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Review Article



# Autologous Antigen-Specific Immunotherapy (AASI): Precision Immune Re-education in Autoimmunity and Beyond

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## Abstract

Autologous antigen-specific immunotherapy (AASI) represents a precision approach to immune modulation. AASI aims to restore tolerance by selectively targeting pathogenic immune responses while sparing global immunity. By leveraging a patient's own immune cells, typically through ex vivo manipulation of dendritic cells or regulatory T cells, AASI offers a promising therapeutic avenue in diseases characterized by antigen-driven immunopathology. Clinically, AASI has gained traction in autoimmune disorders such as type 1 diabetes and multiple sclerosis, where peptide- or tolDC-based platforms are under active investigation. AASI also holds promise for allergen desensitization, induction of transplant tolerance, and emerging applications in cancer immunomodulation, where inverse strategies aim to reverse tumor-induced tolerance. Despite its precision, there are translational challenges, including HLA restriction, scalability of autologous products, and the need for validated biomarkers of immune engagement. Recent breakthroughs in multi-omics, single cell immune-profiling, and modular production under Good Manufacturing Processes (GMP) have helped to address these barriers, enabling deeper mechanistic insight and improved clinical feasibility. Notably, several ongoing trials demonstrated the growing maturity of AASI platforms in diverse indications. It is anticipated that the integration of AI-guided antigen discovery, combination strategies with checkpoint inhibitors or microbiome modulation, and personalized immune-monitoring will drive the next wave of innovation. With increasing regulatory receptivity and technological advancement, AASI is poised to become a transformative modality in the treatment of immune-mediated diseases.

## Introduction

Autologous antigen-specific immunotherapy (AASI) represents a promising frontier in precision immunomodulation, offering the potential to reinstate immune tolerance while minimizing systemic immunosuppression. The central concept involves harvesting a patient's own immune cells and modulating them ex vivo. This is commonly performed through tolerogenic dendritic cells (tolDCs), engineered autologous antigen-presenting cells, or antigen-specific regulatory T cells (Tregs), which are subsequently reintroduced to induce selective immunological deactivation against disease-associated antigens [1]. In the last five years, Phase I clinical trials

employing proinsulin peptide-pulsed tolDCs in type 1 diabetes (T1D) have demonstrated durable antigen-specific responses and elevation of Treg populations, with sustained suppression of autoreactive T cells for up to three years post-treatment. Similar tolDC-based strategies have exhibited safety and early immunologic efficacy in multiple sclerosis and rheumatoid arthritis, with early increases in IL-10-producing CD4+ T cells and reduced proinflammatory responses [2,3].

Advances in biomarker technology, high-dimensional immune profiling, and gene-editing tools such as CRISPR have accelerated the sophistication of AASI, allowing for fine-tuning of antigen specificity, enhancement of tolerogenic phenotypes, and improved cell survival *in vivo* [4,5]. Despite these advances, challenges persist. The optimization of antigen selection for heterogeneous patient populations is a key barrier as well as the capacity to achieve scalable and cost-effective manufacturing and the validation of mechanistic biomarkers linked to clinical benefit [1,6]. This review synthesizes recent progress, emphasizing autologous tolDC therapies, engineered antigen-specific Treg strategies, and precision biomarker validation. We examine mechanistic insights, clinical outcomes, and technological innovations, while identifying critical gaps and proposing pathways for translation into clinical practice.

## Immunological Basis

The restoration of immune tolerance is attempted by reprogramming autoreactive lymphocytes without broad immunosuppression [7]. To achieve this, AASI exploits key elements of central and peripheral tolerance that maintain immune homeostasis and prevent autoimmunity. Central tolerance is established during T and B cell development in the thymus and bone marrow, respectively [8]. Hematopoietic stem cells in the bone marrow give rise to $CD34^+$ T cell progenitors, which migrate to the thymus to undergo T cell lineage commitment and T cell receptor (TCR) development [9]. Through randomized V(D)J recombination, these thymocytes generate a highly diverse TCR repertoire capable of recognizing a vast array of peptide-MHC complexes. In the thymic cortex, positive selection ensures survival of T cells whose TCRs exhibit low-affinity binding to self-peptide-MHC complexes, enabling their differentiation into $CD4^+$ or $CD8^+$ single-positive cells [10]. Cells lacking sufficient MHC interaction undergo apoptosis via death by neglect. However, the stochastic nature of TCR rearrangement inevitably produces clones with high affinity for self-antigens, posing a risk of autoimmunity. These potentially autoreactive cells are typically eliminated during negative selection in the thymic medulla through clonal deletion or, less commonly, receptor editing [11]. A subset of self-reactive thymocytes instead differentiates into thymically derived Tregs (tTregs), which express Foxp3 and are essential for maintaining peripheral immune tolerance [12]. Thymocytes that escape deletion may persist as functionally hyporesponsive or anergic T cells, often expressing surface markers associated with tolerogenic states. These central tolerance mechanisms serve as a critical checkpoint in shaping a self-tolerant yet antigen-responsive T cell repertoire [12].

