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Review

Review

The EBV-MS paradigm: beyond molecular mimicry toward new therapeutic strategies

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Abstract

Epstein-Barr virus (EBV) is now recognized as the definitive environmental driver of multiple sclerosis (MS), shifting the conceptual landscape of this autoimmune disorder to an infection-triggered model. In this review, we systematically evaluate the multidimensional evidence linking EBV to MS. This evidence ranges from epidemiological associations and the identification of mimotopes to emerging therapeutic strategies. We also discuss the broader implications of infection-driven immune dysregulation for autoimmune research. This pathogenic link is underpinned by molecular mimicry, where immune responses against the viral protein EBNA1 cross-react with the central nervous system (CNS) protein GlialCAM. Beyond this initial insult, EBV reprograms B cells to survive and proliferate abnormally, creating a compartmentalized viral reservoir within the CNS that sustains chronic neuroinflammation. These mechanistic insights catalyze a transition from broad immunosuppression to precision therapies targeting the EBV-MS axis, including CNS-penetrant kinase inhibitors and EBV-specific CAR-T cells. By integrating etiological discovery with mechanism-based intervention, the EBV-MS paradigm serves as a blueprint for transforming idiopathic autoimmune diseases into mechanistically tractable conditions with actionable therapeutic targets.

Key words Epstein-Barr virus, multiple sclerosis, autoimmunity, molecular mimicry

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS), with a global prevalence of approximately 2.8 million individuals (35.9 per 100,000) [1]. The incidence of MS continues to rise, including in developing countries [1] and pediatric cohorts [2]. Clinical manifestations encompass a broad spectrum of neurological deficits, such as motor and sensory impairment, visual and oculomotor disturbances, fatigue, ataxia, spasticity, and cognitive decline [3]. The etiology of MS is multifactorial, involving a complex interplay between genetic susceptibility, particularly in immune-related genes, and environmental factors such as infections, smoking and obesity [4].

Epstein-Barr virus (EBV), a ubiquitous human γ-herpesvirus that infects over 95% of adults worldwide, establishes lifelong latency in B cells [5]. Through latency-associated proteins and non-coding RNAs, EBV reprograms B-cell survival and differentiation, enabling persistent infection of memory B cells while evading immune detection [6]. Although most primary EBV infections during childhood are asymptomatic, delayed infection in adolescence frequently causes infectious mononucleosis (IM) [7], which is associated with a 2.3-fold increased risk of developing MS [8]. EBV has also been implicated in various malignancies, *e.g.*, Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma [9] and autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis [10]. These associations underscore EBV's capacity to remodel immune networks via latent antigen expression, molecular mimicry of host signaling molecules [11,12], and modulation of innate and adaptive immune checkpoints [13].

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A leading mechanistic hypothesis linking EBV to MS is molecular mimicry, whereby EBV antigens cross-react with CNS self-antigens [14]. This mechanism offers a plausible explanation for how a common viral infection can initiate a targeted autoimmune response against the CNS [15]. In this review, we examine the evidence linking EBV to MS, from epidemiological associations and mimotope identification to emerging therapeutic approaches, and discuss the wider implications of infection-driven immune dysregulation for autoimmune disease research.

The Causal Link: Integrating Epidemiological and Genetic Evidence

The historical pursuit of an infectious trigger

The concept of an infectious contribution to multiple sclerosis dates to 1884, when Pierre Marie, noting frequent prior infections in patients, postulated an infectious etiology albeit without empirical support [16]. In 1932, Thomas Rivers' systematic review of viruses in neurological disease suggested that they might indirectly provoke pathology via immune activation, although experimental models were then unavailable [17]. Later, in 1962, Adams and Imagawa detected measles virus-neutralizing antibodies in the cerebrospinal fluid (CSF) of MS patients [18]; however, subsequent failures to identify viral nucleic acids refuted a direct causal role. A significant advance came in 1981 when Warner and Carp, observing geographical overlap between MS and infectious mononucleosis, first proposed EBV as a candidate pathogen, hypothesizing that latent B-cell infection could facilitate CNS entry [19]. Kurtzke's analysis of an MS "outbreak" in the Faroe Islands further suggested that delayed infection increases risk, reinforcing the role of infection as an environmental trigger [20]. A key turning point came in 1995, when Wucherpfennig and colleagues showed that myelin basic protein (MBP)-reactive T-cell clones from MS patients cross-react with viral peptides, including those from EBV [21]. In 2008, the study by Lünemann identified MBP-reactive T cells that cross-recognize EBV nuclear antigen 1 (EBNA1) [22]. Together, these findings elevated EBV from a speculative association to a mechanism-based research focus, laying the groundwork for validation in large-scale cohorts (Figure 1).

Temporal sequence: a paradigm shift from prospective cohorts

Establishing the temporal sequence in which EBV infection precedes clinical MS is essential for causal inference. A landmark longitudinal study of ~10 million serial serum samples from U.S. military personnel found that 97% of individuals later diagnosed with MS had seroconverted before symptom onset, while MS was nearly absent in those who remained EBV-naïve [15]. The median interval from seroconversion to the first demyelinating event was approximately five years, and serum neurofilament light chain rose during this latent phase [15]. Independent population registries further confirm that a history of infectious mononucleosis increases MS risk 2- to 3-fold [8,23].

