From HLA Association to Tissue Injury

Lessons from Drug Hypersensitivity and Multiple Sclerosis

Simon Mallal[1,2], Amir Asiaee[3] and Elizabeth Phillips[1,2]

[1] Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[2] Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Western Australia

[3] Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Abstract

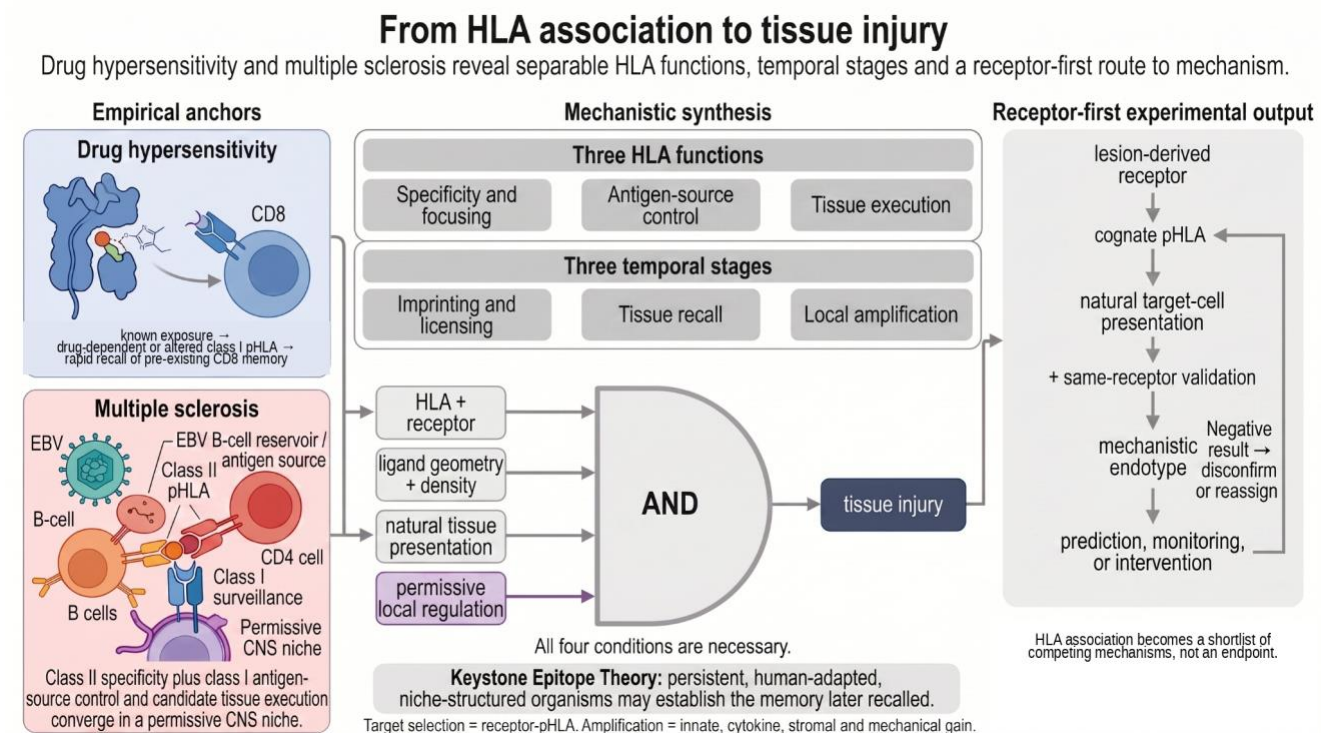
HLA associations are among the strongest genetic signals in immune-mediated disease, yet they rarely explain incomplete penetrance, tissue localization, or opposing effects of different alleles. We use T cell-mediated drug hypersensitivity and multiple sclerosis as complementary mechanistic anchors. Drug hypersensitivity shows that a defined exposure can create or alter a peptide-HLA surface and recruit pre-existing class I-restricted memory. Patch-confirmed abacavir reactions beginning within 36 hours, together with abacavir-responsive cells in drug-unexposed carriers, make de novo naive priming and a concurrent CD4 or B-cell arm non-obligatory at tissue injury. Multiple sclerosis adds a lifelong antigen source and separates HLA-DRB1*15:01-associated class II specificity from class I-dependent control of Epstein-Barr virus antigen pressure and candidate tissue execution. Together, these systems resolve three HLA functions: specificity and focusing, antigen-source control, and tissue execution; and three temporal stages: imprinting and licensing, tissue recall, and local amplification. Injury requires compatible receptor-HLA context, a relevant ligand at sufficient density, natural presentation in the appropriate tissue niche, and permissive local regulation. We separate target selection from innate and cytokine amplification, distinguish antibody-executed disease from cellular architectures, and propose a lesion-anchored receptor-first workflow that converts HLA associations into experimentally adjudicable mechanistic endotypes.

Keywords: HLA; autoimmunity; drug hypersensitivity; multiple sclerosis; Epstein-Barr virus; peptide-HLA; T-cell receptor; tissue-resident memory T cells; molecular mimicry; altered self-presentation; immunopeptidomics

Key points

- Drug hypersensitivity demonstrates rapid class I-restricted tissue recall without obligate de novo naive priming or a concurrent CD4, B-cell, or antibody arm at injury.
- Multiple sclerosis separates class II specificity from class I antigen-source control and candidate tissue execution, which can point in opposite directions in the same individual.
- HLA effects are decomposed into specificity and focusing, antigen-source control, and tissue execution; disease evolves through imprinting, recall, and amplification.
- Clinical injury requires a conjunctive gate comprising receptor-HLA compatibility, a relevant ligand at sufficient density, natural tissue presentation, and permissive local regulation.
- A lesion-anchored receptor-first workflow converts HLA association into mechanistic endotypes with prespecified disconfirming results.

Abbreviations: AChR, acetylcholine receptor; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; MS, multiple sclerosis; NPV, negative predictive value; pHLA, peptide-HLA; PPV, positive predictive value; PTM, post-translational modification; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TCR, T-cell receptor; Tfh, follicular helper T cell; Treg, regulatory T cell; TRM, tissue-resident memory T cell.



