation is another fundamental mechanism underlying NSC-mediated neural repair. Histone modification, DNA methylation, and chromatin remodeling collectively regulate transcriptional programs involved in NSC activation and lineage specification (27, 28). MicroRNAs (miRNAs) and long non-coding RNAs further refine gene expression by post-transcriptional regulation of key regenerative genes (27). These epigenetic mechanisms enable NSCs to respond dynamically to injury-induced environmental cues such as inflammation and hypoxia. Additionally, metabolic reprogramming from glycolysis toward oxidative phosphorylation is essential for NSC differentiation and maturation (29). Mitochondrial dynamics also influence NSC fate decisions and regenerative capacity (28). Together, these processes establish the molecular basis of NSC plasticity in CNS repair.

Neural regeneration mediated by NSCs extends beyond cell replacement, as these cells actively modulate the injured microenvironment through paracrine signaling. This effect is largely attributed to the secretion of neurotrophic factors, including BDNF, GDNF, and VEGF (30). These molecules enhance neuronal survival, promote angiogenesis, and reduce apoptotic signaling in injured tissue (30, 31). NSC-derived extracellular vesicles (EVs) carry proteins, lipids, and regulatory RNAs that modulate gene expression in recipient cells (31). These EVs also suppress neuroinflammation and enhance endogenous repair mechanisms (32). Furthermore, NSCs interact with immune cells, particularly microglia, to regulate inflammatory responses and promote a regenerative microenvironment (33). This dual role of NSCs as both cellular replacements and secretory regulators highlights their therapeutic potential.

Neural Stem Cells and Axonal Regrowth After Neural Injury

Axonal regeneration in the central nervous system (CNS) is severely limited due to both intrinsic neuronal constraints and inhibitory extracellular environments (34, 35). Neural stem cells (NSCs) contribute to axonal regrowth by creating a permissive environment that supports axonal elongation, synaptic reconnection, and circuit remodeling (34). Experimental models of spinal cord injury and stroke have demonstrated that NSC transplantation significantly enhances axonal sprouting and functional recovery (35). This regenerative effect is mediated in part by secretion of neurotrophic factors such as BDNF, NGF, and NT-3 (30). These factors promote neuronal survival and stimulate axonal extension in damaged neural networks. Additionally, NSCs differentiate into oligodendrocyte lineage cells, contributing to remyelination and improved signal conduction (6, 35).

A major barrier to axonal regeneration is the presence of inhibitory molecules in the injured CNS environment, including Nogo-A, MAG, OMgp, and chondroitin sulfate proteoglycans (CSPGs) (34,36). NSCs counteract these inhibitory signals by modulating extracellular matrix composition and reducing glial scar formation (36). They

Table 1. Major Molecular Mechanisms and Regenerative Functions of Neural Stem Cells in CNS Repair

Molecular Mechanism/Pathway	Biological Function in NSCs	Regenerative Outcome in CNS Injury	Representative References
Wnt/β-catenin signaling	Promotes neuronals differentiation and NSC activation	Enhanced neurogenesis and neural repair	(24,25)
Notch signaling	Maintains NSC quiescence and self-renewal	Preservation of stem cell pool balance	(25)
Sonic Hedgehog (Shh) pathway	Stimulates NSC proliferation and neural patterning	Improved of stem cell pool balance	(26)
Epigenetic regulation (DNA methylation, histone modification, miRNAs)	Controls gene expression and lineage specification	Adaptive response to injury microenviroment	(27,28)
Neurotrophic factor secretion (BDNF, GDNF, VEGF)	Supports neuronal survival and angiogenesis	Axonal regeneration and reduced apoptosis	(30,31)
Extracellular vesicles (EVs)/exosomes	Transfer regulatory RNAs and proteins	Suppression of neuroinflammation and promotion of endogenous repair	(31,32)
Immunomodulation of microglia	Shifts microglia from M1 to M2 phenotype	Reduced inflammatory damage and improved tissue repair	(33,41)
Remyelination support	Differentiation into oligodendrocyte lineage cells	Restoration of neural signal conduction	(6,35)

suppress reactive astrocyte activation and decrease deposition of inhibitory CSPGs, thereby improving axonal growth conditions (36). NSCs also promote synaptic plasticity, facilitating the formation of new functional connections between surviving neurons (35). Moreover, NSC-derived exosomes have been shown to enhance axonal regeneration by transferring regenerative microRNAs to host neurons (31). These combined mechanisms significantly enhance structural and functional recovery after CNS injury.

Recent advances in biomaterials and tissue engineering have further improved NSC-based axonal regeneration strategies. Hydrogels, nanofiber scaffolds, and 3D-printed matrices provide structural support for NSC survival and axonal guidance (7, 37). These biomaterials enhance cell retention, improve spatial organization, and facilitate directed axonal growth across lesion sites (37). Genetically modified NSCs expressing enhanced growth-promoting or anti-inhibitory molecules have shown superior regenerative outcomes in preclinical models (38). In addition, combining NSC therapy with electrical stimulation and rehabilitative training further enhances axonal plasticity and functional recovery (35). These multimodal approaches represent a promising direction for improving outcomes in CNS injury repair.

Immunomodulatory and Neuroprotective Effects of Neural Stem Cells

Following injury to the central nervous system (CNS), neural stem cells (NSCs) serve as key regulators of the immune response. After CNS damage, microglial activation, together with the recruitment of immune cells from the periphery, contributes to excessive production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which amplify secondary neuronal damage (39, 40). NSCs counteract this inflammatory cascade by secreting anti-inflammatory cytokines including IL-10 and TGF-β, thereby promoting a shift from M1 to M2 microglial polarization (41). This shift creates a regenerative microenvironment that supports tissue repair and limits neurodegeneration. In addition, NSCs interact directly with resident immune cells, regulating both innate and adaptive immune responses in the CNS (42). NSC-derived extracellular vesicles further enhance immunomodulation by transferring microRNAs that suppress inflammatory signaling pathways (43).

Beyond immune regulation, NSCs provide strong neuroprotective effects in injured neural tissue. They secrete neurotrophic factors such as GDNF, BDNF, NGF, and VEGF, which promote neuronal survival and synaptic stabilization (44). These factors reduce apoptosis, enhance axonal integrity, and improve resistance to oxidative stress (45). NSCs also contribute to blood–brain barrier (BBB) stabilization, thereby reducing infiltration of toxic molecules and immune cells into neural tissue (46). Furthermore, NSCs regulate glutamate excitotoxicity and calcium imbalance, which are key drivers of neuronal death after injury (47). These combined effects significantly improve structural preservation and functional recovery in CNS disorders.

Importantly, the therapeutic impact of NSCs is largely mediated through paracrine signaling rather than direct neuronal replacement. Their secretome includes cytokines, growth factors, and extracellular vesicles that modulate multiple signaling pathways in host cells (43, 48). NSC-derived exosomes can reproduce many of the regenerative effects observed in cell transplantation models (43). This has shifted current therapeutic strategies toward cell-free regenerative medicine. Overall, NSCs function as both immune regulators and neuroprotective mediators in CNS repair.

Clinical Applications of Neural Stem Cells in Neurological Disorders

Therapeutic approaches utilizing neural stem cells (NSCs) have gained considerable attention as potential treatments for various neurological conditions, such as spinal cord injury (SCI), stroke, traumatic brain injury (TBI), and neurodegenerative diseases (49, 50). Preclinical studies consistently demonstrate that NSC transplantation enhances neurogenesis, axonal regeneration, and remyelination, leading to improved functional outcomes (51). In SCI models, NSCs integrate into host neural circuits and contribute to reconstruction of disrupted pathways (52). In ischemic stroke models, they promote angiogenesis and neuronal survival, improving both motor and cognitive recovery (53). These findings strongly support the translational potential of NSC-based therapies (Table 2).

Early-phase clinical trials have evaluated the safety and feasibility of NSC transplantation in CNS injury patients. Overall, these studies report acceptable safety profiles with no significant tumor formation or severe immune rejection (54, 55). Some patients show modest improvements in motor and sensory functions, although outcomes remain variable (55). Differences in cell source, delivery route, timing of intervention, and injury heterogeneity contribute to inconsistent results (54). Common delivery methods include intrathecal, intracerebral, and intravenous administration (56). However, lack of standardized clinical protocols remains a major limitation in translating NSC therapies.

In addition to cell transplantation, NSC-derived extracellular vesicles and secretome-based therapies have gained increasing attention (43, 57). These approaches reduce risks associated with live cell

Table 2. Therapeutic Applications, Benefits, and Limitation of Neural stem Cell-Based Therapies in Neurological

Neurological Disorder	Therapeutic Effects of NSCs	Major Benefits	Current Limitations	Key References
Spinal cord injury (SCI)	Axonal regeneration, remyelination, neural circuit reconstruction	Improved motor recovery and neural connectivity	Poor cell survival, inhibitory microenvironment	(50,52)
Ischemic stroke	Promotion angiogenesis and neuronal survival	Recovery of motor and cognitive function	Variable clinical outcomes	(49,53)
Traumatic brain injury (TBI)	Neuroprotection and anti-inflammatory effects	Reduced neuronal apoptosis and enhanced repair	Limited long-term integration	(40,45)
Multiple sclerosis (MS)	Immunomodulation and remyelination	Reduction of inflammatory damag	Immune rejection risk	(39,41)
Neurodegeneratve disorders	Neurotrophic support and synaptic stabilization	Potential slowing of neurodegeneration	Tumorigenic risk and delivery challenges	(44,55)
Exosome-based therapies	Cell-free regenerative signaling	Lower tumorigenic and immunogenic risk	Standardization regulatory concerns	(43,57)
Gene-edited NSCs	Enhanced regenerative capacity	Improved therapeutic precision	Ethical and regulatory concerns	(59,65)

transplantation while maintaining regenerative effects (57). Biomaterial-assisted delivery systems such as hydrogels and nanoscaffolds improve NSC survival, localization, and integration (58). Gene-edited NSCs with enhanced regenerative properties are also under investigation (59). Despite these advances, long-term safety, optimal dosing, and functional integration remain unresolved challenges (54). Large-scale randomized clinical trials are essential for clinical validation.

Challenges, Limitations, and Future Perspectives

Despite promising progress, several biological and technical challenges limit the clinical translation of NSC-based therapies. One major limitation is poor survival of transplanted NSCs in the hostile post-injury microenvironment categorized by inflammation, oxidative stress, and inhibitory extracellular matrix molecules (60, 61). These factors significantly reduce cell viability and functional integration. Another concern is the risk of uncontrolled proliferation and tumorigenesis, particularly with pluripotent stem cell-derived NSCs (62). Immune rejection in allogeneic transplantation also remains a critical barrier (63). These limitations collectively reduce therapeutic consistency.

Technical challenges include the absence of standardized protocols for NSC derivation, expansion, and transplantation (64). Variability in manufacturing methods leads to inconsistent biological and functional outcomes. Additionally, precise control of NSC differentiation and incorporation into existing neural circuits remains difficult (60). The complexity of CNS architecture further complicates reconstruction of functional connectivity. Ethical concerns regarding embryonic stem cell sources also influence clinical translation pathways (62). Therefore, regulatory standardization is essential for clinical advancement.

Future directions focus on overcoming these limitations through advanced biomedical strategies. Gene-editing technologies such as CRISPR/Cas9 allocate precise enhancement of NSC safety and regenerative capacity (59, 65). Biomaterial scaffolds, nanotechnology, and 3D bioprinting provide structural guidance for axonal growth and neural network reconstruction (58, 66). Exosomes derived from neural stem cells (NSC-derived exosomes) have emerged as a promising cell-free therapeutic approach, offering the potential for enhanced safety compared with cell-based therapies (43, 57). Combination therapies integrating NSCs with pharmacological agents, rehabilitation, and electrical stimulation further enhance functional recovery (67). Ultimately, multidisciplinary approaches will be essential for successful clinical translation.

Controversies and Limitations (Critical View of NSC-Based Therapies)

Despite substantial progress in neural stem cell (NSC)-based therapies, several important controversies and limitations remain that restrict their full clinical translation. One of the most significant challenges is the limited survival and poor functional integration of transplanted NSCs within the injured central nervous system (CNS). Following injury, the local microenvironment becomes strongly detrimental to tissue repair, largely as a result of sustained inflammation, oxidative damage, excitotoxic processes, and inhibitory extracellular matrix molecules, including chondroitin sulfate proteoglycans (68, 69). These factors severely impair NSC survival, differentiation, and synaptic integration, leading to inconsistent and often transient functional recovery in experimental models (69). Another concern associated with NSC-based therapy is the potential for tumor formation and aberrant cell proliferation, especially when neural stem cells are generated from embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) (70). Even small populations of undifferentiated cells can form teratomas or aberrant tissue structures, raising

serious safety concerns for clinical application. In addition, immune rejection remains a critical barrier, especially in allogeneic transplantation, where host immune responses can eliminate grafted cells or reduce their therapeutic efficacy (71). Although immunosuppressive strategies may mitigate rejection, they introduce risks such as systemic immunosuppression and increased susceptibility to infection (71).

A further controversy concerns the mechanism of action of NSCs. While early studies emphasized direct cell replacement, more recent evidence indicates that the majority of therapeutic benefits are mediated across paracrine signaling and extracellular vesicle (EV)-based mechanisms rather than long-term neuronal integration (43, 72). This shift has raised important questions regarding whether NSCs should be used primarily as regenerative grafts or as biological sources for secretome- and exosome-based therapies. However, the optimal balance between these mechanisms remains unclear and likely depends on injury type and disease context.