Genetic susceptibility and viral interplay

The majority of inherited MS risk localizes to the major histocompatibility complex (MHC), particularly HLA class II. The strongest risk allele, HLA-DRB 15:01, encodes a peptide-binding groove that presents hydrophobic epitopes at lower T-cell activation thresholds [24]. MS patients show exaggerated $CD4^+$ and $CD8^+$ T-cell responses to EBV latent antigens, especially EBNA1, which frequently cross-react with myelin peptides [22]. Chromatin immunoprecipitation studies have revealed that the EBV transcription factor EBNA2 occupies enhancer regions near MS risk genes, including *HLA-DRB1*, *TYK2*, *IL2RA*, and *CD40*, upregulating their expression in B cells [25,26]. Thus, MHC architecture not only governs EBV antigen presentation but also raises the probability of the virus being mistaken for itself, forming a molecular bridge between genetic predisposition and environmental triggers.

Mechanisms of Pathogenesis

Molecular mimicry: breaking self-tolerance

A key molecular mimicry event involves sequence homology

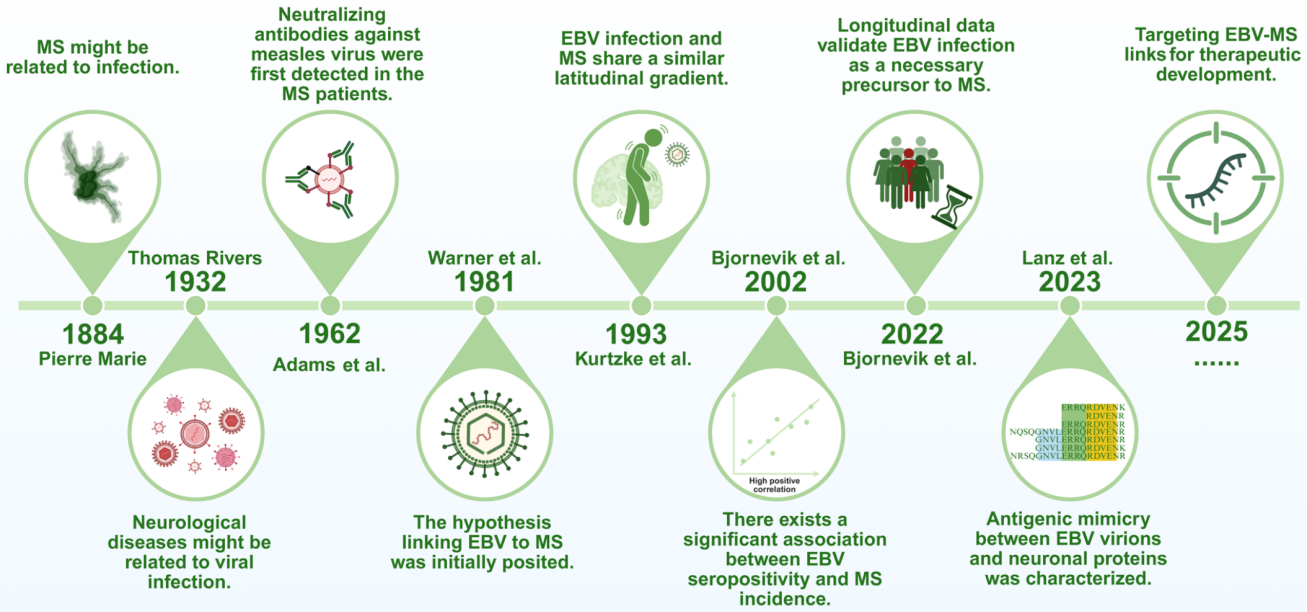


Figure 1. Key historical milestones in MS infectious-trigger research presented on a timeline

between EBNA1 and the CNS adhesion molecule GlialCAM. High-affinity IgG from MS patients binds to both the $EBNA1_{411-426}$ peptide and MBP, indicating a loss of humoral tolerance [14]. Immunizing transgenic mice with $EBNA1_{411-426}$ induces experimental autoimmune encephalomyelitis (EAE) with optic-spinal inflammation, confirming functional cross-reactivity [14]. System-wide screens and single B-cell cloning have extended the mimicry network to additional CNS antigens, αB-crystallin, anoctamin-2 and GlialCAM, each sharing hexameric motifs with EBNA1 that form anchor residues for HLA-DRB1*15:01 [14]. Structural modeling confirms near identical side chain topology between viral and self-epitopes, providing a mechanistic basis for autoantibody generation (Figure 2).

Aberrant B-cell activation and latent persistence

EBV establishes lifelong latency primarily in memory B cells, subverting their normal survival and differentiation pathways. Patients with MS exhibit a 2- to 4-fold increase in EBV load within circulating B cells, and postmortem CNS tissue contains EBV-infected B-cell follicles expressing the latent membrane proteins LMP1 and LMP2A [27]. LMP1 mimics constitutively active CD40 signaling, while LMP2A provides tonic B-cell receptor (BCR)-like signals; together, these viral proteins drive antigen-independent B-cell activation, plasma cell differentiation, and enhanced antigen presentation [28].