Graphical abstract. Drug hypersensitivity and multiple sclerosis are complementary empirical anchors. Together they separate three HLA functions (specificity and focusing, antigen-source control, and tissue execution) from three temporal stages (imprinting and licensing, tissue recall, and local amplification). Clinical injury requires the conjunction of compatible HLA-receptor context, a relevant ligand at sufficient density, natural presentation in the appropriate tissue niche, and permissive local regulation. A lesion-derived receptor workflow links cognate pHLA, natural target-cell presentation, same-receptor validation, mechanistic endotyping, and prediction or intervention. Keystone Epitope Theory is shown as one testable source hypothesis for the memory later recalled.

1. The HLA paradox and scope

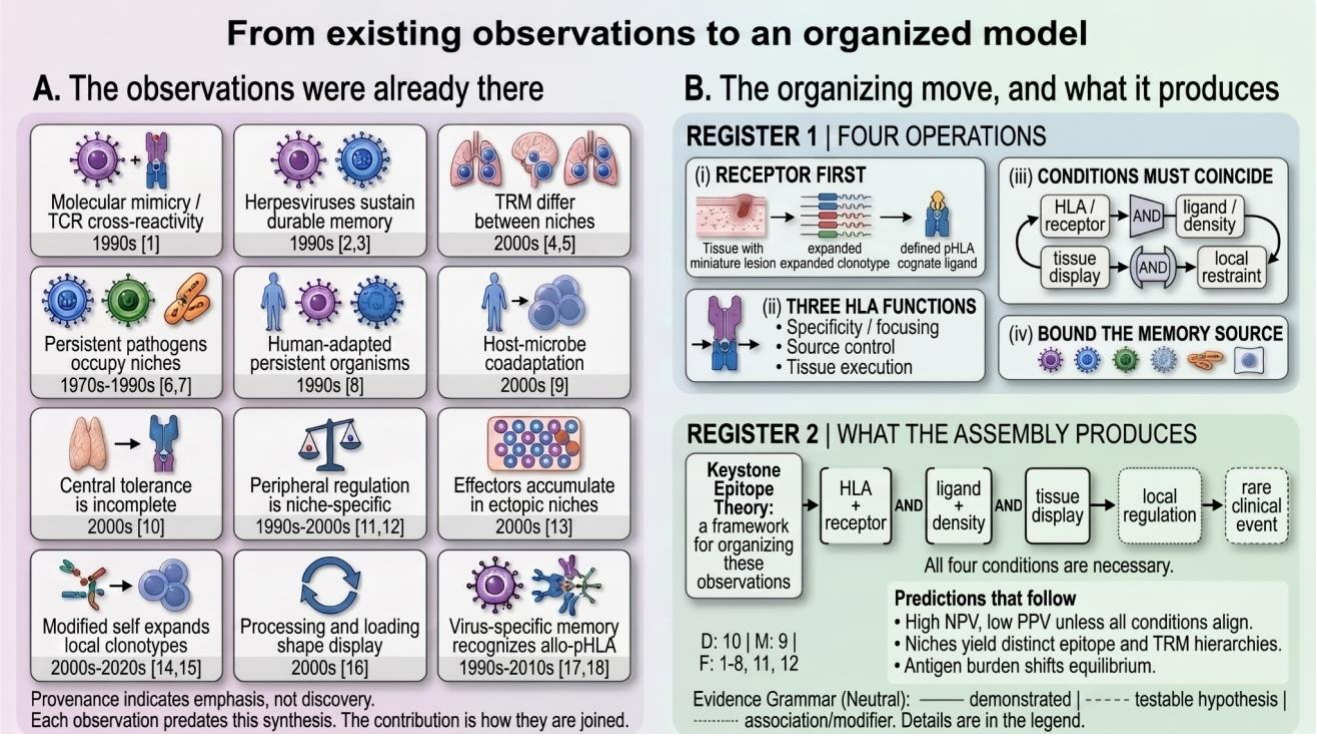


Figure 1. From existing observations to an organized model. Panel A surveys established observations that predate the present synthesis: molecular mimicry and TCR cross-reactivity; durable herpesvirus-specific memory; tissue-specific TRM populations; pathogen-specific niches; human adaptation and host-microbe coadaptation; incomplete central tolerance; niche-specific peripheral regulation; ectopic immune-cell accumulation; modified-self presentation with local clonal expansion; antigen processing and loading; and allo-pHLA recognition by virus-specific memory. The numbered brackets correspond to the primary anchors listed in the references [1-18]. Panel B applies four operations: begin with the lesion-derived receptor; separate specificity and focusing, antigen-source control, and tissue execution; require compatible receptor-HLA context, a relevant ligand at sufficient density, natural tissue presentation, and permissive local regulation to coincide; and bound the candidate source of entrenched memory. Keystone Epitope Theory is named here as a framework for organizing established observations into a falsifiable model, not as the source of those observations. Solid relationships are demonstrated, dashed relationships are testable hypotheses, and dotted relationships are associations or modifiers.

HLA associations can be extraordinarily strong while remaining mechanistically incomplete. In T cell-mediated drug hypersensitivity, positive predictive values range from approximately 0.12% for HLA-B*57:01-associated flucloxacillin liver injury to approximately 55% for immunologically confirmed HLA-B*57:01-associated abacavir hypersensitivity, with most drug-HLA pairs below 10% [19-21]. HLA can therefore be necessary for a narrowly defined phenotype without being sufficient to produce it. Genotype alone also fails to explain why injury localizes to one tissue, why it begins at one time, or why one allele protects while another increases risk in the same disease.

T cell-mediated drug hypersensitivity and multiple sclerosis (MS) provide complementary rather than interchangeable mechanistic anchors. Drug hypersensitivity is not autoimmunity, but it is unusually tractable: exposure is known, the associated HLA can be defined at high resolution, drug-dependent or drug-altered peptide-HLA (pHLA) surfaces can be measured, and the acute lesion can contain the relevant effector population. MS adds a lifelong antigen source, class II-restricted CD4 and B-cell organization, independent class I effects, restricted access to the target tissue, and immune features measured after onset that may be consequences rather than causes.