Finally, the lack of standardized protocols for NSC derivation, expansion, differentiation, and transplantation remains a major translational barrier (73). Variability in cell preparation methods, delivery routes, timing of transplantation, and injury models leads to inconsistent outcomes across studies. Ethical concerns related to the use of embryonic stem cells further complicate regulatory approval and clinical implementation (70). Together, these issues highlight the need for improved standardization, safety optimization, and mechanistic clarity in future NSC research.

Conclusion

Neural stem cells (NSCs) have emerged as a versatile therapeutic approach with considerable potential for promoting repair and recovery following injuries to the central nervous system (CNS). Their regenerative potential extends beyond simple cell replacement, encompassing neuroprotection, immunomodulation, and the secretion of bioactive molecules that reshape the injured neural microenvironment. Through the regulation of inflammatory responses, enhancement of neuronal survival, promotion of axonal regeneration, and support of remyelination, NSCs contribute to both structural and functional recovery in diverse neurological conditions.Findings from preclinical studies provide substantial evidence for the therapeutic effectiveness of NSC-based strategies in experimental models of stroke, spinal cord injury, and traumatic brain injury. However, clinical translation remains limited due to challenges such as poor cell survival, variability in transplantation outcomes, immune rejection, and safety concerns including tumorigenicity. Despite these challenges, recent progress in biomaterials, gene-editing technologies, and cell-free strategies, particularly exosome-based therapies, is opening new avenues for enhancing the therapeutic potential of NSC-based approaches. Collectively, NSCs hold substantial promise as a next-generation regenerative therapy for CNS disorders, although further optimization and validation are essential for routine clinical application.

Future Directions

Future research should address improving the survival, integration, and functional maturation of transplanted NSCs within the hostile post-injury CNS environment. Advanced biomaterial scaffolds, 3D bioprinting technologies, and hydrogel-based delivery systems are expected to enhance cell retention and guide axonal growth. In parallel, gene-editing approaches such as CRISPR/Cas9 may be used to engineer NSCs with enhanced regenerative capacity, reduced immunogenicity, and improved safety profiles. Another major direction is the development of standardized, clinically scalable NSC production protocols to ensure reproducibility across studies and clinical trials.In addition, increasing attention is being directed toward NSC-derived extracellular vesicles and secretome-based therapies as safer, cell-free alternatives. Such strategies could help mitigate several of the potential risks inherent to the transplantation of living cells while retaining therapeutic efficacy. Combination therapies integrating NSCs with pharmacological agents, electrical stimulation, and rehabilitation strategies may further enhance functional recovery. Ultimately, interdisciplinary approaches combining stem cell biology, bioengineering, and clinical neuroscience will be essential to accelerate translation from bench to bedside.

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ATJ
Advanced Therapies Journal

VOL.8 / ISSUE 27 / SPRING 2026

Online ISSN: 2676-7236

DOI:

OPEN ACCESS

Pages: 17-22 / Review Article / Submit: 9 Feb 2026 / Accepted: 20 May 2026

Availablein: https://www.atjournal.ir

Nanotechnology-Driven Targeted Drug Delivery Strategies for the Treatment of Fungal and Viral Infections: A Comprehensive Review

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Abstract:

Nanotechnology has emerged as a promising strategy for improving drug delivery in the treatment of fungal and viral infections. Conventional antifungal and antiviral therapies are often limited by poor aqueous solubility, low bioavailability, systemic adverse effects, and inadequate delivery to intracellular sites of infection. Nanoscale delivery systems can overcome these limitations by improving drug pharmacokinetics, enhancing tissue-specific distribution, and enabling controlled and sustained drug release. Various nanocarriers, including liposomes, polymeric and lipid-based nanoparticles, dendrimers, and biomimetic nanostructures, have demonstrated considerable potential for increasing therapeutic efficacy.

Nanotechnology-based targeting approaches facilitate the preferential delivery of therapeutic agents to infected tissues through active receptor-mediated targeting and passive accumulation associated with inflammation and pathological tissue changes. In fungal infections, nanocarriers can improve drug penetration into biofilms and intracellular fungal niches, thereby enhancing antifungal activity and potentially reducing the development of resistance. In viral infections, nanoparticle-based formulations can enhance intracellular drug delivery, protect antiviral agents from enzymatic degradation, and improve inhibition of viral replication. Stimulus-responsive nanocarriers have further advanced targeted therapy by releasing their payload in response to local physiological conditions, such as changes in pH, enzyme activity, or temperature.

The integration of multifunctional nanoplatforms with artificial intelligence-based design may further support the development of personalized nanomedicine. Despite significant advances, challenges related to scalable manufacturing, regulatory requirements, long-term biosafety, and clinical translation remain. Continued progress in nanomaterial engineering and hybrid delivery systems may facilitate the broader clinical application of nanotechnology for effective and individualized treatment of infectious diseases.

Keywords: Nanotechnology, Targeted drug delivery, Antifungal therapy, Antiviral therapy, Nanocarriers

Introduction

In contemporary drug delivery, nanotechnology has revolutionized therapeutic approaches, serving as a cornerstone for advanced medication administration. offering the ability to engineer carriers at the nanoscale for improved pharmacokinetics, controlled release, and site-specific targeting. In particular, nanocarriers such as liposomes, polymeric nanoparticles, and lipid-

How to Cite this Article:

R. Mohmmadi Gandom Abad" Nanotechnology-Driven Targeted Drug Delivery Strategies for the Treatment of Fungal and Viral Infections: A Comprehensive Review" Advanced Therapies Journal, vol.8, no. 27, pp. 17- 22. 2026.

based systems can be functionalized with ligands that recognize molecular markers on diseased or infected cells, thereby enhancing therapeutic selectivity while minimizing systemic toxicity. These advances have significantly reshaped the landscape of precision medicine by enabling drugs to overcome biological barriers and achieve higher local concentrations at target sites (1).

In the context of infectious diseases, including fungal and viral infections, nanotechnology-based delivery systems provide promising strategies to enhance the efficacy of conventional therapeutics. Many antifungal and antiviral agents suffer from poor solubility, limited bioavailability, and dose-dependent toxicity, which restrict their clinical effectiveness. By utilizing either passive or active targeting strategies, nanoformulations facilitate precise delivery to infected sites while simultaneously shielding therapeutic agents from early degradation and enhancing their intracellular absorption. As a result, these systems not only enhance therapeutic outcomes but also contribute to reducing resistance development and treatment-related adverse effects (2).

Introduction to Nanotechnology in Infectious Disease Therapy

Nanotechnology has revolutionized drug delivery by enabling nanoscale engineering of therapeutic systems for infectious diseases.

These systems improve drug solubility, stability, and bioavailability in biological environments. Targeted delivery reduces off-target toxicity and enhances therapeutic precision in infected tissues. Antifungal and antiviral therapies particularly benefit from nanoscale carriers due to biological barriers. Recent advances emphasize ligand-based targeting for infected cell recognition and selective uptake. Overall, nanotechnology provides a foundation for next-generation antimicrobial therapy (1, 2).

The evolution of nanocarriers such as liposomes, dendrimers, and polymeric nanoparticles has enabled controlled drug release. These platforms enhance intracellular delivery of drugs with poor pharmacokinetic profiles. Active targeting strategies involve receptor-mediated uptake into infected cells. Passive targeting exploits enhanced permeability in inflamed tissues. Such systems improve therapeutic index and reduce systemic toxicity significantly. These innovations have reshaped infectious disease nanomedicine research (3, 4).

Pathophysiology of Fungal and Viral Infections

Fungal infections often involve biofilm formation and intracellular survival mechanisms. These features make conventional antifungal therapy less effective and prone to resistance. Viral infections involve host-cell machinery hijacking, complicating selective drug targeting. Latency and mutation rates further reduce antiviral treatment efficiency. Both pathogens exploit immune evasion strategies to sustain infection. This complexity necessitates advanced delivery approaches (5, 6).

Targeting infected cells requires understanding pathogen-host interactions at molecular levels. Nanocarriers can be engineered to recognize infection-specific biomarkers. This enables selective accumulation at infected tissue sites. Improved cellular uptake enhances intracellular drug concentrations. Such approaches minimize damage to healthy tissues. These mechanisms are central to nanotherapeutic design (7).

Types of Nanocarriers for Drug Delivery

Liposomes are among the most widely used nanocarriers for antifungal and antiviral drugs.

They provide biocompatibility and efficient encapsulation of hydrophilic and lipophilic agents. Surface modification enhances stability and circulation time. Liposomal amphotericin B is a key antifungal example. These systems reduce nephrotoxicity and improve efficacy. Their clinical success supports continued development (8, 9).

The release kinetics of drugs can be precisely modulated and prolonged through the utilization of polymeric nanoparticles. They are synthesized using biodegradable materials such as PLGA. These systems allow precise tuning of drug release kinetics. Functionalization enables targeted delivery to infected cells. Their versatility supports both antiviral and antifungal applications. They remain a major focus of nanomedicine research (10, 11).

Targeting Strategies for Infected Cells

Active targeting involves ligand-receptor interactions on infected cell surfaces. Antibodies, peptides, and aptamers are commonly used targeting ligands. These ligands enhance selective uptake into diseased cells. This improves drug accumulation at infection sites. Reduced systemic exposure minimizes adverse effects. Such strategies increase therapeutic specificity (12, 13).

In inflamed tissues, the accumulation of nanoparticles is primarily driven by the enhanced permeability and retention (EPR) effect, which facilitates passive localization at the site of infection. Infection-induced vascular leakage facilitates nanoparticle accumulation. This mechanism does not require ligand modification. However, specificity is lower compared to active targeting. Combining both strategies enhances therapeutic outcomes. Hybrid approaches are gaining research attention (14).

Nanotechnology in Antifungal Drug Delivery

Fungal pathogens such as Candida and Aspergillus are difficult to treat.

Nanocarriers improve delivery of amphotericin B and azoles. Encapsulation reduces toxicity and enhances therapeutic index. Targeted systems improve penetration into fungal biofilms. This overcomes one of the main barriers in antifungal therapy. Nanomedicine significantly improves treatment outcomes (15, 16).

Lipid-based nanoparticles enhance antifungal drug stability in circulation. They protect active compounds from enzymatic degradation. Controlled release ensures sustained antifungal activity. Surface modification enables fungal cell targeting. These systems reduce recurrence rates of infections. They represent a promising therapeutic advancement (17).

Nanotechnology in Antiviral Drug Delivery

Viruses present unique challenges due to intracellular replication cycles.

Nanoparticles enable direct delivery of antivirals into infected cells. This improves drug concentration at replication sites.RNA viruses particularly benefit from nanocarrier-based delivery. Lipid nanoparticles are widely used in mRNA therapeutics. These systems have transformed antiviral strategies (18, 19).

Nanocarriers also protect antiviral agents from enzymatic degradation. They improve pharmacokinetic profiles and reduce dosing frequency. Targeted delivery enhances inhibition of viral replication. This reduces viral load more effectively than conventional therapy. Nanotechnology is critical in modern antiviral development. It supports rapid therapeutic response in outbreaks (20).

Stimuli-Responsive Nanocarriers

Stimuli-responsive platforms are engineered to trigger drug liberation upon encountering specific environmental cues, allowing for spatio-temporal control over therapeutic release.pH-sensitive nanoparticles release drugs in infected acidic environments. Enzyme-responsive systems react to pathogen-specific enzymes. This enhances site-specific drug activation. Controlled release reduces systemic toxicity. Such systems improve therapeutic precision (21).

Temperature and redox-responsive carriers are also widely studied. These systems respond to infection-induced physiological changes. They allow controlled intracellular drug release. This improves drug efficacy in infected tissues. multi-responsive systems offer enhanced control. They represent next-generation nanomedicine platforms (22).

Overcoming Biological Barriers

Biological barriers limit drug delivery efficiency in infectious diseases. Nanoparticles must cross membranes and evade immune clearance. Surface PEGylation improves circulation time and stability. Cell-penetrating peptides enhance intracellular delivery. These strategies increase therapeutic effectiveness. Barrier penetration remains a key research focus (23).

Blood–brain barrier penetration is critical for viral infections affecting CNS.Nanocarriers enable drug transport across tight junctions. This improves treatment of neurotropic viruses. Targeted delivery reduces neurological damage. Advanced engineering enhances barrier crossing efficiency. This expands therapeutic possibilities (24).

Clinical Translation and Challenges

Despite progress, clinical translation remains challenging. Regulatory approval requires extensive toxicity evaluation.

Scalability of nanoparticle production is a major issue. Batch-to-batch consistency affects therapeutic reliability.

High production costs limit widespread adoption. These challenges slow clinical integration (25).

Immunogenicity and long-term safety remain concerns. Some nanomaterials may trigger immune responses. Pharmacokinetic variability complicates dosing strategies. Standardization of nanomedicine protocols is needed. Clinical trials are gradually addressing these issues. Future success depe

nds on resolving these barriers (26).

Revolutionizing Antifungal and Antiviral Therapeutics: Future Frontiers in Nanotechnology-Driven Targeted Delivery

The paradigm of antifungal and antiviral therapeutics is shifting toward the implementation of multifunctional, intelligent nanoplatforms. A key driver of this evolution is the emergence of theranostic architectures, which integrate diagnostic imaging with targeted therapeutic delivery into a unified system. By facilitating real-time tracking of pathogen dynamics and treatment efficacy, these advanced platforms promise to enhance early-stage detection, ultimately minimizing systemic dissemination and the overall clinical burden of infection.

Furthermore, functionalizing nanoparticle surfaces with specialized ligands including aptamers, peptides, or monoclonal antibodies offers a sophisticated route to augment the discriminatory recognition of infected cells relative to healthy tissues. This level of targeting specificity is particularly important in viral infections, where intracellular replication requires precise intracellular drug delivery. Emerging research also highlights the potential of biomimetic nanocarriers that mimic cellular membranes to improve immune evasion and prolong systemic circulation (1–3).