Crucially, this viral reprogramming mediates the immortalization of autoreactive B-cell clones that would otherwise be eliminated. Under physiological conditions, B cells recognizing self-antigens within the germinal center are destined for apoptosis via negative selection. However, EBV subverts this checkpoint through the upregulation of antiapoptotic proteins. Specifically, LMP1 and EBNA2 induce the expression of BCL-2 family members (*e.g.*, BCL-2, MCL-1, and BFL-1), providing a potent survival signal that mimics physiological CD40 interactions [29]. This mechanism effectively rescues forbidden autoreactive clones from deletion, allowing them to escape immune surveillance and enter the memory B-cell pool as an immortalized, long-lived reservoir capable of sustaining chronic autoimmunity [30].

Consequently, EBV-infected B cells act as potent antigen-presenting cells, priming autoreactive T cells and amplifying cytokine cascades. The frequent detection of oligoclonal IgG targeting EBNA1 and EBNA3C in the CSF further indicates that intrathecal humoral immunity in MS is largely directed against EBV antigens yet cross-reactive with myelin components [28] (Figure 2).

Compartmentalized CNS inflammation and EBV reactivation

Before entering the CNS, EBV^+ memory B cells act as mobile inflammatory engines: LMP1/2A chronically triggers CD40-CD40L and BCR-surrogate signals, inducing GM-CSF, TNF-α and the chemokine CXCL13 that recruit and activate peripheral Th1/Th17 cells and $CD16^+$ monocytes. Virus-rich exosomes simultaneously suppress dendritic cell IL-12 and disrupt astrocytic gap junctions, setting the systemic inflammatory tone to ignite and fueling subsequent intracranial compartmentalization.

In secondary progressive MS, subpial meningeal infiltrates often contain ectopic B-cell follicles with germinal-center reactions. *In situ* hybridization detects EBV-encoded small RNAs and the lytic transactivator BZLF1 within these structures, suggesting intermittent viral reactivation [27,31]. These EBV^+ B cells are encircled by perivascular $CD8^+$ T cells enriched for perforin and granzyme B, indicating a spatially restricted but ineffective cytotoxic response that fails to clear infection while perpetuating tissue damage [27]. Notably, the density of these EBV-infected follicles correlates with the extent of cortical demyelination and neuronal loss, supporting the concept that compartmentalized viral persistence fuels chronic compartmentalized inflammation and progressive disability (Figure 2).

Evasion of immune surveillance

MS patients exhibit both quantitative and qualitative deficits in EBV-specific immunity. *Ex vivo* ELISPOT and HLA class I tetramer assays show reduced frequencies of EBNA1- and EBNA3A-specific $CD8^+$ T cells, which produce less IFN-γ and TNF-α upon challenge [28]. Consequently, EBV-infected B cells can accumulate *in vivo* because they are not promptly eliminated, persisting in a latent state and undergoing periodic reactivation [32]. Natural killer cell cytotoxicity is also impaired in MS, weakening the innate antiviral defense [33]. EBV itself further impedes immune recognition by upregulating checkpoint ligands such as PD-L1 on infected B cells [33]. Together, these mechanisms enable EBV to persist, repeatedly triggering immune activation and creating a chronic pro-inflammatory CNS milieu that amplifies demyelination and neuronal injury, a cornerstone of progressive MS.

However, the landscape of EBV-specific immunity in MS is complex and occasionally contradictory. While some studies highlight immune deficits, others report strikingly elevated viral-specific responses, suggesting immune dysregulation rather than simple insufficiency. For instance, Lünemann and colleagues demonstrated that MS patients harbor expanded frequencies of EBNA1-specific $CD4^+$ T cells that are functionally competent and interferon-γ producing [34]. Similarly, Angelini *et al.* [35] observed increased $CD8^+$ T-cell responses to EBV lytic antigens specifically during the active phase of the disease. These discrepancies likely reflect the heterogeneity of MS stages or a dissociation between T-cell quantity and quality: the immune system may mount a vigorous, blind response that is nonetheless ineffective at clearing the virus, thereby contributing to immunopathology rather than resolution [34,35].

Emerging Therapeutic Strategies Targeting the EBV-MS Axis

Lessons from historical antiviral trials

The development of EBV-targeted therapies is informed by the limitations of earlier interventions. Historical attempts to treat MS with direct antivirals, such as acyclovir and valacyclovir, have yielded disappointing clinical results. These failures provide critical mechanistic insight: standard antivirals target viral DNA polymerase during the lytic phase but are ineffective against latent viral episomes [36]. Since EBV drives MS pathology primarily through latent programs (*e.g.*, LMP1/2A) within memory B cells, therapeutic strategies have shifted from targeting the virus directly to depleting the cellular reservoirs that harbor it.