We use these anchors to resolve different parts of one causal chain. Drug hypersensitivity asks how an established cellular repertoire can be redirected rapidly toward a newly displayed tissue ligand. MS asks how specificity, control of a persistent antigen-bearing reservoir, and tissue execution can be distributed across different HLA alleles and then converge in a permissive CNS niche. Figure 1 assembles the

established observations and the operations used to organize them. The review then distinguishes two broad cellular architectures, an antibody-executed comparator, and a lesion-anchored workflow in which every proposed mechanism has a named disconfirming result.

2. Drug hypersensitivity reveals rapid class I-restricted recall

T cell-mediated drug hypersensitivity provides the most tractable human model of class I-restricted tissue recall because the perturbing small molecule exposure is known and can be introduced experimentally. The upstream chemistry differs among drugs. Covalent haptenation modifies a self protein or peptide; abacavir binds noncovalently within HLA-B*57:01 and alters the presented self repertoire; carbamazepine-associated SJS/TEN involves drug-dependent recognition of peptide-loaded HLA-B*15:02 rather than the same F-pocket mechanism [14 22]. These routes converge on one downstream problem: an HLA class I surface that was previously absent or quantitatively unimportant becomes recognizable to cytotoxic T cells in a specific susceptible tissue.

This distinction separates repertoire permissiveness from disease. Abacavir-responsive CD8 T cells can be expanded from many drug-unexposed HLA-B*57:01-positive donors, yet only a minority of exposed carriers develop hypersensitivity [23]. The risk allele creates a repertoire in which drug-dependent recognition is possible; it does not specify which clonotypes are present, their differentiation state, the source cell displaying the relevant self-peptide, ligand abundance, or the regulatory threshold of the affected tissue. HLA screening is effective because absence of the allele removes a necessary condition. Positive predictive value remains incomplete because the remaining conditions are not measured.

Clinical timing argues that pre-existing memory contributes directly in at least some patients. PREDICT-1 used epicutaneous patch testing to distinguish immunologically confirmed abacavir hypersensitivity from clinically similar syndromes [19]. In a later analysis of the patch-confirmed cases in this blinded randomized trial, symptoms began from 36 hours to 19 days after exposure, with a median of 8 days; 26% began between 36 hours and day 5 [19 23]. Onset at 36 hours is difficult to reconcile with de novo generation of a high-frequency naive response. Conversely, onset during the second or third week does not establish naive priming. It can reflect selection and expansion of rare cross-reactive memory clonotypes, acquisition of effector function, trafficking, and tissue accumulation. Clinical latency is therefore a mixture signal, not a reliable classifier of memory-derived versus naive-derived disease.

The same evidence clarifies the role of CD4 T cells. CD4 help can increase the magnitude or durability of CD8 memory, and CD4-dependent regulatory circuits can determine whether an abacavir-reactive repertoire remains clinically silent [24 25]. These are modulatory roles rather than obligatory steps in proximal class I-mediated tissue injury: the disease-associated drug ligand need not recruit a class II-restricted response, and the reaction can proceed without a concurrent CD4, B-cell, or disease-defining antibody arm. Thus, CD4 cells may shape repertoire formation or tolerance, while an already competent CD8 T cell directly recognizes drug-dependent or altered-self class I pHLA on the target cell.

Danger should be separated in the same temporal way. Inflammatory and costimulatory signals may be important when durable competence is first established during infection, vaccination, or another immunizing encounter. A new danger event need not recur at later drug exposure if competent memory encounters a naturally displayed ligand in a permissive tissue context. Checkpoint tone, cytokines, tissue damage, and innate cells can increase presentation, recruitment, and effector gain, but they need not select the antigenic target. Target selection resides in the receptor-pHLA interaction; innate and inflammatory responses may amplify what follows.

Tissue localization provides an independent constraint. In SJS/TEN, keratinocytes can display the drug-dependent class I surface and are principal targets of cytotoxic injury. Blister-fluid and lesional studies show oligoclonal cytotoxic populations and tissue-specific immune states rather than a uniform systemic response [15 26]. HLA and drug are therefore insufficient. The ligand must be naturally generated in the affected epithelial compartment, the relevant clonotype must reach or occupy that compartment, and net signaling must exceed local inhibitory control. These requirements explain how systemic exposure can produce sharply localized pathology.

The microbial origin of the responsive memory remains a testable proposition, not an established property of every drug reaction. Sooda and colleagues cloned dominant HLA-B*57:01-restricted EBV-specific TCRs and found that they did not recognize the tested abacavir-self complexes in several cell systems; abacavir instead inhibited their cognate EBV pHLA recognition [27]. The latter finding raises a separate possibility that abacavir transiently weakens EBV surveillance and increases antigenic pressure, a source-control effect conceptually parallel to the class I axis in MS. Such an effect cannot by itself account for the fever, rash, gastrointestinal, and systemic manifestations of abacavir hypersensitivity; direct recognition of abacavir-altered self pHLA and tissue injury remain necessary components. Importantly, an HIV Gag TW10/HLA-B*57:01-restricted memory clone has been shown to recognize autologous HLA-B*57:01 only in the presence of abacavir, providing proof of principle that pathogen-selected class I memory can be redirected by the drug [28]. A clinically relevant HLA-B*57:01-restricted receptor that recognizes both a microbial epitope and an abacavir-state self pHLA remains plausible but has not yet been identified. The Sooda result therefore excludes those receptors, ligands, and assay contexts rather than the broader hypothesis. A defensible test begins with a prespecified source-cell panel, identifies naturally presented abacavir-state self-peptides, and asks whether patient-derived receptors recognize both altered self and a bounded set of candidate microbial pHLA complexes.

Drug hypersensitivity therefore contributes more than a list of HLA associations. It demonstrates that class I-restricted tissue injury can involve rapid recall of pre-existing cellular competence; that neither de novo naive priming nor a concurrent class II, B-cell, or antibody program is obligatory; that danger and innate responses can be temporally displaced from target recognition; and that HLA, ligand, receptor, tissue display, and local regulation must be measured separately. Figure 2A summarizes this mechanistic anchor.