A transformative frontier in nanomedicine lies in the synergy between artificial intelligence (AI) and nanoparticle engineering. By leveraging machine learning (ML) algorithms, researchers can transition from empirical trial-and-error to a rational, predictive design framework. These computational models enable the precise optimization of critical physicochemical parameters—such as hydrodynamic diameter, zeta potential, and ligand conjugation density thereby maximizing the efficacy of nanocarriers against fungal and viral targets. Ultimately, this AI-driven paradigm streamlines the development pipeline, significantly shortening the trajectory from laboratory discovery to clinical implementation.

Moreover, personalized nanomedicine is expected to emerge as a key strategy, where nanocarrier design is tailored according to patient-specific infection profiles and genetic background. This is particularly relevant in antiviral therapy, where viral mutations and host variability significantly influence treatment outcomes. Furthermore, hybrid nanocarriers combining organic and inorganic materials are being explored to improve drug stability, responsiveness, and multifunctionality in complex biological environments (4–6).

Conclusion

Nanotechnology-based drug delivery systems represent a transformative advancement in the targeted treatment of fungal and viral infections, offering significant improvements in therapeutic precision, drug stability, and intracellular delivery efficiency. By engineering nanoscale carriers capable of selective interaction with infected cells, these platforms overcome major limitations of conventional antifungal and antiviral therapies, including poor bioavailability, systemic toxicity, and rapid drug degradation. The integration of active and passive targeting strategies further enhances drug accumulation at infection sites, leading to improved clinical outcomes and reduced resistance development.

Despite these promising developments, several challenges remain in translating nanomedicine from laboratory research to clinical practice, including large-scale manufacturing, long-term safety evaluation, and regulatory standardization. However, ongoing progress in smart nanocarriers, stimuli-responsive systems, and AI-assisted design is expected to address these limitations and significantly expand the clinical applicability of targeted nanotherapy. Collectively, nanotechnology continues to redefine the future of infectious disease treatment by enabling more effective, safer, and highly personalized therapeutic strategies.

Acknowledgements

The authors gratefully acknowledge the Biotechnology Research Center of the National Institute of Genetic Engineering and Biotechnology (Iran) for providing essential technical support and resources that facilitated this study.

Author Contributions

All authors played an integral role in the development of this study, sharing responsibilities in conceptual framework formulation, methodological design, comprehensive literature synthesis, and the drafting of the manuscript. Each author participated in drafting, revising, and approving the final version of the manuscript for submission.

Data Availability Statement

The datasets supporting the findings of this study are fully contained within the current manuscript; however, further data or supplementary materials can be provided by the corresponding author upon legitimate inquiry.

Table 1.

Study	Nanocarrier System	Drug / Target	Key Findings	Reference
1	Liposomal nanoparticles	Amphotericin B	Reduced nephrotoxicity and improved antifungal efficacy in systemic infections	Allen et al., 2021
2	PLGA nanoparticles	Fluconazole	Sustained release and enhanced biofilm penetration against Candida spp.	Danhier et al., 2019
3	Solid lipid nanoparticles	Voriconazole	Increased oral bioavailability and improved intracellular delivery	Sercombe et al., 2020
4	PEGylated liposomes	Antiviral agents	Extended circulation time and reduced immune clearance	Wang et al., 2020
5	mRNA lipid nanoparticles	SARS-CoV-2 spike mRNA	Efficient intracellular delivery and high immunogenic response	Hou et al., 2021
6	Polymer-based nanoparticles	Acyclovir	Enhanced antiviral activity and controlled release profile	Patel et al., 2022
7	Targeted antibody-conjugated NPs	HIV inhibitors	Improved selective uptake in infected immune cells	Blanco et al., 2019
8	pH-responsive nanoparticles	Antifungal azoles	Triggered drug release in infected acidic microenvironments	Chen et al., 2019
9	Biomimetic membrane-coated NPs	Broad-spectrum antivirals	Immune evasion and improved biodistribution	Zhang et al., 2024
10	AI-designed hybrid nanoparticles	Multi-antiviral therapy	Optimized drug loading and improved targeting efficiency	Kherlopian et al., 2023

Declarations

Competing Interest

The authors certify that no conflicts of interest, whether financial or personal, exist that could potentially bias the findings or the integrity of the research presented herein.

Ethics Approval and Consent to Participate

Ethical clearance and participant consent were not necessitated for this research, as no human or animal subjects were utilized in the experimental procedures.

Consent for Publication

The absence of individual identifiable data within this study renders the requirement for publication consent unnecessary.

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ATJ
Advanced Therapies Journal

VOL.8 / ISSUE 27 / SPRING 2026

Online ISSN: 2676-7236

DOI: 10.22034/atj.2026.250915

OPEN ACCESS

Pages: 23- 33 / Review Article / Submit: 30 Jan 2026 / Accepted: 22 May 2026

Availablein: https://www.atjournal.ir

Smart Targeted Nanoparticles for Precision Tumor Drug Delivery: Challenges and Opportunities

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Abstract:

Cancer remains a significant global health burden, and the limitations of conventional anticancer therapies have driven the development of innovative nanotechnology-based drug delivery systems. Challenges including inadequate tumor selectivity, systemic toxicity, multidrug resistance, and insufficient therapeutic efficacy have highlighted the need for more precise treatment strategies. Smart targeted nanoparticles have emerged as promising delivery platforms because they combine selective tumor targeting, controlled drug release, prolonged circulation, and multifunctional therapeutic functions.

This review summarizes recent advances in smart nanoparticle-mediated drug delivery for precision oncology. It discusses the fundamental concepts of targeted cancer therapy and examines the major physiological and biological barriers affecting nanoparticle transport, particularly the tumor microenvironment and the limitations of the enhanced permeability and retention (EPR) effect. Additionally, the structural characteristics, biomedical applications, and therapeutic potential of lipid-based, polymeric, inorganic, hybrid, and biomimetic nanoparticles are evaluated. Recent progress in passive and active targeting, ligand-, antibody-, peptide-, and aptamer-mediated delivery, stimuli-responsive nanocarriers, and surface engineering strategies designed to improve tumor specificity and therapeutic outcomes is also discussed.

In addition, current preclinical and clinical developments, biosafety concerns, regulatory considerations, and challenges associated with large-scale manufacturing and clinical translation are comprehensively evaluated. Finally, emerging technologies, including artificial intelligence-assisted nanoparticle design, theranostic nanoplatforms, RNA therapeutics, gene editing, and personalized nanomedicine, are discussed as future directions for improving the efficacy, safety, and clinical applicability of smart targeted nanoparticles. Collectively, these advances position smart nanomedicine as a transformative strategy for achieving personalized and precision cancer therapy.

Keywords: Smart targeted nanoparticles, Precision tumor drug delivery, Tumor microenvironment, Active targeting, Precision nanomedicine.

Introduction

Even with continuous advances in early detection and therapeutic approaches, cancer persists as a major worldwide public health challenge, accounting for a high burden of morbidity and mortality. Conventional anticancer treatments, including chemotherapy, often

How to Cite this Article:

S. F. Tabatabaii, Z. Alipour Fard" Smart Targeted Nanoparticles for Precision Tumor Drug Delivery: Challenges and Opportunities", Advanced Therapies Journal ,vol. 8, no. 27, pp. 23-33, 2026.

suffer from poor tumor selectivity, limited therapeutic efficacy, multidrug resistance, and severe systemic toxicity resulting from nonspecific drug distribution. These challenges have encouraged the advancement of nanotechnology-driven drug delivery platforms designed to optimize pharmacokinetic behavior, increase drug deposition at tumor sites, and reduce unintended systemic toxicity. More recently, smart targeted nanoparticles have gained considerable interest as versatile nanocarriers that combine selective tumor recognition, regulated drug release, and responsiveness to internal or external stimuli, making them highly attractive tools for precision cancer therapy. By taking advantage of tumor-associated biomarkers, abnormal vascular structures, and the distinctive features of the tumor microenvironment, these advanced nanocarriers enhance drug delivery to malignant tissues, thereby improving therapeutic outcomes while limiting systemic adverse effects. In addition, continuous progress in biomaterials, nanoparticle surface modification, and targeted molecular engineering has driven the advancement of personalized nanomedicine, establishing smart nanoparticles as a leading platform for the future of precision cancer treatment (1, 2).

Recent innovations in smart nanoparticle engineering have led to increasingly advanced drug delivery platforms that integrate molecular targeting, stimulus-triggered drug release, diagnostic imaging, and combination therapies into a single nanosystem. Various nanoparticle classes, including organic, inorganic, biomimetic, and hybrid formulations, can be engineered with antibodies, peptides, aptamers, or cell membrane-derived coatings to achieve selective recognition of tumor-specific receptors while improving their ability to overcome biological obstacles such as protein corona formation, rapid immune elimination, and limited penetration into tumor tissues. Although these nanoplatforms have demonstrated encouraging outcomes in preclinical investigations, their clinical implementation is still hindered by tumor heterogeneity, complex manufacturing processes, regulatory requirements, large-scale production challenges, and uncertainties regarding long-term biosafety. Looking ahead, the convergence of artificial intelligence, precision oncology, multi-omics technologies, and patient-tailored nanocarrier engineering is anticipated to enhance the efficiency of targeted drug delivery and accelerate individualized cancer therapy. Accordingly, this review provides a comprehensive overview of recent advances in smart targeted nanoparticles, focusing on their design strategies, targeting mechanisms, clinical development, current limitations, and future prospects for translational cancer research. (3, 4).

Principles of Precision Tumor Drug Delivery

Precision tumor drug delivery has emerged as a fundamental strategy in contemporary cancer treatment, aiming to enhance therapeutic effectiveness while reducing systemic toxicity by directing therapeutic agents specifically to tumor tissues. In contrast to conventional chemotherapy, which often damages both malignant and normal cells, precision-based delivery approaches are designed according to the molecular, cellular, and physiological diversity of individual tumors. This concept combines advances in nanotechnology, biomaterials, molecular biology, and pharmacology to optimize drug distribution, improve pharmacokinetic performance, and facilitate efficient intracellular drug transport. Targeted delivery systems utilize tumor-associated molecular markers, abnormal tumor vasculature, and the distinctive physicochemical properties of the tumor microenvironment to promote selective drug localization. These systems employ both passive targeting, primarily through the enhanced permeability and retention (EPR) effect, and active targeting based on specific ligand–receptor interactions to improve therapeutic performance. Nevertheless, growing evidence indicates that the success of these strategies is strongly influenced by tumor subtype, vascular characteristics, and interpatient biological variability. As a result, precision drug delivery has progressively shifted toward personalized nanomedicine, in which nanotherapeutic platforms are customized to the unique biological features of each patient's tumor, thereby enhancing clinical efficacy while minimizing treatment-related toxicity (5, 6).

The effectiveness of precision tumor drug delivery largely relies on the ability to overcome a series of biological obstacles that impede the transport of therapeutic agents from the bloodstream to their intracellular targets. After systemic administration, nanoparticles are exposed to protein corona formation, recognition by the immune system, rapid elimination through the mononuclear phagocyte system, and inefficient accumulation within tumor tissues. Even after reaching the tumor site, their distribution is frequently hindered by the dense extracellular matrix, elevated interstitial fluid pressure, irregular vascular networks, and the heterogeneous architecture of the tumor microenvironment. To improve delivery efficiency, advanced nanocarriers have been engineered with surface modifications, biomimetic membranes, and stimulus-responsive components that enable site-specific drug release in response to pH changes, enzymatic activity, hypoxia, redox conditions, ultrasound, or magnetic stimulation. These intelligent nanosystems enhance intratumoral penetration, promote efficient cellular uptake, and provide controlled release of therapeutic agents at the intended target. Furthermore, the

incorporation of genomic information, molecular imaging technologies, and artificial intelligence into nanocarrier design is driving the development of individualized therapeutic platforms consistent with the goals of precision oncology. Together, these advances are strengthening the clinical potential of smart nanomedicine and offering promising solutions to overcome the shortcomings of conventional anticancer drug delivery (7, 8).

Biological Barriers to Nanoparticle-Mediated Drug Delivery

The clinical performance of nanoparticle-based drug delivery systems is determined not only by the physicochemical characteristics of the nanocarriers but also by their capacity to navigate a series of physiological and biological barriers encountered after systemic administration. Once introduced into the circulation, nanoparticles rapidly interact with blood components, resulting in protein corona formation, complement activation, and recognition by the mononuclear phagocyte system, which collectively accelerate their elimination and decrease their circulation time. Although surface-engineered nanoparticles can partially prolong systemic persistence, efficient delivery to tumors remains limited by irregular vascular architecture, restricted endothelial translocation, and inadequate extravasation into malignant tissues. Following tumor accumulation, additional obstacles including a dense extracellular matrix, elevated interstitial fluid pressure, abnormal stromal composition, and heterogeneous tissue organization significantly reduce nanoparticle diffusion and uniform drug distribution throughout the tumor mass. Consequently, only a small proportion of the administered dose successfully reaches target cancer cells, compromising overall therapeutic benefit. A detailed understanding of these biological barriers and their interactions with nanocarriers is therefore essential for the rational development of advanced drug delivery platforms. Current research has increasingly focused on designing nanoparticles with immune-evasive properties, biomimetic surface coatings, and engineered interfaces that improve vascular transport, tumor penetration, and selective drug accumulation within malignant tissues (9, 10).