While central tolerance eliminates or redirects the most overtly self-reactive T cells in the thymus, peripheral tolerance mechanisms are essential to control autoreactive clones that escape thymic selection [13]. In secondary lymphoid organs and peripheral tissues, naïve T cells encountering antigen in the absence of appropriate costimulatory signals (e.g., CD28 engagement) undergo functional inactivation (anergy) or deletion via activation-induced cell death (AICD) [14]. Both tTregs and peripherally induced Tregs (pTregs), play a central role in enforcing tolerance by suppressing pathogenic effector responses through contact-dependent inhibition, cytokine secretion (e.g., IL-10, TGF-$\beta$, IL-35), and modulation of APCs. Peripheral tolerance is further reinforced by the tolerogenic properties of specialized APCs, (e.g., immature dendritic cells, tolerogenic macrophages), which promote T cell unresponsiveness rather than activation [15]. Additionally, metabolic constraints, such as tryptophan depletion via indoleamine 2,3-dioxygenase (IDO) and adenosine generation by CD39/CD73, create an immunosuppressive microenvironment that favors tolerance [16]. Mechanisms such as T cell exhaustion, marked by chronic antigen exposure and upregulation of inhibitory receptors like PD-1, CTLA-4, and LAG-3, can also limit autoreactive responses in the context of persistent self-antigen [17]. Together, these diverse pathways function in concert to maintain immune homeostasis and prevent the breakdown of tolerance that underlies autoimmune disease.

Effective AASI must harness and precisely direct these natural tolerance mechanisms. This requires the targeted engagement of immune cell subsets responsible for antigen uptake, processing, and regulation (i.e., dendritic cells, Tregs, antigen-specific effector populations) under conditions that promote immune quiescence rather than activation. APCs-particularly DCs-are central to the initiation and maintenance of tolerance. tolDCs, whether naturally occurring or ex vivo generated, can present self-antigens in a non-inflammatory context, express immunomodulatory molecules (e.g., IL-10, PD-L1), and promote the differentiation of induced Tregs (iTregs) [1,18]. Additional APC populations, such as tolerogenic monocytes and B cells, may contribute under specific conditions, although their roles are less well-defined [19]. Effector and regulatory lymphocytes also participate. CD4+ Tregs (FoxP3+ or Tr1) suppress immune responses via cytokines (e.g., IL-10, TGF-$\beta$), metabolic competition, and modulation of APC function [20]. Regulatory B cells (Bregs) secrete IL-10 and contribute to local immune suppression [21]. In some contexts, antigen-specific CD8+ T cells may either contribute to tolerance via exhaustion or represent a key target for suppression or deletion [22].

Collectively, multiple non-mutually exclusive mechanisms underlie AASI efficacy. Clonal deletion of autoreactive T cells occurs when persistent antigen exposure induces apoptosis or deletional tolerance. Anergy refers to the functional inactivation of T cells in the absence of appropriate co-stimulatory signals. Suppression, mediated by Tregs and tolerogenic APCs, can inhibit effector T cell proliferation and cytokine secretion [23]. T cell exhaustion, often marked by PD-1/CTLA-4 expression, can be harnessed in chron-

ic exposure paradigms for functional silencing [24]. The cytokine milieu plays a determinative role in promoting or impairing tolerance. IL-10, TGF-$\beta$, and IL-2 support regulatory cell differentiation and function. Conversely, the absence of IL-6 and TNF-$\alpha$ is critical to avoid effector priming [25]. Finally, the pathway of antigen presentation, whether via MHC class I (driving CD8+ responses) or MHC class II (engaging CD4+ T cells), can differentially influence tolerance or immunity depending on antigen design and cellular targeting [26].

## Approaches to Antigen-Specific Tolerance Induction

Antigen-specific tolerance can be induced through a variety of platforms that aim to recalibrate immune responses toward self or innocuous antigens, minimizing global immunosuppression. These approaches vary by antigen format, delivery vehicle, and immunologic mechanism of action as briefly described below.