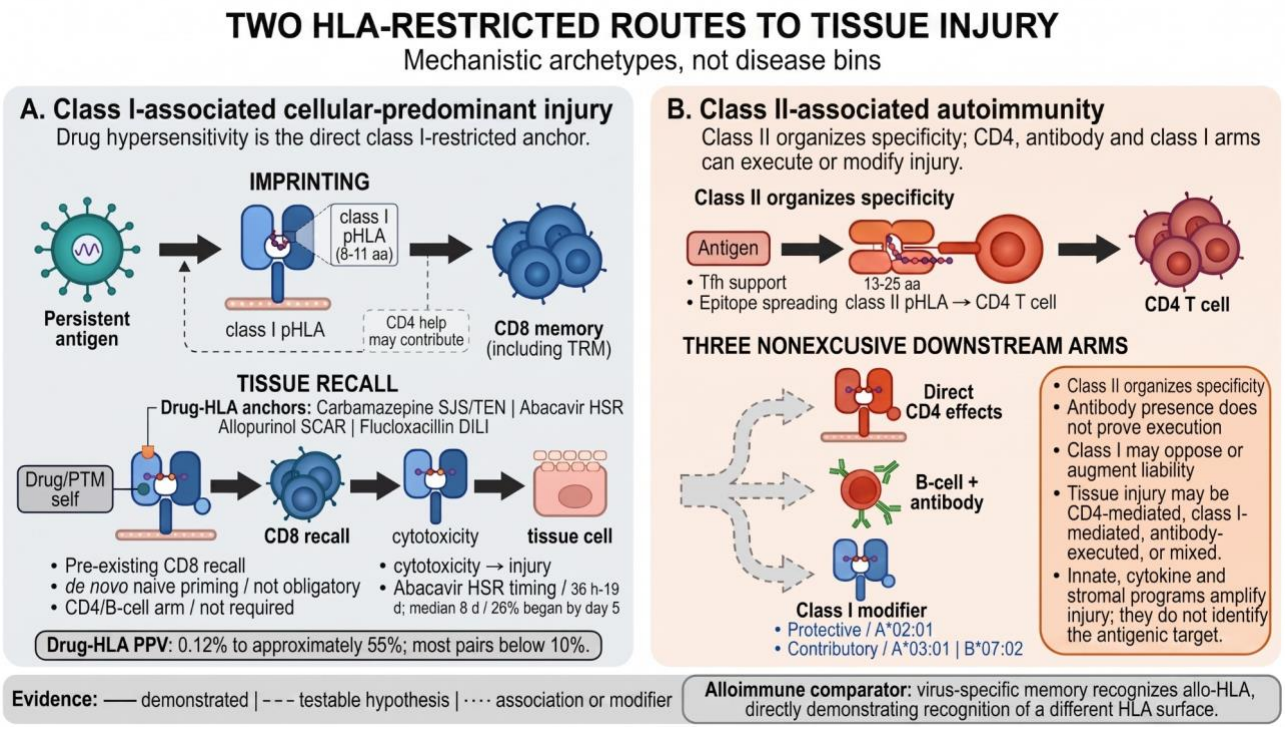


Figure 2. Two HLA-restricted routes to tissue injury. Panel A shows class I-associated, cellular-predominant injury, using T cell-mediated drug hypersensitivity as the direct receptor-level anchor. HLA class I typically presents peptides of 8 to 11 amino acids. A drug-dependent, drug-altered, post-translationally modified, or mimetic pHLA surface can recruit an already competent CD8 population; no class II-restricted response to the disease-associated ligand and no concurrent CD4, B-cell, or disease-defining antibody arm is obligatory at tissue injury. CD4 help may contribute during imprinting. The abacavir inset summarizes the patch-confirmed PREDICT-1 timing distribution: onset from 36 hours to 19 days, median 8 days, with 26% beginning by day 5. Panel B shows class II-associated autoimmunity. HLA class II typically presents peptides of 13 to 25 amino acids and organizes CD4 specificity, Tfh support, B-cell differentiation, and epitope spreading. Tissue injury may then be mediated by direct CD4 effects, antibody execution, a protective or contributory class I arm, or a mixture. The grey footer presents alloimmunity as a comparator: virus-specific memory frequently recognizes allo-HLA, directly demonstrating that pathogen-selected memory can recognize a different HLA surface.

3. Multiple sclerosis separates specificity, antigen-source control and tissue execution

MS adds the features that drug hypersensitivity leaves experimentally fixed: the antigen source persists for life, the dominant risk association is class II, B cells organize both viral persistence and intrathecal immunity, and the target tissue is difficult to sample before secondary recruitment obscures the initiating event. EBV exposure precedes most MS studied prospectively and is associated with a marked increase in risk, yet EBV is nearly universal and cannot be sufficient [29]. The mechanistic problem is not simply to connect EBV with MS, but to identify which HLA-restricted program, acting on which antigen-bearing cell and in which CNS compartment, converts common infection into uncommon disease.

Unlike HLA-A*02:01 and HLA-A*03:01, HLA-DRB1*15:01 has not shown a consistent relationship with detectable circulating EBV DNA and is better interpreted as a qualitative determinant of which EBV and self-peptides are presented to CD4 T cells [30] [31]. It is therefore most plausibly assigned to specificity and focusing rather than used as a surrogate for viral burden. Recent studies support two nonexclusive class II routes. EBNA1 and ANO2 can recruit cross-reactive CD4 populations with overlapping receptor solutions and activated or cytotoxic phenotypes [32]. Independently, EBV infection can remodel the HLA-DRB1*15:01 immunopeptidome and increase presentation of myelin-derived self-peptides without requiring viral-self sequence homology [33]. These mechanisms differ, but both place the class II pHLA surface and responding receptor upstream of generic inflammation.

Class I associations appear to act on a partially separate axis. HLA-A*02:01 is associated with lower MS risk and more effective control of detectable circulating EBV DNA, making protective antiviral surveillance a plausible function [34] [31]. HLA-A*03:01 has been associated with increased detectable EBV DNA, whereas HLA-B*07:02-related findings concern response breadth, exhaustion, CNS-homing phenotypes, and higher anti-EBNA1 responses in particular HLA combinations [30] [35]. These observations should remain separate. They do not establish that HLA-A*03:01 or HLA-B*07:02 directly presents a CNS ligand recognized at tissue injury. Whether either background also contributes through EBV-self cross-reactivity remains an open question and should be tested using the receptor-first workflow in Section 7.