The tumor microenvironment (TME) is a critical factor influencing the efficiency of nanoparticle-mediated drug delivery and significantly affects therapeutic outcomes in cancer treatment. It consists of a complex network of malignant cells, cancer-associated fibroblasts, immune cell populations, extracellular matrix components, aberrant vasculature, and diverse biochemical conditions, including hypoxia, acidic pH, oxidative stress, and increased enzymatic activity. While these distinctive features create valuable opportunities for the design of stimuli-responsive nanocarriers, they also present substantial barriers to deep tumor penetration and homogeneous drug distribution. Conventional passive targeting strategies have largely depended on the enhanced permeability and retention (EPR) effect, in which the leaky architecture of tumor blood vessels and inadequate lymphatic drainage promote nanoparticle accumulation within tumor tissues. Nevertheless, accumulating preclinical and clinical evidence has demonstrated considerable variability in the magnitude of the EPR effect across different tumor types and individual patients, reducing its reliability as a universal mechanism for nanoparticle delivery. Consequently, contemporary approaches integrate passive EPR-mediated targeting with ligand-directed active targeting, modulation of the tumor microenvironment, and stimulus-sensitive drug release systems to enhance targeting accuracy and therapeutic efficacy. A deeper understanding of TME biology and the constraints of the EPR effect is therefore essential for developing personalized nanomedicine platforms capable of overcoming tumor heterogeneity and improving clinical outcomes (11, 12).

Classification of Smart Nanoparticles for Tumor Targeting

Smart nanoparticles developed for precision tumor targeting encompass a broad range of nanoscale delivery systems designed to enhance the selective transport of therapeutic agents to cancer tissues while reducing unwanted systemic adverse effects. These nanocarriers are commonly categorized according to their composition, physicochemical characteristics, and functional properties into lipid-based, polymeric, inorganic, hybrid, and biomimetic platforms. Each class possesses unique features that influence drug encapsulation efficiency, biodegradability, circulation time, targeting performance, and responsiveness to endogenous or externally applied stimuli. Lipid-based nanocarriers are widely recognized for their high biocompatibility and have achieved notable clinical success in delivering anticancer drugs and nucleic acid therapeutics. In contrast, polymeric nanoparticles offer flexible structural design and sustained, controlled drug release, whereas inorganic nanomaterials exhibit distinctive optical, magnetic, and photothermal properties that support both diagnostic imaging and therapeutic applications. More recently, hybrid and biomimetic nanoparticles have been developed to combine the complementary advantages of different nanoplatforms, thereby addressing many limitations associated with traditional delivery systems. Accordingly, a thorough understanding of the classification and engineering principles of smart nanoparticles is essential for selecting the most suitable nanocarrier based on tumor characteristics and specific

therapeutic goals (13, 14).

Continuous advances in nanotechnology have driven the emergence of sophisticated nanoparticle systems that integrate multiple therapeutic and diagnostic functions within a single platform. Modern nanocarriers are increasingly designed to combine selective drug targeting, programmable drug release, molecular imaging, and immune modulation to enhance the effectiveness of cancer therapy. Among these systems, lipid-based nanoparticles remain the most clinically established because of their excellent biocompatibility and well-documented safety profile. Polymeric nanoparticles, on the other hand, provide versatile and highly tunable structures that enable precise control over drug loading and release kinetics. Inorganic nanoparticles possess distinctive optical, magnetic, and thermal properties that make them particularly valuable for diagnostic imaging, magnetic guidance, and photothermal treatment, although issues related to long-term biosafety and biodegradation continue to require careful evaluation. To overcome the limitations of individual nanocarriers, hybrid nanoparticles have been engineered by integrating lipid, polymeric, and inorganic materials into multifunctional platforms with enhanced performance. Furthermore, biomimetic nanocarriers, including cell membrane-coated nanoparticles and exosome-mimicking systems, exploit natural biological properties such as immune escape, prolonged blood circulation, and preferential tumor recognition. The combination of these advanced nanoplatforms with molecular targeting strategies and stimulus-responsive technologies is anticipated to improve the precision of anticancer drug delivery and accelerate the clinical implementation of personalized nanomedicine (15, 16).

Passive and Active Targeting Strategies

Targeted drug delivery has become a cornerstone of modern nanomedicine because it enhances therapeutic efficacy while minimizing systemic toxicity. Nanocarrier-based systems are generally categorized into passive and active targeting approaches, each exploiting distinct biological mechanisms to improve drug accumulation at diseased tissues. Passive targeting primarily relies on the enhanced permeability and retention (EPR) effect, which enables nanoscale carriers to preferentially accumulate within pathological tissues characterized by leaky vasculature and impaired lymphatic drainage. Although passive targeting has demonstrated promising outcomes in several preclinical and clinical settings, its effectiveness is highly influenced by tumor heterogeneity, vascular architecture, and interpatient variability. Consequently, increasing attention has shifted toward active targeting strategies that utilize specific molecular recognition mechanisms to improve cellular uptake and tissue selectivity. The combination of passive accumulation with receptor-mediated targeting has emerged as a promising strategy for overcoming biological barriers and enhancing therapeutic precision in cancer and other diseases (17, 18).

Active targeting strategies are commonly achieved through the surface functionalization of nanocarriers with biological ligands capable of recognizing overexpressed receptors on target cells. Among these approaches, ligand-mediated targeting, antibody-based targeting, peptide-guided delivery, and aptamer-functionalized nanocarriers have shown considerable potential for improving specificity, intracellular internalization, and therapeutic outcomes. Ligands such as folate and transferrin, monoclonal antibodies, receptor-specific peptides, and nucleic acid aptamers enable selective interaction with disease-associated biomarkers while reducing off-target effects. Recent progress in nanotechnology has enabled the design of multifunctional nanocarriers that combine diagnostic imaging, programmable drug release, and selective targeting within a unified therapeutic platform. By integrating these complementary functions, advanced nanosystems can optimize drug pharmacokinetics, enhance biodistribution, and increase treatment efficiency while reducing off-target effects. Such technological advances are anticipated to promote the successful clinical implementation of targeted nanomedicine and broaden its therapeutic applications across diverse disease conditions (19, 20).

Stimuli-Responsive Smart Nanoparticles

Stimuli-responsive nanoparticles have become a prominent class of advanced nanomedicine platforms because they provide spatially and temporally controlled drug release in response to disease-associated or externally applied signals. In contrast to conventional nanocarriers, these engineered systems maintain their structural integrity during circulation but undergo specific physicochemical changes after encountering predetermined stimuli at the target site, enabling localized therapeutic delivery. Endogenous triggers such as acidic pH, elevated glutathione concentrations, increased reactive oxygen species, and disease-associated enzymatic activity are commonly utilized to activate drug release selectively within pathological tissues, thereby limiting premature cargo leakage and reducing systemic adverse effects. These responsive delivery systems enhance drug retention at the target site, improve intracellular uptake, and ultimately

increase therapeutic efficiency. Continuous progress in biomaterials science, polymer engineering, and nanoscale fabrication has further supported the development of multifunctional nanocarriers that combine molecular targeting, stimulus-controlled drug release, and diagnostic imaging within a single platform. Consequently, stimulus-responsive nanosystems are increasingly recognized as key components of precision medicine and hold significant potential for the treatment of cancer, inflammatory disorders, and tissue regeneration (21, 22).

Endogenous stimulus-responsive nanocarriers employ disease-specific biochemical conditions to achieve selective and controlled drug release. For example, pH-sensitive nanoparticles take advantage of the acidic environment of solid tumors and intracellular endosomes to activate therapeutic payload release, whereas redox-responsive systems are designed to respond to the high intracellular glutathione levels characteristic of many cancer cells by breaking reduction-sensitive chemical bonds and promoting efficient cytosolic drug delivery. Likewise, enzyme-responsive nanoparticles enhance targeting specificity by releasing their cargo in the presence of disease-associated enzymes, including matrix metalloproteinases, cathepsins, and hyaluronidases, which are frequently upregulated in pathological tissues. Conversely, exogenous stimulus-responsive nanoplatforms depend on externally applied triggers such as heat, light irradiation, magnetic fields, or ultrasound to regulate drug release with high spatial and temporal precision. These externally controlled systems have demonstrated considerable promise in applications including image-guided therapy, photothermal ablation, magnetic targeting, and ultrasound-assisted drug delivery. Furthermore, incorporating multiple stimulus-responsive mechanisms into a single multifunctional nanocarrier has emerged as an effective approach to overcome biological barriers, enhance therapeutic accuracy, and accelerate the clinical implementation of precision nanomedicine (23, 24).

Surface Engineering and Functionalization of Nanoparticles

Surface engineering has become a fundamental strategy for optimizing the biological performance of nanoparticles by tailoring their physicochemical properties and interactions with biological systems. Since the nanoparticle surface is the first interface encountered after systemic administration, its composition critically influences protein adsorption, biodistribution, circulation time, cellular uptake, and immune recognition. Various surface functionalization approaches have been developed to enhance stability, prolong blood circulation, improve biocompatibility, and facilitate targeted drug deliveryAmong the various surface engineering approaches, polyethylene glycol (PEG) conjugation remains one of the most extensively employed strategies because it forms a protective hydrophilic layer around nanoparticles, thereby reducing protein adsorption, limiting opsonization, and decreasing recognition by the mononuclear phagocyte system. More recently, biomimetic surface modification techniques, particularly cell membrane-coated nanoparticles, have gained considerable attention as they incorporate naturally derived membrane proteins that enhance immune evasion, extend systemic circulation, and improve interactions with target tissues. Collectively, these innovations in nanoparticle surface engineering have strengthened the therapeutic performance of nanomedicine and expanded its potential for the treatment of cancer as well as other complex disorders (25, 26).

In addition to optimizing pharmacokinetic behavior, nanoparticle surface engineering plays a crucial role in enhancing target specificity and reducing immune recognition through the incorporation of functional ligands and biomimetic materials. Surface modification with bioactive molecules, such as peptides, antibodies, aptamers, and small-molecule ligands, facilitates receptor-mediated interactions with diseased cells, thereby improving cellular uptake while limiting nonspecific distribution to healthy tissues. At the same time, strategies designed to evade immune surveillance have progressed beyond traditional PEGylation toward advanced biomimetic approaches. These include coating nanoparticles with membranes derived from erythrocytes, platelets, macrophages, stem cells, or cancer cells, allowing the nanocarriers to retain native membrane proteins that promote self-recognition, prolong blood circulation, and reduce clearance by the immune system. These biomimetic nanoplatforms not only reduce macrophage-mediated clearance but also improve tumor homing and prolong systemic circulation. Consequently, integrating targeting ligands with immune camouflage has become a powerful approach for developing multifunctional nanoparticles with enhanced therapeutic precision and favorable translational potential in precision nanomedicine (27, 28).

Preclinical and Clinical Advances in Smart Targeted Nanomedicine

The continuous advancement of smart targeted nanomedicine has facilitated the transition of innovative nanotherapeutic platforms from experimental research toward clinical application, creating new possibilities for the diagnosis and treatment of complex diseases. Preclinical investigations have consistently shown that

multifunctional nanocarriers can improve the selective accumulation of therapeutic agents at disease sites, optimize pharmacokinetic behavior, minimize systemic adverse effects, and overcome biological barriers that restrict the effectiveness of conventional treatments. These studies have confirmed the potential of diverse targeting strategies, stimulus-responsive delivery systems, and biomimetic nanoparticles in a wide range of disease models, with particularly encouraging outcomes in oncology. In addition, the integration of imaging technologies with nanomedicine has enabled noninvasive visualization of nanoparticle distribution and treatment responses, providing valuable information for refining nanocarrier design before clinical implementation. Together, these advances have strengthened the scientific basis for translating intelligent nanoparticle systems into clinical practice and have accelerated the progression of nanomedicine from laboratory investigation to human therapeutic applications (29, 30).

The clinical advancement of nanomedicine is evidenced by the expanding number of clinical investigations and the increasing availability of nanotechnology-based therapeutics approved for medical use by regulatory authorities. Approved nanomedicines including liposomal drug formulations, albumin-bound nanoparticles, lipid nanoparticle platforms for nucleic acid delivery, and iron oxide–based nanomaterials—have demonstrated superior therapeutic performance and improved safety profiles compared with many conventional drug formulations. At the same time, a broad range of next-generation nanotherapeutics incorporating receptor-specific targeting ligands, stimulus-responsive drug release systems, and integrated diagnostic imaging functions are undergoing clinical assessment. Nevertheless, the widespread clinical adoption of these technologies remains limited by challenges such as scalable manufacturing, regulatory harmonization, long-term safety evaluation, and variability in patient responses. Addressing these issues will require sustained interdisciplinary collaboration among biomaterials researchers, clinicians, pharmaceutical developers, and regulatory organizations to accelerate the development of safe, effective, and personalized nanomedicine for future clinical applications (31, 32).

Safety, Toxicity, and Regulatory Considerations

The effective integration of nanomedicine into clinical practice requires not only demonstrated therapeutic benefit but also rigorous evaluation of nanoparticle safety, biological compatibility, and adherence to regulatory standards. Owing to their distinctive physicochemical properties, such as nanoscale dimensions, large surface-to-volume ratios, and highly adaptable surface characteristics, nanoparticles interact with biological environments in ways that differ markedly from conventional drug formulations. Therefore, comprehensive biocompatibility assessment has become a fundamental aspect of preclinical development, focusing on minimizing immune activation, ensuring appropriate biodegradation, and reducing unintended toxicity in healthy tissues. Furthermore, the biodistribution, metabolic processing, and long-term biological fate of nanomaterials require thorough investigation to evaluate the potential risks associated with prolonged tissue retention, bioaccumulation, and chronic exposure. Comprehensive characterization of these parameters is essential for predicting nanoparticle clearance pathways, assessing long-term biosafety, and supporting the safe clinical translation of nanomedicine. Advances in nanotoxicology have provided valuable insights into the relationships between nanoparticle composition, surface properties, and biological responses, supporting the rational design of safer nanocarriers. These considerations are fundamental for improving the benefit-risk profile of smart targeted nanomedicines and facilitating their successful clinical application (33, 34).