Immunomodulation

BTK inhibitors

Bruton's tyrosine kinase (BTK) inhibitors have emerged as a pivotal strategy to address the compartmentalized smoldering neuroin-

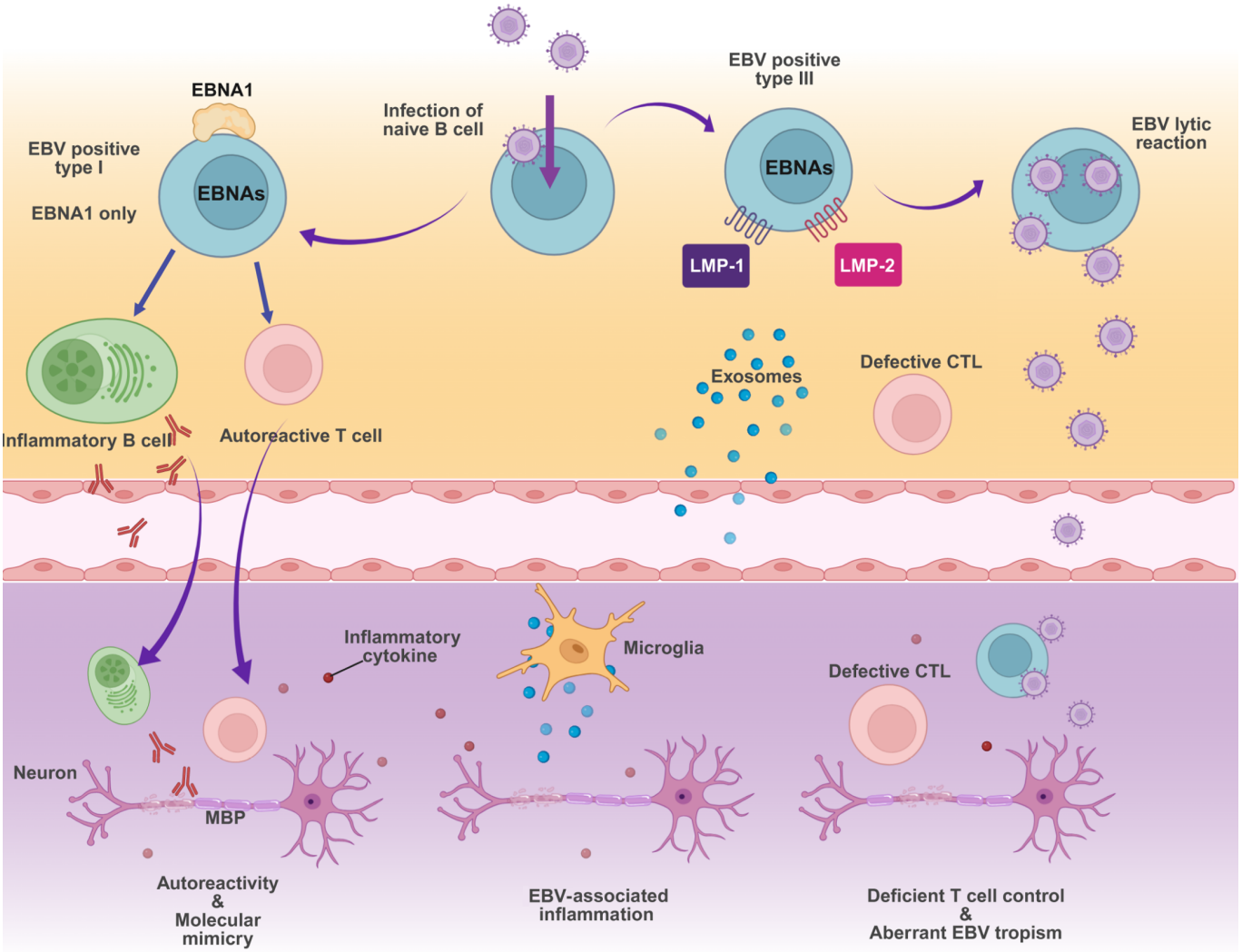


Figure 2. An overview of the underlying pathogenic mechanisms of MS EBV infects B cells and cycles from latency III (EBNAs, LMP-1/2) to EBNA1-dominant latency I with intermittent lytic reactivation, reprogramming B-cell functions to enhance antigen presentation. Molecular mimicry initiates autoreactivity; infected B cells and their extracellular vesicles fuel local inflammation. Inadequate cytotoxic T-cell clearance sustains EBV-driven inflammation and culminates in progressive demyelination and neuronal injury. EBNA1: Epstein-Barr nuclear antigen-1; LMP-1: latent membrane protein-1; LMP-2: latent membrane protein-2; CTL: cytotoxic T lymphocyte; MBP: myelin basic protein.

flammation that persists behind the blood-brain barrier, a pathological niche where conventional peripheral B-cell depleting antibodies often fall short [37,38]. Mechanistically, BTK serves as a critical node in BCR signaling, a pathway specifically hijacked by EBV LMP2A to drive abnormal B-cell survival and activation [11]. Beyond its role in B cells, BTK is highly expressed in myeloid cells such as microglia, where its inhibition dampens the pro-inflammatory environment at chronic lesion rims and reduces B cell:T-cell interactions through metabolic reprogramming [39,40]. These dual actions have translated into divergent clinical outcomes in recent trials: while evobrutinib failed to meet its primary endpoints in phase III relapsing MS trials [41], tolebrutinib achieved a significant milestone in the HERCULES trial by delaying disability progression in nonrelapsing secondary progressive MS, although it failed to reduce relapses in its GEMINI trials [37,38] (Table 1). Furthermore, fenebrutinib continues to be evaluated for its high selectivity and potential in primary progressive MS [38]. Despite these therapeutic promises, the clinical trajectory of BTKIs is complicated by significant safety concerns, most notably asymptomatic hepatotoxicity, which has triggered multiple FDA clinical holds [37,40]. Furthermore, because BTKIs modulate rather than deplete B cells, they face a potency ceiling compared to therapies that physically eradicate the EBV reservoir, suggesting that their future role may be specialized in managing progression independent of relapse activity [38,40].