The negative class I result is therefore central, not inconvenient. Expanded EBV-specific CD8 clonotypes recovered from MS CSF or lesions recognized viral antigens, but the tested receptors did not recognize the screened homologous self-peptides [36]. Limited receptor and peptide coverage prevents global exclusion of native or modified CNS ligands. The study nevertheless excludes the claim that EBV specificity alone establishes pathogenic molecular mimicry. Some lesion-enriched CD8 cells may represent protective antiviral surveillance, some may contribute through an untested ligand, and others may be secondary recruits. Receptor, exact HLA, natural target-cell presentation, and function must be resolved before causality is assigned.

B cells create a second functional separation. They are the persistent reservoir for EBV, professional antigen-presenting cells for class II recall, sources of antibody and cytokines, and potential residents of perivascular or meningeal inflammatory niches. Meningeal follicle-like structures and B-cell-rich perivascular compartments are associated with local T-cell interactions and tissue injury in subsets of MS, but abundant EBV-positive cells are not consistently detected at every active site [13] [37]. The relevant question is whether an EBV-affected or antigen-bearing B-cell compartment sustains sufficient presentation, survival signals, or recruitment to amplify a receptor-defined response.

The CNS adds an anatomical gate. Gadolinium enhancement can precede conventional lesion evolution, showing that focal blood-brain barrier permeability is an early feature of many new lesions [38] [39]. It does not identify the initiating leukocyte population or prove that infected memory B cells enter first. Activated T cells, monocytes, endothelial changes, and B cells may contribute in different sequences. Once access is available, perivascular or meningeal niches can support recall, local survival, antigen capture, and epitope spreading. The same antiviral effectors that constrain EBV in lymphoid tissue could become damaging if a cross-reactive clonotype encounters an inadequately tolerated CNS pHLA surface

in this ectopic context. In the predator analogy used in Figure 3, the cross-reactive clonotype is the predator; the persistent organism is the sustaining antigen source.

Humoral findings should likewise be assigned to the correct endpoint. Oligoclonal IgG, anti-EBNA1 titers, Fc properties, and a preclinical autoantibody-defined minority endotype may report antigen exposure, class II focusing, B-cell selection, amplification, or direct antibody injury in particular patients [40]. They do not establish one universal antibody-executed mechanism for MS. Class II association does not make antibody obligatory, just as antibody detection does not prove that antibody is the proximal tissue-damaging effector.

MS therefore shows why an HLA association should not be treated as one variable. HLA genotype can distribute at least three functions: specificity and focusing of memory, control of the persistent antigen source, and tissue execution through recognition of the surface displayed at injury. HLA-DRB1*15:01, HLA-A*02:01, HLA-A*03:01, and HLA-B*07:02 may influence different functions and can point in opposite directions in the same individual. Clinical disease requires those functions to converge with CNS access, natural ligand presentation, and permissive local regulation. Figure 3 presents this endpoint-separated architecture and keeps demonstrated class II mechanisms distinct from candidate class I tissue execution.

Environmental and physiological modifiers should be positioned against the component they alter rather than listed as independent causes. Primary EBV timing acts principally on imprinting; vitamin D and ultraviolet exposure may influence HLA-DRB1*15:01 expression and regulatory calibration [41]; smoking can modify HLA-associated risk, anti-EBNA1 responses, and inflammatory tone [42] [43]. HLA and ERAP variation shape peptide supply and reservoir control, blood-brain barrier and endothelial state shape access, and checkpoint tone shapes local restraint. Table 1 positions these modifiers within the analytical architecture.

Table 1. Major MS modifiers and their position in the analytical architecture

Modifier	Position in the model	What to measure	Interpretation
Primary EBV timing and inflammatory context	Imprinting and licensing	Age at infection; infectious mononucleosis; EBV strain; clonotype breadth and homing	A modifier of repertoire formation, not a sufficient cause.
Vitamin D and ultraviolet exposure	Class II expression and regulatory calibration	25-hydroxyvitamin D; UV exposure; VDR activity; HLA-DRB1*15:01 expression; Treg and activation thresholds	Test as a modifier of specificity or restraint, not as a single pathway [41].
Smoking	Antigen pressure and local amplification	Smoking exposure; HLA interaction; anti-EBNA1 features; inflammatory and endothelial state	May increase antigen pressure or reduce restraint [42] [43].
HLA and ERAP variation	Peptide supply and antigen-source control	High-resolution HLA and ERAP genotype; immunopeptidome; EBV DNA or transcript burden; receptor function	Effects are endpoint-, allele-, and substrate-specific [30] [31].
BBB and endothelial state	Access to the CNS niche	Dynamic MRI; adhesion molecules; junctional integrity; endothelial activation; T- and B-cell trafficking	Separate focal access from EBV reservoir burden [38] [39].
Checkpoint and regulatory tone	Permissive local regulation	PD-1/PD-L1; CTLA-4; Treg; cytokines; ligand density; activation thresholds	Determines whether receptor-defined recall becomes injury.