In parallel with safety assessment, comprehensive pharmacokinetic evaluation and regulatory standardization are critical for the development of clinically successful nanomedicines. Pharmacokinetic studies investigate nanoparticle absorption, biodistribution, metabolism, clearance, and interactions with the mononuclear phagocyte system, all of which influence therapeutic efficacy and potential toxicity. Regulatory agencies increasingly require standardized characterization methods, reproducible manufacturing processes, validated analytical techniques, and rigorous quality control to ensure product consistency and patient safety. The successful commercialization of nanomedicine requires strict adherence to Good Manufacturing Practice (GMP) standards, implementation of quality-by-design (QbD) strategies, and compliance with internationally aligned regulatory requirements to ensure the consistent production of safe and effective nanotherapeutics. Although considerable progress has been achieved in the field, important challenges remain, including the lack of standardized evaluation methods, the need for comprehensive long-term safety assessments, and the development of regulatory policies specifically tailored to multifunctional nanoparticle-based therapeutics. Overcoming these limitations will be essential for facilitating regulatory approval, promoting large-scale manufacturing, and supporting the broad clinical integration of next-generation smart nanomedicine platforms (35, 36).

Current Challenges Limiting Clinical Translation

Although targeted nanomedicine has achieved substantial scientific progress, the transition of nanoparticle-based therapeutics from experimental studies to routine clinical application continues to face numerous biological and technological limitations. A key challenge is the pronounced heterogeneity of tumors, which gives rise to considerable differences in vascular architecture, receptor availability, extracellular matrix organization, and immune cell composition both among patients and within individual tumor lesions. This variability compromises the consistency of nanoparticle accumulation and often diminishes the therapeutic benefits observed in preclinical models. Furthermore, inefficient intratumoral transport caused by a dense extracellular matrix, elevated interstitial fluid pressure, and disorganized tumor vasculature restricts the deep penetration and uniform distribution of nanocarriers throughout malignant tissues. Together, these factors contribute to variable treatment outcomes and help explain the gap between encouraging laboratory findings and relatively limited clinical success. Consequently, strategies aimed at overcoming tumor heterogeneity and enhancing nanoparticle transport within tumors have become major priorities in the design of next-generation nanomedicine platforms (37, 38).

In addition to biological barriers, the broad clinical adoption of smart nanomedicines is constrained by significant manufacturing, economic, and regulatory challenges. The transition from laboratory-scale production to industrial manufacturing demands scalable, reliable, and economically sustainable processes that consistently preserve critical nanoparticle attributes, including particle size, structural composition, physicochemical stability, and batch-to-batch uniformity. Maintaining these quality parameters is essential to ensure product reproducibility, therapeutic performance, and compliance with regulatory standards during large-scale production. However, the complexity of multifunctional nanocarriers often increases production costs and complicates industrial scale-up. Moreover, the absence of universally accepted regulatory frameworks and standardized characterization methods creates additional barriers for product approval and commercialization. Regulatory agencies require comprehensive evidence regarding quality, pharmacokinetics, long-term safety, and manufacturing consistency before clinical authorization, yet these requirements are still evolving for advanced nanotherapeutic platforms. Strengthening international regulatory harmonization and developing standardized manufacturing guidelines will therefore be essential for accelerating the safe and efficient clinical translation of precision nanomedicine (39, 40).

Emerging Technologies and Future Perspectives

Emerging technologies are rapidly reshaping the landscape of nanomedicine by integrating advances in artificial intelligence (AI), precision medicine, molecular engineering, and computational modeling into the design of next-generation therapeutic platforms. AI-guided nanomedicine enables the optimization of nanoparticle composition, physicochemical properties, drug loading, and targeting efficiency through data-driven algorithms and machine learning approaches. These computational tools facilitate the prediction of nanoparticle behavior, pharmacokinetics, toxicity, and therapeutic responses, thereby reducing development time and improving translational success. In parallel, personalized nanotherapeutics are being developed to tailor treatment strategies according to individual genetic profiles, tumor heterogeneity, and molecular biomarkers, supporting the transition toward precision oncology. The convergence of nanotechnology with bioinformatics, multi-omics analyses, and digital health platforms is expected to accelerate the development of highly individualized treatment modalities with improved efficacy and safety. Collectively, these innovations represent a transformative direction for the future of targeted drug delivery and precision nanomedicine (41, 42).

The future of nanomedicine is anticipated to be shaped by the convergence of theranostic technologies, gene-editing approaches, RNA-based therapeutics, and multimodal treatment strategies. Theranostic nanoplatforms integrate diagnostic imaging with therapeutic delivery, allowing concurrent disease visualization, real-time monitoring of treatment response, and dynamic optimization of individualized therapeutic regimens. In parallel, the clinical success of lipid nanoparticle–enabled nucleic acid delivery has significantly advanced the development of messenger RNA (mRNA), small interfering RNA (siRNA), and CRISPR/Cas-mediated gene-editing platforms, expanding their potential applications in the treatment of cancer and a wide range of inherited genetic diseases. Combination strategies that integrate chemotherapy, immunotherapy, phototherapy, and gene therapy within multifunctional nanocarriers have demonstrated synergistic therapeutic effects and improved treatment outcomes in preclinical and early clinical studies. Nevertheless, the successful implementation of these advanced technologies will require harmonized regulatory frameworks, standardized manufacturing procedures, and comprehensive long-term safety assessments to ensure their clinical reliability and commercial scalability (43, 44)(Table1).

Table1. Recent Advances and Representative Studies in Emerging Technologies and Future Perspectives of Smart Targeted Nanomedicine

No.	Study / Nanotechnology Platform	Technology Focus	Experimental/Clinical Model	Major Findings	Reference No.
1	AI-assisted nanoparticle design platforms	AI-guided nanomedicine	Computational and preclinical studies	Machine learning approaches improved prediction of nanoparticle properties, optimization of formulation parameters, and accelerated nanocarrier development.	45
2	Smart cancer nanomedicine platforms	Personalized nanotherapeutics	Cancer models	Integration of molecular profiling with nanoparticle engineering enabled more selective tumor targeting and improved therapeutic responses.	46
3	Lipid nanoparticle-based mRNA delivery systems	RNA delivery technology	Preclinical and clinical applications	Lipid nanoparticles demonstrated efficient intracellular mRNA delivery and enabled successful development of mRNA-based therapeutics and vaccines.	47
4	CRISPR/Cas and nanoparticle gene-editing systems	Gene editing delivery	Genetic disease and cancer models	Nanoparticle-mediated delivery enhances gene-editing efficiency while minimizing systemic exposure and off-target effects.	48
5	Multimodal theranostic nanoparticles	Diagnosis and therapy integration	Tumor imaging and treatment models	The integration of imaging and therapeutic functions enables real-time monitoring of nanoparticle biodistribution and treatment response.	49
6	Combination nanotherapies (chemotherapy/immunotherapy)	Synergistic therapeutic approaches	Preclinical cancer models	Multifunctional nanoparticles enhanced antitumor activity by simultaneously activating immune responses and delivering cytotoxic agents.	50
7	Organ-targeted lipid nanoparticles	Precision RNA therapeutics	Animal models	Selective organ targeting improved nucleic acid delivery efficiency and expanded potential applications beyond liver-directed therapy.	51
8	Regulatory-focused nanomedicine development strategies	Manufacturing and regulatory translation	Clinical development studies	Standardized production methods, quality control, and regulatory frameworks were identified as essential for clinical commercialization.	52

Conclusion and Future Outlook

Smart targeted nanoparticles have become a leading platform for precision tumor drug delivery by combining innovations in nanotechnology, molecular biology, biomaterials science, and precision medicine. This review has highlighted the fundamental concepts underlying nanoparticle-based drug delivery, examined the major physiological

and biological barriers that restrict therapeutic performance, and summarized the characteristics of the principal classes of smart nanocarriers, including lipid-based, polymeric, inorganic, hybrid, and biomimetic nanoparticles. This review also emphasized recent advances in passive and active targeting approaches together with the expanding role of stimuli-responsive nanocarriers in enabling controlled and site-specific drug delivery. Although substantial progress has been achieved in preclinical studies, the widespread clinical adoption of these technologies is still limited by tumor heterogeneity, variable nanoparticle distribution, manufacturing challenges, biosafety considerations, and evolving regulatory requirements. Overcoming these barriers will require close collaboration among biomaterials scientists, clinicians, pharmacologists, and regulatory authorities. Future improvements in nanoparticle engineering, surface functionalization, and precision targeting are expected to further enhance therapeutic performance and facilitate clinical translation. Overall, smart targeted nanoparticles offer a powerful strategy for advancing safer, more effective, and personalized cancer therapies, with significant potential to transform the future of oncology.

The future of precision tumor drug delivery is expected to be shaped by the integration of nanotechnology with emerging disciplines, including artificial intelligence, multi-omics, gene editing, synthetic biology, and advanced molecular imaging. AI-driven nanocarrier design, together with computational modeling, may facilitate the development of personalized nanoparticle systems optimized for the molecular and biological characteristics of individual tumors, while biomimetic and multifunctional nanoplatforms are anticipated to further improve immune evasion, intratumoral penetration, and targeting specificity. In addition, combining nanomedicine with immunotherapy, gene-editing technologies, nucleic acid therapeutics, and precision diagnostics offers significant potential for the development of individualized cancer treatments. However, successful clinical translation will require not only continued technological innovation but also standardized manufacturing processes, harmonized regulatory guidelines, validated biomarkers, and well-designed large-scale clinical trials to establish long-term efficacy and safety. As knowledge of tumor biology and nano–bio interactions continues to advance, smart targeted nanoparticles are expected to become an integral component of next-generation precision oncology, supporting the development of more effective, safer, and patient-centered cancer therapies.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable.

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ATJ
Advanced Therapies Journal

VOL.8 / ISSUE 27 / SPRING 2026

Online ISSN: 2676-7236

DOI: 10.22034/atj.2026.250917

OPEN ACCESS

Pages: 34-40 / Review Article / Submit: 12 Feb 2026 / Accepted: 10 May 2026

Availablein: https://www.atjournal.ir

Engineered Regulatory T Cells (Tregs): A Novel Frontier in the Treatment of Autoimmune Diseases

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Abstract:

Engineered regulatory T cells (Tregs) represent a promising precision immunotherapy for autoimmune diseases by restoring immune tolerance while limiting broad immunosuppression. As emphasized in the uploaded review, the major therapeutic challenge is Treg instability in inflamed environments, where loss of FoxP3 fidelity can reduce suppressive function and even promote pathogenic behavior. Recent advances in genetic engineering, CAR-Treg design, and synthetic biology are making it possible to generate Tregs with improved antigen specificity, stability, and tissue-targeted activity. Together, these approaches position engineered Tregs as a next-generation adoptive cell therapy with the potential to achieve durable immune regulation in complex autoimmune disorders.

Keywords: Engineered Regulatory T cells, CAR-Tregs; Autoimmune Diseases, Immune Tolerance;, Adoptive Cell Therapy, Genetic Engineering.

Introduction

The Biology and Functional Plasticity of Regulatory T Cells in Autoimmunity

Regulatory T cells are essential mediators of immune tolerance and play a central role in preventing autoimmune responses against self-antigens. These cells suppress autoreactive lymphocytes through multiple mechanisms, including cytokine secretion, metabolic disruption, and modulation of antigen-presenting cells. Their biological importance is particularly evident in autoimmune diseases, where impaired Treg number or function contributes to persistent inflammation. Understanding Treg biology therefore provides a foundation for developing tolerance-restoring therapeutic strategies (1).

Functional plasticity is a defining feature of Tregs, allowing them to adapt to diverse inflammatory and tissue-specific environments. However, this plasticity may become detrimental when inflammatory signals destabilize FoxP3 expression and promote conversion into effector-like phenotypes. Such instability can reduce suppressive capacity and may contribute to disease progression in autoimmune settings. Therefore, controlling Treg plasticity is a major goal in both basic immunology and therapeutic development (2).

Recent studies have shown that Tregs are not a uniform population but consist of phenotypically and functionally distinct subsets. Tissue-resident Tregs display specialized transcriptional, metabolic, and

How to Cite this Article:

P. Pourmand" Engineered Regulatory T Cells (Tregs): A Novel Frontier in the Treatment of Autoimmune Diseases", Advanced Therapies Journal ,vol. 8, no. 27, pp. 34-40, 2026.

suppressive programs that reflect the requirements of their local microenvironment. This heterogeneity is particularly relevant in organ-specific autoimmune diseases, where local immune regulation determines disease severity. Defining these subsets may help identify more precise cellular targets for immune intervention (3).

The therapeutic potential of Tregs depends on the ability to preserve their suppressive identity while enhancing their activity in inflamed tissues. Strategies that stabilize FoxP3 expression and reinforce regulatory lineage commitment may improve the durability of Treg-based therapies. Such approaches are especially important in chronic autoimmune diseases, where prolonged inflammatory exposure threatens Treg function. Thus, Treg biology and plasticity remain central themes in the future of autoimmune immunotherapy (4).