CD20-directed B-cell depletion

CD20-directed B-cell depletion stands as a cornerstone of MS therapy, founded on the premise that memory B cells are the primary reservoir for latent EBV and serve as pivotal antigen-presenting cells in the autoimmune cascade [37]. Mechanistically, monoclonal antibodies such as rituximab, ocrelizumab, ofatumumab, and ublituximab achieve high-efficacy disease modulation by selectively depleting CD20-expressing B-cell populations, with ocrelizumab notably providing the first approved intervention for primary progressive MS [42]. However, the clinical utility of these agents is increasingly recognized to have a potency ceiling,

Table 1. The drug research and development pipeline for MS therapeutics

Therapeutic category	Representative therapy	Mode of action	Development stage
Immunomodulatory therapy	BTK inhibitors (*e.g.*, Tolebrutinib, Fenebrutinib)	Inhibits BTK signaling to suppress B-cell and microglial activation, reducing CNS inflammation.	Phase III
	Anti-CD20 mAb (*e.g.*, Ocrelizumab, Ofatumumab)	By binding to CD20 on the surface of B lymphocytes, it depletes $CD20^+$ B cells and suppresses autoimmune attack.	Approved
	Chemokine antagonists (*e.g.*, CCR5 or CXCR5 antagonists)	Blocks immune cell trafficking across the BBB, mitigating CNS inflammatory infiltration.	Preclinical
Cell-based therapy	CAR T-cell therapy (CD19 or BCMA targeted)	Penetrate the CNS and selectively engage BCMA on the surface of plasma cells to eliminate pathogenic plasma cells.	Phase I/II
	EBV-specific CTLs (*e.g.*, ATA188)	Restores antiviral surveillance using *ex vivo* expanded EBV-specific cytotoxic T-lymphocytes to selectively eliminate infected B cells.	Failed phase II
Neuro reparative agents	GPR17 antagonist (*e.g.*, PTD802)	Promotes oligodendrocyte differentiation and remyelination by releasing GPR17-mediated inhibition.	Phase I
	Mesenchymal stromal cell transplantation	Provides neuroprotective and anti-inflammatory effects to enhance myelin repair and functional recovery.	Preclinical

primarily because their action is largely restricted to peripheral B cells due to poor penetration into the CNS parenchyma and meningeal follicles [37]. Consequently, longitudinally persistent B-cell clones within the cerebrospinal fluid can resist treatment, and the persistence of CD20-negative long-lived plasma cells ensures that intrathecal antibody production and compartmentalized inflammation remain largely unabated [43]. This lack of durability in controlling CNS-intrinsic pathology and the failure to fully eradicate the viral-autoimmune driver highlight the critical need for next-generation strategies that can breach tissue sanctuaries to achieve a more profound immunological reset [38] (Table 1).

Targeting the CCL5/CCR5 and CXCL13/CXCR5 signaling axes

Precision interception of the CCL5/CCR5 and CXCL13/CXCR5 signaling axes represents a sophisticated strategy to block the recruitment of pathogenic leukocytes to the CNS [38,44]. These axes serve as core navigational signals, guiding EBV-infected and autoreactive immune cells across the blood–brain barrier (BBB). Regarding pathological mechanisms, the CCL5/CCR5 axis primarily drives the infiltration of proinflammatory Th1 cells, $CD8^+$ T cells, and monocytes, directly inducing acute neuroinflammation and early demyelinating injury through the release of proinflammatory cytokines [38]. Concurrently, CXCL13 levels in the cerebrospinal fluid (CSF) of MS patients are significantly elevated. By binding to its receptor CXCR5, it specifically recruits pathogenic B cells and follicular helper T cells into the CNS [44,45]. The activation of this axis further promotes the compartmentalized pathology of the disease: CXCL13 acts as a central force in organizing ectopic meningeal lymphoid follicles. These structures provide a hypoxic sanctuary for the persistent latency and periodic reactivation of EBV. Consequently, disrupting these signaling pathways not only restricts cell trafficking but also destabilizes germinal center-like structures, thereby re-exposing latent viral reservoirs to immune clearance [37,38]. However, such therapies face the trafficking vs. persistence paradox in clinical translation [37,38]. While intercepting chemotactic signals effectively prevents new pathogenic cells from entering the CNS, the efficacy in clearing persistent B-cell clones, which have already colonized central tissues and operate independently of peripheral signaling, remains limited [43]. This spatially compartmentalized pathological feature constitutes an efficacy ceiling for current anti-chemotactic treatments when addressing smoldering inflammation in progressive MS [37].