*Peptide-based immunotherapies* involve the administration of soluble native or altered peptide ligands (APLs) derived from disease-relevant autoantigens. These peptides are typically presented in a non-inflammatory context to promote T cell anergy, deletion, or the induction of Tregs [27]. Recent strategies incorporate minimal immunodominant epitopes to avoid off-target effects and epitope spreading. Some platforms also leverage epitope spreading intramolecularly to generate broader, self-reinforcing tolerance across antigen variants, as seen in T1D and multiple sclerosis (MS) [28].

*Autologous* ***tolDCs*** represent a leading AASI platform. These cells are differentiated ex vivo using agents such as dexamethasone, vitamin D3, or rapamycin, and pulsed with disease-relevant antigens to induce regulatory or anergic T cell responses upon reinfusion [29]. Alternative cell types include antigen-loaded B cells and erythrocytes, the latter exploiting the natural tolerogenic clearance of apoptotic red blood cells to induce peripheral tolerance [30].

*Plasmid DNA and mRNA-based vaccines* encoding self-antigens can promote endogenous expression in a tolerogenic context. These strategies rely on *in vivo* expression in muscle or APCs, which present the encoded antigen under non-inflammatory conditions to induce tolerance [31]. Lipid nanoparticle (LNP) delivery and electroporation platforms have been adapted from cancer vaccine technology to enhance uptake and expression efficiency for tolerogenic indications [31].

Biodegradable nanoparticles, particularly those based on poly (lactic-co-glycolic acid) (PLGA), can encapsulate antigens with immunomodulatory agents (e.g., IL-10, rapamycin) to direct dendritic cell programming toward tolerance [32]. Emerging technologies exploit apoptotic mimicry, using phosphatidylserine or other signals to drive uptake through tolerogenic pathways. Surface engineering allows for targeting of lymph node-resident APCs, enhancing precision and reducing systemic exposure [33].

Adoptive transfer of Tregs involving either polyclonal or antigen-specific Tregs, has demonstrated efficacy in preclinical and early clinical studies. Antigen-specific Tregs, enriched ex vivo or generated via TCR transduction, exhibit superior suppressive function and tissue homing [34]. Recent advances in Chimeric Antigen Receptor (CAR)-Tregs allow for programmable antigen recognition, extending this modality to transplant tolerance and autoimmunity [35]. However, ensuring lineage stability and avoiding off-target suppression remains a challenge.

## Clinical Applications

The precision approach is being implemented across a broad spectrum of immunologically mediated diseases tailored for both suppressive and stimulatory immunotherapeutic strategies depending on the clinical context [36].

## Autoimmune Diseases

In T1D, AASI has advanced rapidly with peptide-based therapies targeting insulin, GAD65, or proinsulin epitopes. The D-Sense trial and others have demonstrated that proinsulin peptide-pulsed tolDCs can reduce autoreactivity and support regulatory T cell expansion without systemic immunosuppression [1,6]. Intradermal and nanoparticle formulations are under investigation for their ability to deliver antigens in tolerogenic contexts while avoiding systemic activation. Liu administered a mixture of six selective, $\beta$-cell peptides intradermally to patients with recent-onset T1D in a randomized placebo-controlled study at monthly doses of 10, 100, and 500 $\mu$g for 24 weeks [37]. Treatment was accompanied by significant changes in islet-specific immune responses and a dose-dependent increase in Treg expression of the canonical transcription factor FOXP3 and changes in Treg gene expression showing promise as a strategy to correct immune regulatory defects fundamental to the pathobiology of T1D. In a placebo-controlled, dose escalation phase 1 clinical trial in nine adult patients with long-standing T1D Nikolic *et al* [1] demonstrated the safety and feasibility of two (prime-boost) vaccinations with tolDC pulsed with a proinsulin peptide which induced a profound and durable decline in pre-existing autoimmune responses to the vaccine peptide up to three years post-treatment. In addition, a temporary decline in CD4 and CD8+ T-cell responses to other islet autoantigens was observed.

In MS, nanoparticle-based delivery of myelin peptides such as MOG or MBP encapsulated in poly(lactide-co-glycolide) (PLGA) has shown success in early-phase trials. These systems target lymphoid tissue or monocyte-derived DCs to induce antigen-specific Tregs and Tr1 cells [38].