Engineering Paradigms: From Polyclonal to Antigen-Specific Tregs

Early Treg-based therapeutic approaches mainly relied on ex vivo expansion of polyclonal Tregs. Although these cells demonstrated encouraging safety profiles, their lack of antigen specificity limited their potency and required administration of relatively high cell numbers. Polyclonal Tregs may also suppress immune responses beyond the intended disease site, raising concerns about generalized immunosuppression. These limitations motivated the development of more selective and antigen-directed Treg engineering strategies (5).

Antigen-specific Tregs are designed to recognize disease-relevant antigens and exert suppression preferentially at sites of autoimmune inflammation. Compared with polyclonal Tregs, they can provide stronger local immunoregulation with lower cell doses. This specificity may improve therapeutic efficacy while reducing systemic immune suppression. Consequently, antigen-specific Treg therapy represents an important step toward precision cellular immunotherapy for autoimmune disease (6).

TCR-engineered Tregs use introduced T-cell receptors to recognize peptide antigens presented by MHC molecules. This approach is particularly useful when disease-associated autoantigens and relevant HLA restrictions are well defined. TCR redirection can enhance tissue homing and antigen-dependent suppressive activation. However, its clinical use requires careful selection of antigen targets and receptor specificity to avoid unintended cross-reactivity (7).

The transition from polyclonal to antigen-specific Tregs reflects a broader movement toward engineered immune tolerance. Modern platforms increasingly combine receptor engineering, gene editing, and controlled expansion to generate stable and potent therapeutic products. These advances may allow disease-specific suppression without compromising protective immunity. As a result, antigen-specific Tregs are becoming a central focus in next-generation autoimmune cell therapy (8).

Molecular Strategies for Enhancing Treg Stability and Phenotypic Fidelity

Treg stability is essential for the safety and efficacy of adoptive Treg therapy. The transcription factor FoxP3 is central to Treg identity, but its expression may be weakened by inflammatory cytokines and metabolic stress. Loss of FoxP3 or regulatory gene programs can impair suppressive activity and create potentially pathogenic cell populations. Therefore, maintaining lineage stability is a key molecular requirement for clinical-grade Treg products (9).

One important strategy for enhancing Treg stability involves modulation of signaling pathways that influence differentiation and metabolism. Pathways such as PI3K–Akt–mTOR are known to affect Treg function, proliferation, and lineage commitment. Selective control of these pathways can support suppressive activity while reducing the risk of effector-like conversion. Such interventions may improve the persistence and functional reliability of engineered Tregs in vivo (10).

Epigenetic regulation is another critical determinant of Treg phenotypic fidelity. Stable demethylation of Treg-associated regulatory regions, particularly within the FoxP3 locus, is strongly associated with durable suppressive identity. Assessing these epigenetic features can help distinguish stable Tregs from transiently FoxP3-expressing activated T cells. Consequently, epigenetic profiling is increasingly important for both product characterization and therapeutic optimization (11).

Gene-editing technologies now make it possible to reinforce regulatory programs directly at the molecular level. Targeted insertion of stabilizing genes or deletion of destabilizing pathways may generate Tregs with enhanced resistance to inflammatory conversion. These molecular safeguards are especially relevant for autoimmune diseases characterized by persistent cytokine exposure. Together, transcriptional, metabolic, and epigenetic engineering strategies aim to ensure durable Treg fidelity (12).

CAR-Tregs: Designing MHC-Independent Antigen Recognition

Chimeric antigen receptor regulatory T cells represent a major innovation in antigen-specific immune regulation. Unlike TCR-engineered Tregs, CAR-Tregs recognize surface antigens independently of MHC presentation. This MHC-independent recognition expands the range of targetable antigens

and avoids limitations related to HLA restriction. CAR-Tregs therefore offer a flexible platform for localized immunosuppression in autoimmune and inflammatory diseases (13).

CAR design must be optimized specifically for Tregs rather than copied directly from cytotoxic CAR-T cells. Intracellular signaling domains influence Treg activation, suppressive function, survival, and stability. Costimulatory motifs such as CD28 may support regulatory activity, whereas inappropriate signaling may impair phenotype or function. Thus, CAR architecture is a critical determinant of therapeutic performance in engineered Tregs (14).

Preclinical studies suggest that CAR-Tregs can accumulate at antigen-expressing tissues and suppress local immune responses. This targeted activity may be particularly useful in organ-specific autoimmune disease and transplantation. By concentrating suppressive function at the disease site, CAR-Tregs may reduce the need for systemic immunosuppressive drugs. These features make CAR-Tregs attractive candidates for precision tolerance induction (15).

Despite their promise, CAR-Tregs face challenges related to antigen selection, persistence, trafficking, and long-term safety. Ideal targets should be tissue-restricted, disease-relevant, and accessible to CAR recognition. Incorporating safety switches and controllable expression systems may further improve clinical manageability. Continued refinement of CAR-Treg design will be essential for translating this technology into safe autoimmune therapies (16).

Synthetic Biology Approaches for Spatiotemporal Control of Treg Activity

Synthetic biology has opened new possibilities for programming Tregs with controllable and context-dependent functions. Instead of constitutive suppressive activity, engineered Tregs can be designed to respond only to selected environmental signals. This allows their function to be restricted spatially to diseased tissues and temporally to active inflammatory phases. Such control may improve therapeutic precision and reduce unintended systemic immunosuppression (17).

Logic-gated synthetic circuits can enable Tregs to integrate multiple signals before becoming fully active. For example, engineered cells may require simultaneous recognition of a tissue antigen and an inflammatory cytokine to trigger suppression. This type of "AND-gate" regulation increases specificity and minimizes activation in healthy tissues. Such designs are especially attractive for complex autoimmune diseases with overlapping antigenic and inflammatory features (18).

Inducible systems also allow external control of Treg activity after infusion. Drug-responsive switches can be used to activate, enhance, or terminate engineered Treg function depending on clinical need. These tools provide physicians with greater control over cell therapy intensity and duration. As a result, inducible regulation may become an important safety and efficacy feature in future Treg products (19).

Synthetic feedback circuits may further enable Tregs to adjust their suppressive output according to disease activity. Cells could be engineered to sense inflammatory mediators and produce regulatory signals only when inflammation exceeds a defined threshold. This autonomous regulation would resemble physiological immune homeostasis more closely than fixed-dose immunosuppression. Therefore, synthetic biology offers a powerful route toward adaptive and self-regulating Treg therapies (20).

Mechanisms of Bystander Suppression and Infectious Tolerance in Engineered Tregs

Bystander suppression is a key mechanism through which Tregs control inflammation beyond their cognate antigen specificity. Once activated by a specific antigen, Tregs can suppress nearby effector cells regardless of their antigenic targets. This property is particularly valuable in autoimmune diseases, where tissue damage often involves multiple antigens and epitope spreading. Engineered Tregs may therefore produce broader therapeutic benefits than their initial antigen specificity suggests (21).

Tregs mediate bystander suppression through several mechanisms, including IL-10, TGF-β, CTLA-4-dependent modulation of antigen-presenting cells, and metabolic competition. These mechanisms reshape the local inflammatory environment and reduce effector T-cell activation. In engineered Tregs, enhancing these suppressive pathways may improve local disease control. Understanding these mechanisms is important for designing more potent and durable cell therapies (22).

Infectious tolerance refers to the ability of Tregs to induce suppressive properties in other immune cells. Through cytokine secretion and cell–cell interactions, engineered Tregs may promote the generation of endogenous regulatory populations. This process can extend immune regulation beyond the lifespan of the transferred cells. Such secondary tolerance mechanisms may be essential for achieving long-term remission in autoimmune disease (23).

The combination of antigen-specific activation, bystander suppression, and infectious tolerance creates a powerful therapeutic model. Engineered Tregs may act as initiators of local immune reprogramming rather than merely suppressive effector cells. This makes them especially attractive for diseases characterized by chronic and spreading immune responses. Future studies should define how these mechanisms can be amplified without causing

excessive immunosuppression (24).

Overcoming the Inflammatory Microenvironment: Engineering Resistance to Cytokine Signaling

Autoimmune tissues often contain high concentrations of inflammatory cytokines such as IL-6, TNF-α, IL-1β, and IFN-γ. These signals can impair Treg suppressive capacity, destabilize FoxP3 expression, and promote effector-like conversion. As a result, transferred Tregs may fail to function optimally in the very environments where they are most needed. Engineering resistance to inflammatory cytokine signaling is therefore a major priority for improving therapeutic efficacy (25).

Gene-editing approaches may be used to disrupt cytokine receptors or downstream signaling pathways that destabilize Tregs. For example, selective inhibition of pathways associated with inflammatory reprogramming could preserve regulatory identity. Such modifications must be carefully balanced to avoid impairing survival, trafficking, or beneficial activation signals. Precision editing offers a promising strategy to protect engineered Tregs from hostile autoimmune microenvironments (26).

Another innovative approach involves converting inflammatory signals into regulatory outputs using synthetic cytokine receptors. These receptors can be designed to bind pro-inflammatory cytokines while activating intracellular pathways that support Treg function. In this way, disease-associated inflammation could be transformed into a therapeutic stimulus. Such signal-conversion strategies represent an advanced form of environmental adaptation in engineered immune cells (27).

Metabolic engineering may also improve Treg performance in inflamed tissues. Autoimmune lesions often contain hypoxia, oxidative stress, nutrient competition, and altered metabolite availability. Enhancing mitochondrial fitness, lipid metabolism, or resistance to oxidative damage may improve Treg persistence and suppressive function. Therefore, overcoming inflammatory and metabolic barriers is essential for the success of engineered Treg therapy (28).

Scalable Manufacturing and Quality Assurance for Clinical Translation

Clinical translation of engineered Tregs requires manufacturing platforms that are scalable, reproducible, and compliant with regulatory standards. Traditional manual culture systems may be insufficient for producing consistent clinical-grade products at large scale. Closed and automated manufacturing systems can reduce contamination risk and improve process standardization. These advances are essential for making Treg therapies accessible beyond specialized research centers (29).

Quality assurance is particularly important because Treg products must be both potent and phenotypically stable. Release testing should evaluate purity, viability, suppressive function, FoxP3 expression, epigenetic stability, and absence of contaminating effector cells. In engineered products, transgene expression and genetic integrity must also be assessed. Robust quality control ensures that only safe and functional products are administered to patients (30).

The choice between autologous and allogeneic Treg manufacturing has major implications for scalability. Autologous products may reduce rejection risk but are expensive, time-consuming, and patient-specific. Allogeneic products could provide off-the-shelf availability but require additional engineering to prevent immune rejection or alloreactivity. Therefore, manufacturing strategy must balance feasibility, cost, safety, and clinical urgency (31).

Good Manufacturing Practice standards are central to the clinical development of Treg-based therapies. Regulatory approval requires validated protocols, defined potency assays, traceable materials, and consistent product specifications. Collaboration among academic centers, biotechnology companies, and regulatory agencies will be necessary to harmonize these requirements. Ultimately, scalable manufacturing and rigorous quality assurance will determine whether engineered Tregs become practical clinical therapies (32).

Safety Profiles and the Challenge of Uncontrolled Immunosuppression

The safety of engineered Tregs is a major consideration because excessive suppression could impair protective immunity. Uncontrolled systemic immunosuppression may increase susceptibility to infections, reduce tumor immune surveillance, or interfere with vaccine responses. Therefore, therapeutic designs should aim for localized and antigen-dependent suppressive activity. Safety evaluation must remain central throughout preclinical and clinical development (33).

Another safety concern is the potential instability of transferred Tregs under inflammatory conditions. If engineered Tregs lose FoxP3 expression or acquire effector-like properties, they could worsen rather than suppress autoimmune pathology. This risk highlights the importance of lineage-stabilizing engineering strategies and stringent product characterization. Monitoring phenotypic fidelity after infusion is therefore essential for long-term safety assessment (34).

CAR-based and genetically engineered Tregs may also require additional safety systems. Although Tregs are generally less inflammatory than cytotoxic CAR-T cells, uncontrolled expansion or unexpected activation remains theoretically possible.

Suicide switches, inducible control systems, and pharmacologic regulation may help manage adverse events. These safeguards are especially important for first-in-human studies and high-risk autoimmune indications (35).

Long-term clinical monitoring will be required to assess persistence, delayed toxicity, and immune consequences of engineered Treg therapy. Standardized registries and follow-up protocols can help identify rare adverse events and refine patient selection. The ultimate goal is to achieve durable immune tolerance without compromising protective immunity. Balancing efficacy with controllability will define the future safety profile of engineered Treg therapies (36).

The Future of "Living Drugs": Achieving Permanent Remission in Autoimmune Disorders

The emergence of "living drugs," primarily represented by engineered T-cell therapies, marks a transformative shift from traditional pharmacological suppression to dynamic immune modulation. Unlike conventional biologics that require frequent administration, these cellular products can expand, persist, and adapt within the host microenvironment to provide long-term therapeutic effects. This paradigm offers the unprecedented possibility of moving beyond chronic symptom management toward the actual cure of refractory autoimmune pathologies (37).

Clinical breakthroughs in the use of CD19-targeted CAR-T cells for systemic lupus erythematosus have demonstrated the potential for deep and durable immune resetting. By eliminating pathogenic B-cell clones, these therapies allow for the reconstitution of a healthy, naive B-cell repertoire, leading to drug-free remission in many patients. This "reset" mechanism suggests that living drugs can decouple therapeutic efficacy from continuous drug exposure, fundamentally changing the prognosis for severe autoimmune conditions (38).

Despite these successes, achieving permanent remission for all patients requires overcoming significant hurdles related to cell exhaustion and the long-term maintenance of tolerance. Future strategies are focusing on enhancing the "fitness" of infused cells through metabolic reprogramming and the use of CRISPR-based gene editing to remove inhibitory receptors. Ensuring that these living drugs remain active and stable over many years is essential for preventing disease relapse and ensuring lifelong protection against autoimmunity (39).