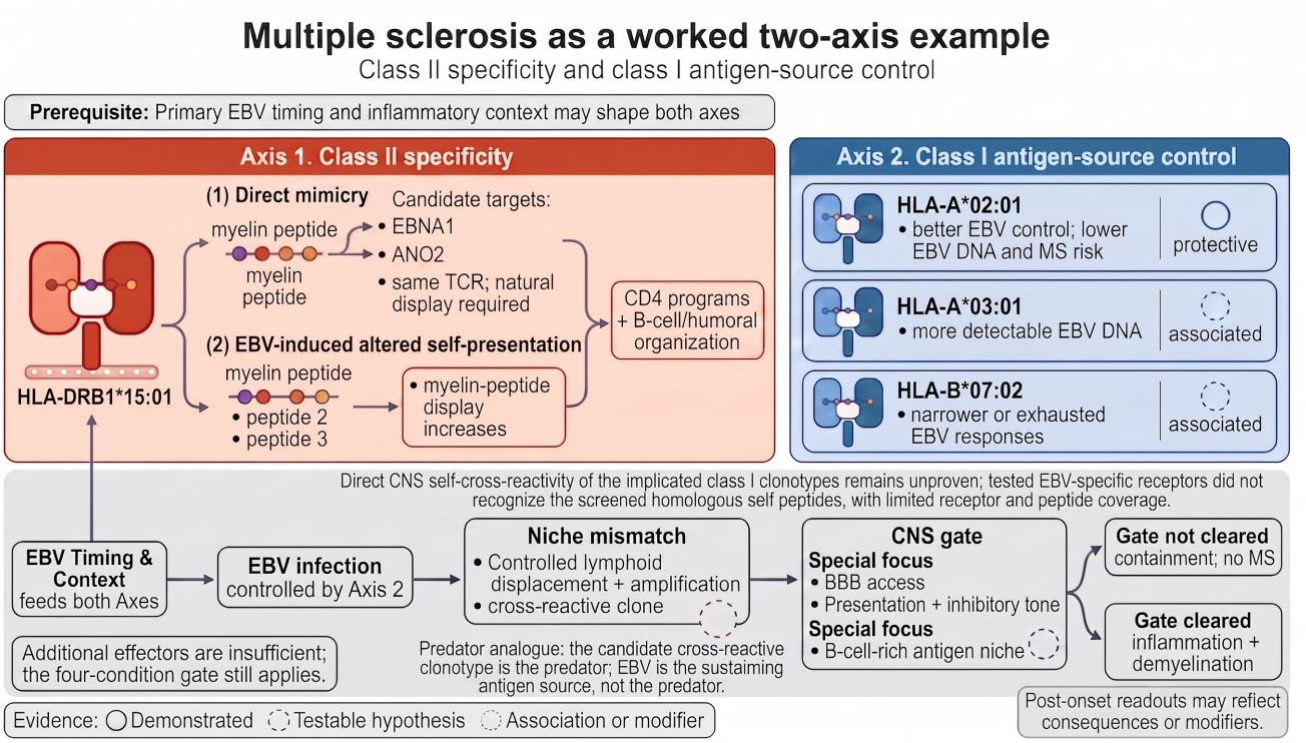


Figure 3. Multiple sclerosis as a worked two-axis example. The figure separates HLA-DRB1*15:01-associated class II specificity from class I-dependent control of EBV antigen pressure and candidate tissue execution. Axis 1 shows two nonexclusive class II routes: receptor-level EBNA1-ANO2 cross-recognition and EBV-induced remodeling of the HLA-DRB1*15:01 self-immunopeptidome. Axis 2 distinguishes HLA-A*02:01-associated protective antiviral control from HLA-A*03:01- and HLA-B*07:02-associated contexts with different evidence concerning detectable EBV DNA, response breadth, exhaustion, and CNS-homing phenotypes. Direct CNS self-cross-reactivity of the implicated class I clonotypes is yet to be proven; the tested EBV-specific receptors did not recognize the screened homologous self-peptides, but TCR and peptide coverage were limited. The lower register depicts focal BBB access, B-cell-rich antigen-amplifier niches, natural presentation, and inhibitory tone as the CNS gate. In the limited predator-spillover analogy, the candidate cross-reactive clonotype is the predator, and EBV is the sustaining antigen source. Additional effectors are insufficient unless the four-condition gate is cleared. Post-onset EBV DNA, antibody features, exhaustion, CNS residency, oligoclonal bands, treatment effects, and epitope spreading may be consequences or modifiers rather than the initiating liability.

4. What the two anchors jointly reveal

Taken together, drug hypersensitivity and MS show that an HLA association is a coordinate in a causal system, not the system itself. Drug hypersensitivity makes the exposure, restricting allele, altered ligand, and acute tissue response experimentally accessible. MS reveals what becomes visible when the antigen source persists, and different alleles influence different endpoints. Together, they provide a decomposition that can be applied without assuming whether the dominant downstream executor is CD8 T cells, CD4 T cells, antibody, or an innate amplifier.

First, HLA genotype distributes three separable functions. Specificity and focusing determine which pHLA-specific memory is built and maintained. Antigen-source control determines how effectively a persistent antigen-bearing cell or reservoir is constrained. Tissue execution determines which pHLA surface is recognized at injury. In a drug reaction, the same class I allele can shape the responsive repertoire and later display the drug-dependent target, while control of the memory-forming pathogen is usually not the proximate variable that starts the reaction. In MS, HLA-DRB1*15:01 is most plausibly assigned to qualitative class II specificity, whereas HLA-A*02:01 is consistent with protective control of EBV antigen pressure. HLA-A*03:01 and HLA-B*07:02 may mark less effective or qualitatively different antiviral control [30] [31]. A second, unresolved possibility is that class I-restricted clonotypes in these backgrounds directly recognize a CNS self or altered-self ligand; this candidate tissue-execution mechanism requires same-TCR, exact-HLA, and natural-presentation evidence. One allele can perform more than one function, and alleles in the same individual can point in opposite directions.

Second, disease evolution separates into three temporal stages. In this review, imprinting denotes the selective expansion, differentiation, and anatomical positioning of antigen-experienced clonotypes during an initial immune encounter. Licensing denotes acquisition of durable effector competence and the regulatory set-points that govern later recall; it is not used here in the NK-cell education sense. These processes usually occur in a context that supplies inflammation and costimulation.

They need not be repeated at injury. In drug hypersensitivity, an already licensed cross-reactive memory clone may respond directly to a newly displayed drug-dependent or altered-self class I pHLA and breach local restraint without a new round of naive priming. Tissue recall occurs when licensed memory later encounters a native, modified, mimetic, or infection-remodeled ligand. Local amplification then determines the magnitude and persistence of injury through cytokines, innate cells, stromal programs, barrier access, mechanical inputs, and regulatory failure. This temporal separation accommodates an important role for danger during initial licensing and later amplification without requiring a new danger event to select the target at every recall episode [23] [26].

Third, clinical injury requires a conjunctive four-condition gate: (i) compatible HLA and receptor context; (ii) compatible ligand geometry at sufficient density; (iii) natural presentation in the relevant tissue niche; and (iv) permissive local regulatory conditions. Antigen burden belongs within the ligand condition. The gate is not a product in which an extreme value for one factor compensates for absence of another. Failure of any necessary condition blocks the defined event. This architecture explains why absence of a narrowly required allele can provide high negative predictive value while possession of the allele has low positive predictive value. It also identifies what must be measured beyond genotype: receptor availability, natural ligand display, anatomical co-localization, and inhibitory tone.