Cell-based therapies

B-cell directed CAR T-cell therapy

B-cell-directed chimeric antigen receptor (CAR) T-cell therapy represents a transformative leap aimed at surmounting the potency ceiling of conventional monoclonal antibodies, which often fail to penetrate CNS tissue sanctuaries or eliminate CD20-negative plasma cells [38]. By engineering T cells to target CD19 or B-cell maturation antigen (BCMA), this approach enables the deep depletion of both peripheral and tissue-resident B-lineage cells, theoretically facilitating an immunological reset [46]. Early clinical success in other refractory autoimmune diseases suggests that CAR T cells can migrate into inflamed tissues and dismantle established pathogenic clones that resist standard therapies [46]. In the context of MS, clinical trials are now investigating BCMA-targeted CAR T cells to specifically ablate the long-lived plasma cells responsible for persistent intrathecal antibody production and chronic compartmentalized inflammation [37] (Table 1). However, the clinical integration of CAR T-cell therapy is tempered by substantial challenges, including the risk of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, as well as the immense logistical and economic hurdles associated with individualized cell manufacturing [46]. Furthermore, the long-term safety of profound and sustained B-cell aplasia in MS patients remains a critical unknown that necessitates rigorous longitudinal monitoring [38].

EBV antigen-directed cellular therapy

EBV antigen-directed cellular therapy represents a precision

immunotherapeutic approach designed to re-establish immune surveillance and selectively eliminate the latent viral reservoir that drives MS pathology [47]. The rationale for this strategy is rooted in the observation that MS patients often exhibit defective T-cell control over EBV-infected B cells, allowing these pathogenic clones to persist and flourish within the CNS [47]. By utilizing autologous or allogeneic EBV-specific cytotoxic T lymphocytes expanded *ex vivo* to target latent proteins such as EBNA1 and LMP1/2A, this therapy aims to dismantle compartmentalized inflammation at its source [47]. Early-phase clinical data, particularly with the off-the-shelf allogeneic T-cell therapy ATA188, initially provided biological signals of sustained disability improvement and reduced CNS lesion activity in a subset of progressive MS patients [47]. However, the clinical trajectory of this modality faced a significant setback with the results of the Phase 2 EMBOLD study, which failed to meet its primary endpoint of confirmed disability improvement compared to placebo [38]. This failure underscores the profound complexity of the EBV-MS axis and suggests that while viral-specific clearance remains a compelling mechanism, its translation into broad clinical efficacy may require earlier intervention, more potent cell products, or combination strategies to overcome the established neurodegenerative environment of advanced MS [37,38] (Table 1).

Promoting regeneration

Promoting neural regeneration through GPR17 antagonism represents a critical expansion of MS therapy beyond mere immunosuppression, focusing on restoring the myelin sheath to prevent permanent axonal loss [48]. GPR17 is an orphan G protein-coupled receptor primarily expressed on oligodendrocyte progenitor cells (OPCs), where it functions as an intrinsic differentiation brake that downregulates OPC maturation into myelinating oligodendrocytes [48]. In MS lesions, persistent or dysregulated GPR17 expression often halts this maturation process, contributing to the failure of spontaneous remyelination [38,48]. By blocking GPR17 with selective antagonists, transitioning from earlier tool compounds such as HAMI3379 to the first clinical candidate, PTD802 researchers aim to release the brake and accelerate the repair of damaged white matter [48] (Table 1). While several neuroprotective and remyelinating strategies are now being explored in clinical trials, the field faces significant hurdles, including the technical difficulty of quantifying remyelination *in vivo* and the necessity of coadministering these agents with potent anti-inflammatory therapies to protect newly formed myelin from ongoing immune attack [37]. Furthermore, the narrow therapeutic window available for effective remyelination before the onset of irreversible gliosis remains a major obstacle to achieving broad clinical efficacy in progressive MS [37,38].

Concluding remarks for therapeutics

Future therapeutic innovations should address the distinct potency ceiling observed with current standard-of-care regimens. While anti-CD20 monoclonal antibodies efficiently deplete B cells in the peripheral blood, they exhibit poor penetration into secondary lymphoid organs and the CNS. Consequently, tissue-resident memory B cells, the primary sanctuary for latent EBV, often survive in these sequestration niches, driving disease persistence and limiting long-term durability [43]. In contrast, CAR-T cells act as living drugs with superior biodistribution, actively migrating into tissues to achieve deep depletion of these secluded viral reservoirs that are inaccessible to antibodies [46]. However, the efficacy of this deep depletion will be balanced against safety risks. Therefore, the next generation of therapeutics needs to bridge this gap: developing strategies to enhance the CNS penetrance of biologics (*e.g.*, brain-shuttle antibodies) or engineering safer cellular constructs, aiming to achieve the sterilizing depth of CAR-T cells with the safety profile of monoclonal antibodies.

The Infection-mimicry-dysregulation Paradigm

High-throughput platforms for mimotope discovery

Mapping the antibody-antigen interface between EBV and CNS proteins is now feasible with multiplexed peptide-display technologies. Phage display combines immunoprecipitation (PhIP-Seq) with next-generation sequencing of 10^9 member random-peptide libraries, enabling unbiased discovery of linear mimotopes recognized by serum or CSF IgG [49]. Peptide microarrays immobilize > 100,000 overlapping 15-mers spanning the entire EBV proteome and candidate myelin antigens, allowing high-throughput seroprofiling across populations, although fixed peptides rarely recapture conformational or posttranslationally-modified epitopes. Microbial or yeast surface display can present folded domains up to 300 residues, restoring native disulfide bonds and glycosylation. Fluorescence-activated cell sorting then quantifies binding avidity and enables iterative mutagenesis to refine core residues [50]. Integrative application of these platforms has yielded convergent evidence: phage display retrieved $EBNA1_{401\text{-}408}$ mimics that are recognized by oligoclonal IgG in > 70% of MS CSF samples; subsequent microarray validation narrowed the cross-reactive core to aa411–426, which shares a pYRVX motif with GlialCAM and MBP; immunization of HLA-DRB1*15:01 transgenic mice with this peptide triggered optic-spinal EAE, fulfilling modified Koch's molecular postulates [25,51]. Collectively, the triad of phage display (discovery), peptide arrays (population mapping), and cellular display (conformational validation) provides a complementary workflow to chart the mimotope landscape from EBV to CNS autoantigens.