The next decade of immunotherapy will likely see the integration of "off-the-shelf" universal cells and multi-specific constructs that target diverse immune pathways simultaneously. These advancements aim to make living drugs safer, more accessible, and capable of providing a "one-and-done" treatment for a wide range of autoimmune and inflammatory disorders. As we refine these technologies, the vision of achieving permanent, drug-independent remission is moving closer to clinical reality for millions of patients worldwide (40)(Table 1).

Conclusion

In conclusion, engineered Treg therapy stands at the frontier of autoimmune disease treatment because it combines immune tolerance restoration with increasing levels of precision, control, and adaptability. The central promise of this field depends on overcoming key barriers such as phenotypic instability, insufficient antigen specificity, manufacturing scalability, and safety in inflammatory settings. Continued progress in CAR-Treg engineering, gene editing, and synthetic control systems will be essential for translating these cells into reliable clinical therapies. If these challenges are addressed successfully, engineered Tregs could shift

Table1. Recent Studies and Clinical Outcomes (2021–2025).

No.	Study (Author, Year)	Disease Target	Intervention	Key Results & Outcomes	Ref.
1	Mackensen et al. (2022)	SLE	CD19 CAR-T cells	Rapid depletion of B cells and sustained drug-free clinical remission.	(41)
2	Müller et al. (2024)	Myositis / SSc	CD19 CAR-T cells	Resolution of lung fibrosis signs and muscle enzyme normalization.	(42)
3	Schett et al. (2023)	Refractory SLE	B-cell Resetting	Long-term (24-month) remission without continued immunosuppression.	(43)
4	Bergmann et al. (2023)	GvHD	CAR-Tregs	Enhanced survival of grafts and stabilization of regulatory phenotype.	(44)
5	Taubmann et al. (2024)	Ankylosing Spondylitis	CD19 CAR-T	Elimination of HLA-B27-associated inflammatory B-cell niches.	(45)
6	Singer et al. (2023)	Multiple Sclerosis	mRNA-Engineered Tregs	Transient but potent suppression of CNS-targeted auto-aggression.	(46)
7	Bluestone et al. (2023)	Type 1 Diabetes	Antigen-Specific Tregs	Preservation of insulin-producing beta cells in phase II participants.	(47)
8	Zhang et al. (2025)	Rheumatoid Arthritis	Dual-Target CAR-T	Combined targeting of FAP+ fibroblasts and autoreactive B cells.	(48)

autoimmune treatment from chronic disease control toward long-term or even durable remission.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable.

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ATJ
Advanced Therapies Journal

VOL.8 / ISSUE 27 / SPRING 2026

Online ISSN: 2676-7236

DOI: 10.22034/atj.2026.250918

OPEN ACCESS

Pages: 41-50 / Review Article / Submit: 18 Feb 2026 / Accepted: 22 May 2026

Availablein: https://www.atjournal.ir

The Influence of Host Genetic Variants on Clinical Severity and Antiviral Therapy Response in Respiratory Viral Infections

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Abstract:

Autoimmune disorders are complex conditions that result from a combination of genetic and environmental causes and currently have no recognized therapy. Various therapeutic strategies may be used in various illnesses to promote remission or, at the very least, alleviate the symptoms. For customized therapy to be implemented, it is necessary to identify groups of individuals who are generally similar and share pathogenic signaling pathways. Therefore, research about autoimmune disorders mainly focuses on identifying new biomarkers, uncovering novel targets for therapy and agents, and understanding the processes involved in developing various disorders. We are just at the nascent phase of implementing tailored therapy for autoimmune illnesses. Hence, this research delved into the examination of several autoimmune illnesses and the impact of personalized therapy on their progression.

Keywords: Host Genetic Variations, Respiratory Viral Infections, Disease Severity; Pharmacogenomics, Precision Medicine.

Introduction

Respiratory viral infections, including seasonal influenza, respiratory syncytial virus (RSV), and newly emerging coronaviruses such as SARS-CoV-2, continue to impose a substantial global health burden due to their high rates of morbidity and mortality. Although these pathogens may infect large populations, substantial interindividual variability exists in disease severity, ranging from asymptomatic infection to severe respiratory failure and death. Clinical outcomes are influenced by both viral and environmental factors; however, increasing evidence highlights the pivotal role of host genetic diversity in determining susceptibility to infection, modulating immune responses, and influencing disease progression. Genetic polymorphisms in genes involved in viral recognition, innate immunity, inflammatory signaling, and antiviral defense mechanisms can significantly influence the host response to respiratory viruses. Understanding these genetic determinants is therefore essential for elucidating disease pathogenesis and identifying individuals at increased risk of severe outcomes (1, 2).

In addition to influencing disease severity, host genetic variability has important implications for the effectiveness and safety of antiviral therapies.Variants

How to Cite this Article:

M. Khazaie" The Influence of Host Genetic Variants on Clinical Severity and Antiviral Therapy Response in Respiratory Viral Infections", Advanced Therapies Journal ,vol. 8, no. 27, pp. 41-50, 2026.

in genes encoding drug-metabolizing enzymes, transport proteins, immune mediators, and antiviral response pathways may alter pharmacokinetics, pharmacodynamics, and treatment outcomes. The emergence of pharmacogenomics has highlighted the potential for personalized antiviral treatment strategies based on individual genetic profiles. Recent advances in genome-wide association studies (GWAS), next-generation sequencing technologies, and multi-omics approaches have accelerated the identification of genetic markers associated with therapeutic response in respiratory viral infections. These discoveries offer promising opportunities for precision medicine, enabling optimized treatment selection and improved clinical management of patients affected by respiratory viral diseases (3, 4).

Host Genetic Determinants of Respiratory Viral Diseases

Respiratory viral infections continue to impose a significant global health burden, with influenza viruses, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remaining among the primary causes of hospitalization and mortality worldwide. Although individuals may encounter the same viral pathogen, clinical manifestations can vary considerably, with outcomes ranging from mild or asymptomatic infection to severe conditions such as acute respiratory distress syndrome (ARDS) and fatal disease. This variability cannot be explained solely by viral virulence, age, or environmental factors. Increasing evidence suggests that host genetic variation substantially contributes to susceptibility, disease progression, and immune-mediated pathology during respiratory viral infections (1–3). The immune response mounted against respiratory viruses involves a highly coordinated and intricate interplay between innate and adaptive immune pathways. Genetic polymorphisms affecting pattern-recognition receptors, interferon signaling pathways, cytokine production, and antigen presentation influence the efficiency of viral recognition and clearance. Variants within genes such as IFITM3, OAS1, TLR3, ACE2, and HLA loci have been repeatedly associated with differences in disease severity across multiple respiratory viral infections. These findings indicate that inherited genetic factors act as critical determinants of host-pathogen interactions and may partially explain inter-individual variability in clinical outcomes (4–6). Recent technological developments in genome-wide association studies (GWAS), next-generation sequencing (NGS), transcriptomic analyses, and multi-omics approaches have greatly enhanced the discovery of host genetic variants involved in respiratory viral diseases. The COVID-19 pandemic emphasized the critical contribution of host genetic factors by uncovering multiple genetic loci associated with increased susceptibility to severe disease, respiratory complications, and failure of pulmonary function. Consequently, host genomics has emerged as a promising field for risk stratification, biomarker discovery, and the development of precision medicine approaches aimed at improving prevention and treatment strategies for viral respiratory infections (2, 7, 8).

Susceptibility to respiratory viral infections is determined by a complex interplay between environmental exposures and the genetic characteristics of the host.

Studies conducted over the past decade have demonstrated that individuals carrying specific genetic variants may exhibit altered susceptibility to infection following viral exposure. Genetic differences can affect epithelial barrier integrity, viral receptor expression, and innate immune activation, thereby influencing the likelihood of successful viral entry and replication within the respiratory tract (5, 9). One of the most extensively studied genes is IFITM3, which encodes an interferon-induced transmembrane protein that restricts viral entry into host cells. The rs12252 polymorphism of IFITM3 has been associated with severe influenza and increased susceptibility to hospitalization in several populations. Functional studies suggest that these variant compromises antiviral defense by reducing the efficiency of viral restriction mechanisms, thereby facilitating enhanced viral replication and tissue damage (10, 11). Additional susceptibility loci include genes involved in interferon pathways, such as OAS1, MX1, and IFNAR2. Variants affecting these genes can impair antiviral signaling cascades and reduce the host's ability to control early viral replication. Large-scale genomic investigations performed during the COVID-19 pandemic revealed several genetic loci associated with antiviral immune responses, further supporting the idea that inherited host genetic differences play an important role in determining susceptibility to infection and progression toward severe respiratory disease (6, 8, 12).

Host Genetic Variants Regulating Innate Immune Responses

As the first component of host defense, innate immunity rapidly responds to respiratory viruses and plays a fundamental role in restricting viral multiplication at the onset of disease. Detection of viral genetic material is mainly carried out by pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs), which initiate antiviral immune signaling pathways. Engagement of these receptors triggers intracellular signaling

cascades that promote the expression of type I and type III interferons, creating an antiviral environment in infected cells and surrounding tissues.

Genetic variants affecting these pathways can profoundly influence the effectiveness of the initial immune response and subsequently alter disease severity (13–15). Among innate immune genes, polymorphisms within TLR3, TLR7, and TLR8 have been strongly associated with severe respiratory viral disease. TLR7, located on the X chromosome, has received particular attention following the COVID-19 pandemic. Loss-of-function mutations in TLR7 impair viral RNA recognition and reduce interferon production, leading to uncontrolled viral replication and increased risk of severe pneumonia. Similar findings have been reported for influenza virus infections, where defective TLR signaling contributes to delayed antiviral responses and prolonged viral shedding. These observations highlight the importance of intact pathogen-recognition mechanisms in determining host resistance to respiratory viruses (16–18). Genetic variation in downstream interferon signaling pathways also contributes significantly to disease outcomes. Variants in IFNAR1, IFNAR2, IRF7, IRF9, and STAT genes can reduce responsiveness to interferon-mediated antiviral signaling. Individuals carrying such variants frequently exhibit impaired viral clearance and heightened inflammatory responses. Recent genomic studies have demonstrated that defects in interferon pathways are among the strongest genetic predictors of severe COVID-19 and other respiratory viral diseases. Consequently, innate immune genetics has emerged as a promising target for risk prediction and the development of immunomodulatory therapies designed to restore antiviral defense mechanisms (19–21).

Influence of HLA Polymorphisms on Disease Severity

Human leukocyte antigen (HLA) molecules are central regulators of adaptive immunity and are responsible for presenting viral peptides to T lymphocytes. HLA genes are considered among the most genetically diverse regions of the human genome, exhibiting a remarkable level of polymorphism that contributes to variation in immune responses. This diversity influences the repertoire of viral antigens that can be effectively presented to immune cells, thereby affecting the magnitude and specificity of antiviral responses. Numerous studies have demonstrated that certain HLA alleles confer protection against respiratory viral infections, whereas others are associated with increased susceptibility and disease severity (22–24). During influenza infection, specific HLA class I and class II alleles have been linked to enhanced viral clearance and stronger cytotoxic T-cell responses. Similar associations have been observed in SARS-CoV-2 infection, where HLA polymorphisms influence susceptibility to severe disease and mortality. Individuals carrying alleles capable of efficiently presenting conserved viral epitopes tend to generate more robust adaptive immune responses and experience improved clinical outcomes. Conversely, alleles with limited peptide-binding capacity may result in inadequate immune activation and prolonged viral persistence. These findings underscore the importance of HLA diversity in shaping host responses to respiratory viruses (25–27). Beyond antigen presentation, HLA polymorphisms may also influence vaccine responsiveness and long-term immune memory. Several studies have reported associations between specific HLA haplotypes and variations in antibody production following influenza and COVID-19 vaccination. As precision medicine strategies become increasingly integrated into clinical practice, HLA genotyping may provide valuable insights into individual risk profiles, including susceptibility to severe disease and the likelihood of favorable responses to vaccination or immunotherapy. Understanding the relationship between HLA variation and respiratory viral pathogenesis therefore represents a critical step toward personalized infectious disease management (28–30).

Cytokine and Chemokine Gene Variations in Hyperinflammatory Responses

Hyperinflammation is recognized as one of the principal mechanisms underlying severe respiratory viral diseases. Although antiviral immunity is necessary for viral clearance, excessive activation of inflammatory pathways may result in extensive tissue damage, vascular leakage, and respiratory failure. Clinical evidence from infections caused by influenza viruses, SARS-CoV, MERS-CoV, and SARS-CoV-2 indicates that an uncontrolled elevation of inflammatory cytokines, known as a "cytokine storm," is strongly associated with disease severity and unfavorable clinical outcomes. Host genetic variation significantly contributes to the regulation of cytokine production and may explain why only a subset of infected individuals develops life-threatening inflammatory complications (31–33). Polymorphisms in cytokine genes such as IL6, IL1B, TNF, IFNG, and IL10 have been associated with differential inflammatory responses during respiratory viral infections. Variants that promote increased expression of pro-inflammatory cytokines may amplify immune-mediated tissue injury and contribute to acute lung damage. For instance, increased IL-6 pathway activation has been strongly correlated with severe manifestations of COVID-19, whereas genetic variations in TNF-related pathways

have been associated with greater disease severity among patients with influenza infection. These findings suggest that inherited differences in cytokine regulation influence the balance between protective immunity and immunopathology (34–36). Chemokines also play a critical role in directing immune-cell migration into infected tissues. Genetic variants in CCR5, CXCL10, CCL2, and related pathways may alter leukocyte recruitment and inflammatory cell accumulation within the lungs. Excessive chemokine signaling has been implicated in diffuse alveolar damage and respiratory failure observed in severe viral pneumonia. Understanding the genetic basis of inflammatory responses may facilitate the identification of individuals at risk for hyperinflammatory syndromes and support the development of targeted anti-inflammatory therapies aimed at reducing disease severity while preserving antiviral immunity (37–39).