In rheumatoid arthritis (RA), achieving therapeutic tolerance RA ideally requires precise targeting of the autoreactive T cells driving pathology. However, in RA, the specific antigenic targets of these T cells often remain unidentified and vary among individuals due to differences in their HLA genotypes. This heterogeneity complicates the development of antigen-specific tolerogenic therapies. While citrullinated peptides have been implicated as key autoantigens-particularly among individuals with the shared epitope HLA-DRB1 alleles and circulating anti-citrullinated protein antibodies (ACPAs).

The HLA-DRB1 subgroup represents only about two-thirds of RA patients [39,40]. Even within this ACPA-positive population, responses vary to different citrullinated peptides, and patients who are ACPA-negative typically do not mount T cell responses to these epitopes. As a result, a broader strategy might involve targeting T cells that recognize a conserved self-antigen, not directly involved in disease pathology but expressed in inflamed synovial tissues and naturally participating in immune regulation. Such surrogate autoantigens could provide a more universal platform for tolerance induction in RA [41]. Li and colleagues [42] recently reviewed the potential of RA-related self-antigens, nucleic acids, immunomodulators, or cytokines, tolerogenic nanoparticles-also known as immunomodulatory nano-preparations-have to regulate local immune responses and ultimately induce antigen-specific immune tolerance.

In a proof-of-concept study, Zhang and colleagues [43] demonstrated that anti-FITC CAR-T cells could be specifically redirected and kill hybridoma cells generated by immunization with antigenic peptides, and autoreactive B cell subsets from RA patients via recognition of corresponding FITC-labelled citrullinated peptide epitopes. Additionally, the cytotoxicity of the CAR-T cells was dependent on the presence of the peptides and occurred in a dose-dependent manner. Stoppelenburg *et al* [44] report the design of the phase I/II, investigator-initiated, open-label, dose-escalation trial TOLERANT evaluating the intranodal administration of tolDCs in patients with RA that are in remission under immunosuppressive therapy. The (co-)primary endpoints are safety and feasibility and the secondary endpoints include the immunological effects of the treatment, with clinical effects as exploratory outcomes.

**Inflammatory bowel disease (IBD)**

In IBD, novel cellular immunotherapies and immune cell depleting therapies in IBD, including CAR-T cell approaches, Tr1 and Treg cells and cell depleting antibodies such as rosnilimab are being investigated [45].

In systemic lupus erythematosus (SLE), is a chronic complex systemic autoimmune disease characterized by multiple autoantibodies and clinical manifestations, with the potential to affect nearly every organ. SLE treatments, including corticosteroids and immunosuppressive drugs, have greatly increased survival rates, but there is no curative therapy and SLE management is limited by drug complications and toxicities. There is an obvious clinical need for safe, effective SLE treatments. While *in vivo* expansion of Tregs have been associated with improvement in SLE disease markers and clinical manifestations the expansion is short-lived and unstable. However, ASIT approaches may establish long-lived immunological tolerance. DNA nanoparticles and tolerogenic B cell approaches targeting nucleosomal autoantigens are being developed to restore peripheral tolerance [46].

## Allergy and Asthma

Allergen-specific immunotherapy (AIT) is among the most clinically mature forms of AASI. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are widely used in allergic rhinitis and venom allergy, with long-term desensitization attributed to regulatory T and B cell induction and IgG4 class switching [47]. Novel epicutaneous and oral tolerance protocols are being explored in food allergies, such as peanut desensitization, with varying success due to differences in mucosal immune responses [48]. Biomarker-guided stratification (e.g., basophil activation tests, epitope specificity) helps improve responder prediction in AIT.

## Organ Transplantation

Induction of donor-specific tolerance is a key goal in transplant immunology. Emerging Treg-based therapies, including polyclonal or donor-antigen-expanded autologous Tregs, have entered early clinical trials with encouraging safety data and preliminary evidence of alloreactivity suppression. Similarly, tolDC-based approaches aim to present donor-derived peptides in a tolerogenic context to prevent graft rejection. In kidney transplantation, studies combining calcineurin inhibitors with tolDC infusion are ongoing (e.g., NCT04208919).

## Oncology

In contrast to autoimmune diseases, oncology uses inverse AASI principles, reversing tolerance toward tumor-specific or neoantigenic epitopes. Immune checkpoint blockade (e.g., anti-PD-1/CTLA-4) works by disabling Treg- and exhaustion-mediated tolerance [49]. Novel strategies aim to modulate ASI to enhance tumor immunity, including neoantigen-based personalized cancer vaccines that deliver MHC-I/II-restricted peptides using mRNA, DNA, or dendritic cell vectors [50]. These approaches aim to convert tolerized tumor-specific T cells into active cytotoxic cells capable of tumor eradication.