The interlaboratory comparability of PhIP-Seq mimotope maps remains limited. Variations in peptide length, tiling offset, and amplification rounds can shift the number of positive peptides in the same serum by an order of magnitude [52]; concurrent use of p values, Z scores, or fold-change thresholds has yielded no consensus cutoff [53]. Sample-processing protocols differ in freeze-thaw cycles, IVIG interference handling, and mock-IP batch correction, amplifying technical noise [54]. Multicenter studies share insufficient replicates across sites, restricting cross-cohort validation. Critically, the absence of host HLA restriction data reduces antibody positivity to a measure of binding, without indication of presentation or pathogenicity [55]. Integrating six-digit HLA typing and binding prediction into a single quality-control framework (Table 2), alongside library parameters, processing steps, and batch adjustment, will enable data harmonization and facilitate the clinical translation of mimotope discovery [56].

A functional validation pipeline for mimotope translation

Mimotopes identified by high-throughput screening require multi-tiered validation to establish relevance, specificity, and functional capacity toward native self-antigens. *In vitro*, ELISA is a first-line assay, quantifying differential binding of patient versus control sera to candidate peptides and calculating diagnostic sensitivity/specifi-

Table 2. Comparison of advantages and disadvantages of mimotope identification

Assay	Primary strength	Limitation
Enzyme-linked immunosorbent assay (ELISA)	High-throughput serological screening	Solid-phase distortion of conformational epitopes
Radioligand binding assay (RLBA)	Detects native, full-length protein binding	Incapable of residue-level epitope resolution
Split-luciferase binding assay (SLBA)	Quantitative single-residue mapping	High susceptibility to peptide-fragmentation artefacts
Activation-induced marker (AIM) assay	Functional, cytokine-independent read-out	Prone to non-specific activation noise
Peptide-MHC tetramer staining	Precise single-cell specificity	Strictly constrained by specific HLA-restricted alleles

city. Immunoblotting then verifies that the mimotope corresponds to the expected band of the target protein, strengthening the "mimotope-to-native" evidence chain. In rheumatoid arthritis, for instance, a highly antigenic peptide from carbonic anhydrase III (CAIII) discriminates patients from controls in ELISA and maps to the correct CAIII band on western blot, exemplifying successful mimotope antigen alignment [57].

When higher sensitivity or specificity is needed, orthogonal assays are deployed in combination (Table 2). The radioligand binding assay (RLBA) uses ^{35}S-labeled full-length protein as bait to capture serum antibodies; its high signal-to-noise ratio makes it ideal for validating candidate antigens in expanded cohorts, although fine epitope mapping is not possible. Recent large-scale, multidisease studies have employed RLBA to confirm novel autoantigens emerging from PhIP-Seq screens [58]. A split-luciferase binding assay (SLBA) coupled with systematic alanine scanning quantifies the contribution of individual residues to the interaction, pinpointing core 9-mers or critical side chains in a nonradioactive, high-throughput format. A study used SLBA plus residue-level mutagenesis to define viral self cross-reactive epitopes, corroborating the results with downstream functional read-outs [56].

T-cell validation employs tetramer or activation-induced marker (AIM) approaches. Fluorochrome-labeled peptide MHC tetramers fish out antigen-specific T cells when the epitope and restricting HLA allele are known, whereas AIM (CD69, CD137, CD40L, and OX40) captures any peptide-activated T-cell population without a priori epitope information. Used together, they can reveal dual TCR recognition of viral and self-homologs at single-cell resolution [56]. Tetramer staining is constrained by HLA polymorphisms and demands large PBMC numbers, while AIM read-outs were controlled for nonspecific activation (Table 2).

For causal evidence, CNS autoimmunity research relies on EAE. EBNA1 epitopes that mimic GlialCAM exacerbate EAE, functionally linking a viral mimic to CNS demyelination [14]. Cross-disease comparisons highlight the gap between immunological activity and clinical efficacy. In systemic lupus erythematosus, the classic DWEYS decapeptide elicits anti-dsDNA antibodies and glomerular immune deposits in healthy mice, recapitulating a lupus-like phenotype [59]. Conversely, in type 1 diabetes, the altered peptide ligand NBI-6024, despite robust *in vitro* and *in vivo* immunogenicity, failed to preserve β-cell function in a randomized controlled trial, underscoring that epitope affinity does not guarantee therapeutic benefit [60]. These technologies are complementary but have boundary conditions; thus, multidimensional, concordant evidence is required before drawing biological or clinical inferences.