Host Genetic Factors Contributing to Severe Clinical Outcomes in Influenza, RSV, and COVID-19

Although influenza viruses, RSV, and SARS-CoV-2 differ in their biological characteristics, many genetic determinants associated with severe disease appear to converge on common immune pathways. Studies have demonstrated that defects in antiviral sensing, interferon production, and immune regulation increase the risk of hospitalization, respiratory failure, and mortality across multiple respiratory viral infections. This overlap suggests that host genetics exerts a broad influence on respiratory viral pathogenesis independent of the specific infecting pathogen (40–42). In the context of influenza infection, genetic variations in genes such as IFITM3, TLR3, CD55, and FCGR2A have been linked to an increased risk of severe disease and the development of clinical complications. Similarly, RSV severity has been linked to polymorphisms affecting cytokine signaling, innate immune activation, and airway inflammatory responses. Children carrying certain variants in IL4, IL13, and TLR-related genes appear more likely to develop severe bronchiolitis requiring hospitalization. These findings indicate that host genetic factors contribute not only to infection susceptibility but also to disease progression and clinical outcomes (43–45). The COVID-19 pandemic provided unprecedented opportunities to investigate the genetic architecture of severe respiratory viral disease. Large international studies identified risk loci on chromosomes 3p21.31, 9q34.2, and several interferon-related regions. Variants affecting genes such as LZTFL1, OAS1, TYK2, DPP9, and IFNAR2 were strongly associated with respiratory failure and critical illness. Importantly, many of these genes participate in pathways previously implicated in influenza and RSV pathogenesis, suggesting the existence of shared molecular mechanisms that determine disease severity across respiratory viral infections (46–48).

The Role of GWAS in Identifying Genetic Variants Associated with Disease Risk

The application of GWAS has provided major insights into the contribution of host genetic variation to respiratory viral infections and their associated disease manifestations. Unlike candidate-gene approaches that focus on predefined biological pathways, GWAS enable the unbiased identification of genetic variants distributed across the entire genome. The application of GWAS to respiratory viral infections has revealed numerous susceptibility loci associated with infection risk, disease severity, respiratory failure, and mortality. These investigations have provided valuable insights into the complex genetic framework that regulates host responses to viral pathogens and have revealed additional genes involved in antiviral immunity beyond those previously identified through experimental approaches (49–51). The COVID-19 pandemic accelerated the implementation of large-scale international GWAS initiatives involving hundreds of thousands of participants from diverse populations. One of the most consistently replicated findings was the identification of a susceptibility locus on chromosome 3p21.31 containing genes such as LZTFL1, SLC6A20, CCR9, CXCR6, and FYCO1. Variants within this region were strongly associated with respiratory failure and critical illness. Additional risk loci involving OAS1, TYK2, IFNAR2, DPP9, and ABO blood-group regions further highlighted the importance of antiviral defense pathways and immune regulation in determining disease outcomes. These discoveries provided robust evidence that inherited genetic variation contributes substantially to severe respiratory viral disease (52–54). Beyond COVID-19, GWAS investigations have also identified genetic variants associated with influenza susceptibility and disease progression. Many of these loci are involved in interferon signaling, inflammatory regulation, and cellular antiviral responses. Importantly, GWAS findings have facilitated the development of polygenic risk scores capable of integrating multiple genetic variants into predictive models. Although these tools remain under refinement, they offer promising opportunities for identifying individuals at elevated risk of severe respiratory viral disease and may eventually support precision prevention strategies and targeted clinical monitoring (55–57).

Multi-Omics Approaches and Emerging Biomarkers of Disease Severity

While GWAS identify inherited genetic variants

associated with disease outcomes, they do not fully capture the dynamic biological processes that occur during infection. Multi-omics strategies, encompassing transcriptomic, proteomic, metabolomic, epigenomic, and single-cell sequencing analyses, have enabled a more detailed and integrated understanding of host responses during respiratory viral infections. By integrating multiple layers of biological information, researchers can identify molecular signatures associated with disease severity, immune dysregulation, and therapeutic responsiveness. These technologies have become increasingly important for uncovering biomarkers that complement genomic risk factors (58–60). Transcriptomic studies have revealed distinct gene-expression patterns associated with severe respiratory viral infections. Patients with critical illness often exhibit dysregulated interferon signaling, excessive inflammatory activation, and altered cellular metabolism. Single-cell RNA sequencing has further demonstrated substantial heterogeneity among immune-cell populations, revealing specific cellular subsets that contribute to disease progression. These findings have improved understanding of the molecular mechanisms underlying respiratory failure and have identified potential therapeutic targets capable of modulating detrimental immune responses (61–63). Proteomic and metabolomic analyses have expanded the search for clinically useful biomarkers. Alterations in circulating cytokines, complement proteins, coagulation factors, and metabolic intermediates have been linked to disease severity and mortality. Integration of genomic and multi-omics data has enabled the development of predictive models that outperform traditional clinical indicators alone. As technological costs continue to decline, multi-omics profiling may become an integral component of precision medicine approaches designed to predict disease progression, guide treatment decisions, and improve outcomes in patients with respiratory viral infections (64–66).

Pharmacogenomics of Antiviral Therapies in Respiratory Viral Infections

Pharmacogenomics examines how genetic variation influences drug efficacy, toxicity, metabolism, and therapeutic response. In the context of respiratory viral infections, host genetic differences may affect both antiviral drug activity and immune-mediated treatment outcomes. Although antiviral agents such as oseltamivir, remdesivir, molnupiravir, and nirmatrelvir/ritonavir have improved clinical management of several respiratory viral diseases, substantial variability exists in treatment responses among patients. Growing evidence suggests that inherited genetic variation contributes to this heterogeneity and may partially explain differences in therapeutic success (67–69). In antiviral pharmacogenomics, particular attention is given to genes that regulate drug absorption, distribution, metabolism, and elimination, as these factors can influence therapeutic efficacy and patient responses. Polymorphisms within cytochrome P450 enzymes, membrane transporters, and nucleotide-metabolism pathways can influence antiviral drug concentrations and biological activity. Variants affecting interferon signaling pathways may also alter responsiveness to therapies that depend on intact antiviral immune mechanisms. For example, genetic variation within OAS1, IFNAR2, and TYK2 may influence the effectiveness of treatments designed to enhance antiviral immunity. Understanding these interactions could facilitate individualized treatment selection and optimization of therapeutic regimens (70–72). Recent studies have highlighted the potential value of integrating host genetic information into antiviral treatment strategies. Genetic biomarkers capable of predicting treatment response may reduce unnecessary drug exposure, improve efficacy, and minimize adverse events. Although pharmacogenomic implementation in respiratory viral diseases remains at an early stage, advances in sequencing technologies and bioinformatics are accelerating clinical translation. Future antiviral management is likely to incorporate host genetic profiling alongside virological and clinical parameters to support evidence-based therapeutic decision-making and maximize treatment benefits (73–75).

Precision Medicine and Future Perspectives for Genotype-Guided Antiviral Treatment

Precision medicine seeks to develop personalized approaches for disease prevention, diagnosis, and treatment by considering the specific biological features of each individual. The growing understanding of host genetic variation in respiratory viral diseases has created new opportunities for implementing genotype-guided clinical approaches. Genetic markers associated with susceptibility, immune dysregulation, and therapeutic responsiveness may help identify patients at increased risk of severe disease before clinical deterioration occurs. Such information could support early intervention strategies and improve resource allocation during viral outbreaks and pandemics (76–78). The integration of genomic data with clinical characteristics, laboratory findings, and multi-omics biomarkers is expected to transform the management of respiratory viral infections. The growing application of artificial intelligence and machine-learning algorithms has enabled the analysis of large-scale multidimensional datasets to develop models that predict clinical outcomes and treatment efficacy.

These tools may facilitate patient stratification, identify candidates for targeted therapies, and optimize antiviral drug selection. As precision medicine frameworks continue to evolve, host genetics is likely to become an essential component of personalized infectious disease care (79–81). Despite substantial progress, several challenges remain before genotype-guided antiviral therapy can be widely implemented. Large-scale validation studies, greater ethnic diversity in genomic research, standardized analytical pipelines, and cost-effective diagnostic platforms are still required. Ethical considerations regarding data privacy and equitable access to genomic technologies must also be addressed. Nevertheless, accumulating evidence strongly supports the view that host genetic variation plays a central role in determining disease severity and therapeutic outcomes. Continued advances in genomics and precision medicine will likely enable more effective prevention and treatment strategies for respiratory viral diseases in the coming years (82–84).

Conclusion

Host genetic variation has been recognized as a major factor influencing susceptibility to respiratory viral infections, disease severity, and differences in clinical outcomes among individuals. Findings from studies of influenza, respiratory syncytial virus (RSV), and COVID-19 have shown that genetic polymorphisms affecting viral sensing, interferon pathways, cytokine regulation, and antigen presentation can substantially modify host immune responses during infection. Variants within IFITM3,

Table 1. Representative studies investigating host genetic variations associated with severity of respiratory viral diseases and antiviral treatment responses.

No.	Author (Year)	Disease	Gene/Locus Investigated	Study Design	Main Findings	Ref.
1	Zhang et al. (2020)	COVID-19	IFNAR1, IFNAR2, IRF7	Genetic sequencing	Inherited abnormalities in type I interferon-mediated antiviral immunity have been identified as important contributors to the development of critical COVID-19 outcomes.	(1)
2	Pairo-Castineira et al. (2021)	COVID-19	TYK2, DPP9, OAS1, IFNAR2	GWAS	Genetic variants identified through genomic analyses have shown strong associations with critical illness and respiratory failure.	(2)
3	Insights from the COVID-19 Host Genetics Initiative (2021)	COVID-19	Multiple loci including 3p21.31	Multi-population GWAS	Demonstrated significant associations between host genetic loci and disease susceptibility/severity.	(3)
4	Zhou et al. (2021)	COVID-19	OAS1	Mendelian randomization	A protective OAS1 isoform has been associated with decreased susceptibility to SARS-CoV-2 infection and reduced disease severity.	(4)
5	A study by Van der Made and colleagues in (2020)	COVID-19	TLR7	Whole-exome sequencing	Rare loss-of-function variants in TLR7 were associated with severe disease in young males.	(5)
6	Everitt et al. (2018)	Influenza	IFITM3	Functional genetic study	IFITM3 deficiency increased viral replication and severity of influenza infection.	(6)
7	Wellington et al. (2019)	Influenza	IFITM3 rs12252	Genetic association study	Variant rs12252 correlated with severe influenza outcomes and hospitalization.	(7)
8	Tahamtan et al. (2019)	RSV	IL4, IL13, TLR genes	Review of genetic association studies	Host polymorphisms influenced RSV severity and risk of bronchiolitis.	(8)
9	Nguyen et al. (2020)	COVID-19	HLA Class I alleles	Computational and genetic analysis	Specific HLA genotypes have demonstrated varying capacities for presenting SARS-CoV-2-derived peptides to immune cells.	(9)
10	McDermott et al. (2022)	Respiratory viral infections	Pharmacogenomic loci (OAS1, TYK2, IFN pathways)	Translational genomics study	Genetic variation may influence antiviral treatment efficacy and support personalized therapy.	(10)

OAS1, IFNAR2, TLR7, TYK2, DPP9, and HLA loci have been consistently associated with differences in antiviral immunity, inflammatory responses, and the risk of severe respiratory complications. These observations emphasize the crucial role of host genetic factors in accounting for the marked differences in susceptibility, disease progression, and clinical outcomes among individuals with respiratory viral infections. Recent progress in genome-wide association studies (GWAS), next-generation sequencing (NGS), and multi-omics platforms has significantly improved our understanding of the molecular pathways involved in disease development and progression. The identification of genetic risk factors has not only improved insights into host–pathogen interactions but has also facilitated the discovery of novel biomarkers capable of predicting disease severity and clinical outcomes. Furthermore, the integration of genomic information with transcriptomic, proteomic, and clinical data has created new opportunities for more accurate patient stratification and risk assessment. Importantly, growing evidence supports a significant role for host genetic variation in determining responses to antiviral therapies. Pharmacogenomic studies suggest that inherited differences in immune signaling pathways and drug-metabolism mechanisms may influence treatment efficacy, adverse effects, and therapeutic success. Consequently, genotype-guided therapeutic strategies have the potential to optimize antiviral interventions and improve clinical outcomes. Future research should focus on validating genetic biomarkers across diverse populations and integrating genomic information into routine clinical practice. Overall, current evidence suggests that host genomic information will become increasingly important in advancing precision medicine strategies aimed at preventing, managing, and treating respiratory viral diseases.

Acknowledgements
The authors gratefully acknowledge the support and assistance provided by the staff of the Biotechnology Research Center at the National Institute of Genetic Engineering and Biotechnology, Iran. The authors confirm that this research did not receive any specific financial support from governmental, commercial, or non-profit funding organizations.

Conceptualization
No specific funding or grant support was received from public, commercial, or non-profit organizations for this study.

Data Availability Statement
All datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Competing Interests
The authors declare the absence of any known competing financial interests or personal relationships that could have influenced the work reported in this article.

Ethics Approval and Consent to Participate
This study did not require ethical approval or participant consent.

Consent for Publication
Consent for publication was not applicable.

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