These decompositions impose evidence discipline. An allele association does not establish receptor-level restriction; an expanded pathogen-specific clone in a lesion does not establish pathogenic cross-recognition; an autoantibody does not establish antibody execution; and a phenotype measured after onset does not automatically identify the pre-onset liability. Each observation must be assigned to the endpoint it measures. This is especially important in MS, where blood EBV DNA, exhaustion, CNS residency, antibody Fc state, and oligoclonal bands can reflect predisposition, established disease, treatment, or combinations of these states [36] [35] [31].

At this point, we use Keystone Epitope Theory to name the organizing hypothesis that persistent, human-adapted, niche-structured organisms can focus durable memory on conserved pHLA targets, creating vulnerability when a tissue ligand recruits the same receptor program above local restraint [26]. The established observations, three HLA functions, and four-condition gate do not depend on accepting that source hypothesis. The source claim is independently falsifiable. A lesion-derived receptor that maps coherently to native or modified self without a demonstrable persistent-organism imprint would support antigen-specific disease while weakening the strict keystone explanation for that endotype. Figure 1 therefore presents a provisional synthesis and the operations used to correct it, not a completed taxonomy. Table 2 contrasts what each empirical anchor resolves and the general inference that follows.

Table 2. What the two empirical anchors resolve

Mechanistic question	Drug hypersensitivity	Multiple sclerosis	General inference
Antigen source or exposure	Known small-molecule exposure; the altered or drug-dependent pHLA can be generated experimentally.	Persistent EBV B-cell reservoir; antigen quantity, state, and location are incompletely observed.	Separate the source of immune memory from the tissue ligand recognized at injury.
HLA functions most directly resolved	Specificity and focusing plus tissue execution.	Class II specificity, class I antigen-source control, and candidate class I execution.	HLA genotype distributes separable functions rather than acting as one risk variable.
Temporal inference	Very early reactions can recruit pre-existing CD8 memory; later onset does not prove naive priming.	Primary EBV timing may shape imprinting; CNS injury is later recall and amplification.	Imprinting, tissue recall, and amplification should be analyzed separately.
Proximal tissue effector	Class I-restricted CD8 cellular injury is directly testable.	CD4, CD8, B-cell, antibody, and myeloid contributions vary by endotype.	The tissue executor must be demonstrated rather than inferred from HLA association.

Mechanistic question	Drug hypersensitivity	Multiple sclerosis	General inference
Tissue access	Blister fluid and affected skin permit direct lesion sampling.	CSF provides partial access; early CNS parenchyma is rarely available.	The strength of positive and negative evidence depends on tissue and disease stage.
Decisive unresolved question	Which pre-existing receptor recognizes the drug-dependent or altered-self pHLA?	Which receptor-HLA-ligand circuit links EBV biology to CNS injury?	Start from the lesion-derived receptor and require natural presentation and same-receptor validation.

5. Two cellular archetypes and an antibody-executed comparator

The resulting categories are mechanistic archetypes, not permanent disease bins. They describe where specificity is organized and which arm executes tissue injury. A diagnostic label may contain more than one endotype, and the dominant architecture may change with tissue or disease stage. Figure 2 and Supplementary Table S1 compare the three patterns.

In class I-associated, cellular-predominant immunopathology, an 8- to 11-amino-acid peptide is displayed by HLA class I on the target cell and recognized by a CD8 receptor. Drug hypersensitivity provides the direct receptor-level anchor: a disease-antigen-specific class II response, disease-defining autoantibody, and concurrent CD4 or B-cell arm are not obligatory at tissue injury. CD4 help may contribute when memory is formed, but it is not a defining requirement of the proximal class I drug reaction. Tissue localization follows the conjunction of target-cell expression, peptide processing, HLA display, receptor availability, and local amplification. Selected drug reactions and HLA-C*06:02-positive psoriasis have receptor-level evidence linking a defined pHLA surface to disease-relevant T cells [14] [22] [44]. In many spontaneous class I-associated diseases, only the allele association or pathway genetics is established; the exact pathogenic receptor, peptide, and restricting HLA remain to be demonstrated. The terminology should preserve that evidentiary distinction: disease categories are class I-associated, whereas class I-restricted is reserved for demonstrated receptor biology.

In class II-associated autoimmunity, 13- to 25-amino-acid peptides presented by HLA-DR, HLA-DQ, or HLA-DP organize CD4 specificity. The downstream response can diverge into direct inflammatory or cytotoxic CD4 activity, Tfh-dependent B-cell and antibody programs, or a class I arm that protects through antigen-source control or contributes to tissue execution. MS illustrates why these branches must remain separate: class II can focus the EBV and self-response while class I background modifies reservoir control, and antibodies can mark exposure or amplify disease without being the universal proximal executor. Type 1 diabetes and celiac disease similarly combine strong class II organization with important cellular tissue-execution programs [45] [46] [47].

As summarized in Supplementary Figure S1, the antibody-executed group is defined more strictly. Antibody is assigned as the proximal effector only when target-specific transfer, receptor modulation, adhesion disruption, complement- or Fc-dependent injury, or an equivalent causal experiment has been demonstrated. Class II associations can be strong because class-switched, affinity-matured autoantibodies usually require CD4 and Tfh support, but those cells need not remain at the tissue when antibody acts. AChR myasthenia gravis, AQP4-IgG-positive neuromyelitis optica spectrum disorder, and pemphigus vulgaris illustrate receptor dysfunction, complement- or Fc-mediated injury, and adhesion failure, respectively [48] [49] [50]. This is not a purely humoral disease: cellular immunity builds and regulates the response, while antibodies execute the defining lesion. Antibody-positive autoimmune nodopathies belong in this group when NF155-, CNTN1-, or related antibodies directly disrupt nodal or paranodal function, although the strength of transfer evidence varies by target and antibody subclass.

The archetypes predict different decisive readouts. Class I cellular disease requires a coherent target-cell pHLA, lesion-enriched receptor, and functional cellular injury circuit. Class II-associated mixed disease requires assignment of class II specificity separately from any protective or damaging class I arm and from antibody function. Antibody-executed disease requires target-specific causal evidence, not merely seropositivity. Predictive values are not intrinsic properties of HLA class. They depend on prevalence, exposure, phenotype definition, ancestry, the allele or haplotype tested, and how closely the assay approaches the proximal mechanism.