## Key Challenges in Clinical Translation

Despite promising preclinical and early clinical outcomes, the broad implementation of autologous antigen-specific immunotherapy remains constrained by several critical translational challenges. These span technical, immunological, and regulatory domains necessitating systematically addressing to ensure efficacy, safety, and scalability across immune-mediated diseases. A foundational hurdle is the accurate identification of disease-driving antigens. In autoimmunity, pathogenic epitopes may differ among individuals and over time due to epitope spreading and post-translational modifications, complicating selection of tolerogenic targets [51]. Moreover, many target antigens are also expressed in healthy tissues, increasing the risk of inducing broad immunosuppression. High-throughput proteomics and single-cell TCR/BCR sequencing have improved epitope discovery but are still limited by disease heterogeneity and poor tissue accessibility [52].

Many AASI platforms, particularly peptide-based or MHC-loaded constructs, are constrained by HLA genotype restrictions, limiting their applicability across diverse patient populations. For example, HLA-DRB1*04:01-restricted peptides used in RA or T1D fail to elicit responses in individuals with alternative alleles [53], necessi-

tating development of multi-epitope formulations or HLA-agnostic delivery systems such as nanoparticles or tolDCs. Furthermore, patient-specific immunological variables (e.g., prior antigen exposure, cytokine milieu, TCR repertoire diversity) introduce additional heterogeneity in therapeutic response [54,55].

Strategies typically involve ex vivo manipulation of autologous immune cells, such as antigen-pulsed tolDCs or expanded Tregs. While these approaches allow for high specificity and individualized tolerization, they pose substantial challenges related to manufacturing logistics, sterility assurance, batch consistency, and GMP compliance [56]. Compared to off-the-shelf biologics, autologous cell-based therapies are resource-intensive and less scalable, though emerging solutions such as modular closed-system automation and centralized production hubs are being developed to address these limitations [57].

Despite the promise of AASI, off-target immunomodulation remains a concern. The risk of bystander suppression, generalized immunosuppression, or inadvertent tolerization of protective immune responses, particularly in settings with dynamic or poorly defined autoantigen repertoires, necessitate stringent safety strategies. Preclinical studies have shown that high antigen doses or pro-inflammatory delivery contexts can promote off-target effects and immune deviation. Thus, low-dose, non-inflammatory antigen presentation and precise antigen selection are essential to maximize specificity while minimizing risk.

A persistent bottleneck in AASI clinical development is the lack of validated, fit-for-purpose biomarkers to track immunological engagement and tolerance induction. Traditional clinical endpoints often lag behind molecular effects. Promising biomarker candidates include antigen-specific T cell frequency and phenotype, Treg-to-Teffector (Teff) ratios, cytokine signatures (e.g., IL-10, TGF-$\beta$), and TCR clonotype tracking, though standardization and assay reproducibility remain key barriers to widespread implementation [58]. Advances in single-cell multiomics, mass cytometry, and spatial transcriptomics may enable higher-resolution immune monitoring in future AASI trials.

## Recent Breakthroughs and Trials

The clinical landscape for autologous ASI has evolved rapidly over the past five years, with several pivotal trials advancing through early and mid-stage development. Although regulatory agencies are increasingly requiring long-term safety follow-up, especially for AASI platforms involving gene-edited or persistently modified immune cells, persistent efforts reflect increasing translational maturity, driven by improved antigen-targeting platforms, regulatory engagement, and high-resolution immunomonitoring tools.

A wave of precision-designed AASI candidates has entered clinical testing across autoimmune and neurodegenerative diseases. The AUTOTAC-T1D (Autologous Tolerogenic Antigen-specific Cell Therapy in Type 1 Diabetes) Phase I trial (NCT04590872) is evaluating autologous tolerogenic dendritic cells pulsed with proinsulin C19-A3 peptide in recent-onset T1D. NeuroVax (NCT02149706)is a TCR peptide vaccine targeting FOXP3-specific T cells to amplify regulatory networks in MS using conserved TCR regions to expand protective Treg populations and has received orphan designation from the FDA for secondary progressive MS. The Tolerion (formerly Bayhill Therapeutics) lead program, TOL-3021, is a DNA vaccine encoding proinsulin administered intramuscularly that was studied in a Phase II trial in T1D showing durable antigen-specific immune modulation and a favorable safety profile [27]. therapies.