Technological convergence and cohort-driven insights

The EBV-MS model exemplifies a broader phenomenon in which microbial epitopes that mimic self-antigens trigger autoimmunity in genetically susceptible hosts. Large sero-epidemiological studies show that EBV seroconversion precedes MS onset with a hazard ratio of 32 (95% CI: 24–44) after adjusting for other viral exposures [15]. Mechanistically, monoclonal antibodies from MS brain plaques bind to both EBNA1 and GlialCAM with nanomolar affinity, and corresponding T-cell clones recognize both epitopes in the context of HLA-DRB1*15:01 [14]. Analogous mimicry events underpin SARS-CoV-2-associated multisystem inflammatory syndrome in children (MIS-C; viral N-protein vs SNX8) [61], coxsackievirus B-induced type 1 diabetes (2C protein vs GAD65) [62], and *Campylobacter*-triggered Guillain-Barré syndrome (lipooligosaccharide vs GM1 ganglioside). Thus, the "infection-mimicry-loss of tolerance" sequence appears to be a generic etiological engine amenable to therapeutic interception.

However, the causal robustness of this bridge remains contingent on stripping away layers of confounding influences. Linkage disequilibrium between HLA-DRB1*15:01 and high EBV antibody titers requires onboard stratification by six-digit HLA typing and adjustment for polygenic risk scores [63]. CMV, HHV-6 or other coinfections can be quantified with VirScan and bundled into a viral-exposure index to prevent multivirus synergy from inflating immune signals [64]. Smoking, low vitamin D and obesity independently enhance EBV reactivation; standardized questionnaires combined with 6-monthly serum 25-OH-D measurements allow dynamic estimation of interactive effects [65]. The association of microbe-derived flagellin antibodies with disease underscores the need for baseline oral or stool metagenomic sequencing, with diversity or butyrate-production capacity entered as covariates [66]. Most critically, EBV antibody titers follow individual slopes during the asymptomatic window; single-time-point sampling may misclassify a transient peak as a sustained high titer [15]. Prospective studies should therefore collect at least three serial time points and estimate personal slopes with mixed-effect models, replacing conventional single-point odds ratios. Systematically controlling these variables will move the EBV-MS model from strong association to a falsifiable causal framework [67] (Figure 3).

Concluding Remarks

Research into virus-induced autoimmunity is transitioning from hypothesis-driven approaches to a systematic, data-centric paradigm, exemplified by the trajectory of EBV and multiple sclerosis studies [15]. This progression reveals a generalizable framework for autoimmune research, structured around three interconnected pillars.

Etiological discovery begins with unbiased mimotope screening. Technologies such as PhIP-Seq enable proteome-wide antibody profiling [58], while immune peptidomics identifies naturally presented self- and viral peptides, linking molecular mimicry to

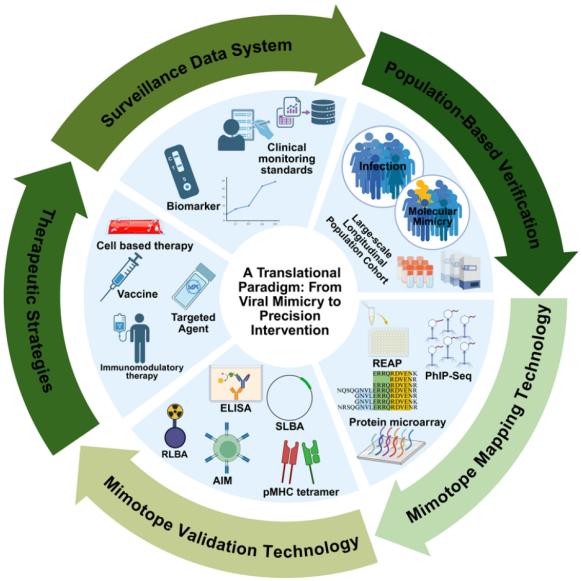


Figure 3. A translational paradigm: from viral mimicry to precision intervention Grounded in large-scale longitudinal population cohorts to establish temporal causal sequences, this integrated framework utilizes high-throughput mimotope mapping technologies and multidimensional validation pipelines to characterize the viral self-cross-reactive landscape. These mechanistic insights facilitate the development of targeted therapeutic strategies, including vaccines, immunomodulatory agents, and cell-based therapies, which are systematically coupled with long-term surveillance data systems and clinical monitoring standards to ensure therapeutic durability and safety, thereby defining a new iterative cycle for the management of infection-driven autoimmune diseases.

aberrant T-cell activation [54]. Deep mutational scanning and AI-based structural prediction further refine epitope characterization [68]. These approaches, integrated with high-throughput immune sequencing and validated in multicenter prospective cohorts, establish a causal foundation while accounting for potential microbial cofactors [15].

Mechanism-based therapy leverages these insights to deliver precision interventions. Moving beyond broad immunosuppression, the focus shifts to selectively targeting pathogenic cells or pathways using small molecules, cellular therapies, or biologics tailored to viral or self-antigens with the goal of re-establishing immune homeostasis [69].

Complication surveillance closes the loop through systematic, long-term monitoring of multiorgan sequelae. Incorporating functional assays, imaging, and biomarkers into follow-up protocols, as exemplified by registries such as MSBase and studies of post-COVID autoimmunity, enables improved outcome tracking and quality of life [70].

Together, these components form an iterative cycle from trigger identification to intervention and outcome assessment. By harmonizing clinical data with multiomics profiling, this framework transforms autoimmune disease management from empiricism into a verifiable, mechanism-guided paradigm (Figure 3).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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