The ImmTOR platform from Selecta Biosciences, delivers co-encapsulated rapamycin with antigen to tolerize against specific proteins, initially applied to minimize anti-drug antibody formation. Recent iterations have expanded to autoimmune disease (e.g., IgA nephropathy) and enzymopathy settings, with trials ongoing in both rare and common indications [59]. Together, these programs illustrate the diverse technological modalities being applied converging on restoring antigen-specific tolerance.

In response, regulatory bodies are increasingly accommodating innovative approaches through expedited pathways. The FDA granted Fast Track and Orphan Drug designations to AASI products in MS (NeuroVax), T1D (TOL-3021), and certain rare autoimmune encephalitides. The European Medicines Agency (EMA) has also embraced AASI through the Adaptive Pathways initiative, especially for individualized cell-based interventions where randomized controlled trials may be infeasible. The PRIME designation has also been leveraged to accelerate tolDC and Treg-based programs. These regulatory advances reflect increasing clinical and regulatory confidence in AASI as a class and the need for early engagement between developers and agencies to align on endpoints, biomarker validation, and manufacturing standards.

## Future Outlook

The rapid evolution, catalyzed by innovations in systems biology, computational modeling, and combinatorial therapeutics offer the potential to overcome many of the limitations historically associated with AASI and are reshaping the next generation of precision immunotherapies. Artificial intelligence (AI) and machine learning (ML) are increasingly being applied to immunological datasets to uncover disease-relevant autoantigens, predict individual immune responses, and stratify patients most likely to benefit. The integration of immunosequencing and multi-omics is transforming trial design and interpretation. High-throughput TCR and BCR sequencing provide the opportunity for tracking of clonal dynamics in antigen-specific T cell subsets, especially in response to vaccines or cell therapies. These platforms integrate genomics, transcriptomics, TCR/BCR repertoire profiling, epitope prediction algorithms, and proteomic mass spectrometry to define immunodominant and post-translationally modified epitopes with high disease relevance. In parallel, multiomic datasets are enabling predictive models of tolerance induction by mapping the molecular signatures of responders versus non-responders. These tools are expected to inform dynamic, patient-specific antigen formulations and biomarker-guided trial designs. Technological advances now allow for

high-throughput antigen screening, single-cell immunoprofiling, and on-chip T cell activation assays, accelerating the development of personalized ASI products. Libraries of predicted neo-antigens or self-epitopes can be rapidly screened using microfluidic T cell activation platforms, enabling real-time optimization of peptide panels tailored to individual immune landscapes. Platforms are increasingly leveraging CRISPR-based gene editing and transcriptomic reprogramming to fine-tune their specificity, persistence, and suppressive functions. Given the complexity of autoimmune and inflammatory disorders, standalone AASI may benefit from combination approaches that enhance its efficacy and durability. For example, checkpoint modulation (e.g., low-dose anti-PD-1 or CTLA-4-Ig) to transiently reduce effector T cell activation and facilitate regulatory dominance during administration. In addition, anti-inflammatory co-therapies, including rapamycin-loaded nanoparticles or IL-2 variants, promote Treg expansion and inhibit inflammatory milieu during antigen exposure, while microbiome-directed therapies, which modulate mucosal antigen presentation and systemic immune tone, offering synergistic potential with oral or epicutaneous ASI platforms. These combination regimens hold potential to broaden AASI responsiveness across diverse patient populations while maintaining antigen specificity. Continued advancements in proteomics and metabolomics, particularly from plasma and exosomes, facilitate monitoring tolerogenic cytokine milieus (e.g., IL-10, TGF-$\beta$) and metabolic rewiring post-therapy. These innovations are critical for developing fit-for-purpose biomarkers that align with regulatory expectations and clarify mechanisms of action, particularly in Phase I/II trials where traditional clinical endpoints may be less sensitive.

While AASI has traditionally emphasized autologous platforms to avoid off-target reactivity and ensure MHC compatibility, emerging efforts are exploring partially HLA-matched allogeneic approaches to improve scalability and manufacturing feasibility. Engineered off-the-shelf tolerogenic dendritic cells and Tregs derived from induced pluripotent stem cells (iPSCs) or universal donor lines are under development and could reduce time, cost, and inter-batch variability [60]. However, these strategies require additional safeguards to mitigate alloimmunogenic risks. Looking forward, hybrid models combining universal cell sources with patient-specific antigen loads may offer the optimal balance between personalization and scalability.

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