6. Applying the architecture across diseases

Supplementary Tables S2A and S2B apply the architecture across selected diseases without forcing one diagnosis into one box. The useful question is not which label a disease receives, but which HLA function, ligand, tissue compartment, and proximal effector are demonstrated in a defined endotype, and what observation would reassign that conclusion.

Psoriasis provides the clearest spontaneous class I-associated example. A lesion-derived CD8 receptor recognizes the melanocyte antigen ADAMTSL5 in HLA-C*06:02, and ERAP1 controls generation and abundance of the presented epitope [44,51]. This establishes a native-self pHLA-receptor circuit while leaving its initiating history unresolved. IL-17, TNF, keratinocytes, dendritic cells, and neutrophils amplify the lesion but do not substitute for the antigenic target. Psoriasis therefore shows why target selection and tissue gain should be measured separately.

Type 1 diabetes and celiac disease reveal a different distribution of functions. In type 1 diabetes, HLA-DQ2.5 and HLA-DQ8 strongly organize class II risk, and multiple islet autoantibodies stage progression. HLA-A2-restricted CD8 T cells recognize naturally presented preproinsulin and other beta-cell peptides and can kill beta cells, providing a receptor-defined tissue-execution arm [52 45 53 54 55]. Pancreatic CD8 TCRs and self-targets are increasingly resolved, but systematic testing against persistent-virus epitopes and infection-remodeled self remains limited. A recent pancreatic-TCR study identified strongly beta-cell-reactive CD8 populations selectively in type 1 diabetes and found no beta-cell cross-reactivity among the virus-specific pancreatic receptors tested [56]. This is a bounded negative result rather than a comprehensive exclusion of persistent-virus or modified-self mechanisms.

In celiac disease, HLA-DQ2.5- or HLA-DQ8-restricted gluten-specific CD4 cells and transglutaminase 2-dependent deamidation define the afferent antigenic program. HLA-A2-restricted gliadin-specific CD8 responses and enriched gluten-triggered CD8 TCR rearrangements in duodenal tissue support an epithelial tissue-execution compartment [57 58 46 47]. Microbial-gliadin cross-reactivity, natural processing, and TCR-pHLA structural convergence have already been demonstrated for the class II arm [59]. A comparable persistent-organism or modified-self cross-reactive mechanism in the CD8 epithelial-effector compartment has not been systematically excluded.

Disease-defining antibodies are diagnostically powerful in both type 1 diabetes and celiac disease, but their presence does not establish antibody execution. Here, antibody execution means that antigen-specific antibody is itself a proximal cause of target dysfunction or injury, demonstrated by transfer, receptor modulation, complement or Fc dependence, or equivalent causal evidence. Diagnostic autoantibodies do not exclude T-cell mechanisms, including KET-type mechanisms, unless such causal antibody evidence is obtained.

Post-translational modification provides a bridge across otherwise different diseases. A drug can alter the HLA-bound repertoire or create a drug-dependent surface; citrullination generates or strengthens HLA-DR-restricted targets in rheumatoid arthritis; and transglutaminase 2 deamidation increases gluten peptide recognition in celiac disease. Citrullinated tenascin-C and vimentin-specific CD4 responses, together with anti-citrullinated peptide antibodies that precede arthritis, establish an important class II, PTM, and antibody-amplified architecture in rheumatoid arthritis [60 61 62]. Rheumatoid synovium also contains perforin-positive cytotoxic CD4 populations and clonally expanded granzyme K-positive CD8 cells [63 64]. Exact class I pHLA-TCR circuits and persistent-microbial imprinting of these cytotoxic CD4 or CD8 populations have not been mapped systematically; a contributory KET-type cellular mechanism is therefore neither demonstrated nor excluded.

Isolevuglandin (IsoLG) adduction in hypertension provides a particularly informative modified-self example. Recent work identified H-2Db-restricted IsoLG-adducted self-peptides recognized by tissue-enriched effector-memory CD8 T cells and showed that peptide-pulsed dendritic cells could augment hypertension after adoptive transfer [65 66]. Human HLA alleles also differed in their capacity to display IsoLG-adducted peptides. These findings provide strong proof of principle for class I-restricted modified-self recognition without a required antibody executor; a persistent microbial memory source, and therefore a strict KET mechanism, remains to be tested.

Diseases that do not fit cleanly within one archetype are particularly useful because they expose which variables remain unresolved. Narcolepsy type 1 combines an exceptionally strong HLA-DQB1*06:02 association with selective hypocretin-neuron loss, autoreactive CD4 and CD8 cells, and no reproducible disease-defining autoantibody [67] [68] [69]. The proximal receptor-pHLA circuit and tissue executor remain incompletely defined.

Axial spondyloarthritis is provisionally placed within the class I-associated, cellular-predominant group. HLA-B*27:05, ERAP1, disease-associated TCRs recognizing bacterial and self-peptides, absence of a disease-defining autoantibody, and restricted enthesial or axial injury support that assignment [16] [70] [71]. IL-17, TNF, stromal responses, and biomechanical inputs are treated as amplifiers rather than evidence for a class II arm. The unresolved issue is the sustaining antigenic source: the enteric YeiH history may reflect broader niche-calibrating exposure, whereas persistent human-adapted intracellular candidates, including herpesviruses, remain to be tested against lesion-relevant receptors.

Systemic lupus erythematosus should not be treated as one mechanistic entity. Autoantibody-defined groups, including Ro/La, nucleosome/Sm/RNP/dsDNA, antiphospholipid, and broadly autoantibody-negative profiles, differ in clinical manifestations and HLA-DRB1 associations [72] [73] [74]. Each autoantibody-clinical endotype should be analyzed separately for antibody execution, class II specificity, and any class I or cytotoxic T-cell contribution rather than using SLE as a single disease category.

Across these examples, similar causal components can recur despite different chemistry and effector systems: a tissue generates or increases a recognizable ligand, an HLA-restricted repertoire encounters it, and local amplification determines whether recognition becomes injury. Demonstration of a self pHLA-TCR circuit establishes antigen-specific autoimmunity, but it does not by itself identify the memory-forming microbial source proposed by strict KET. Conversely, if an adequately powered lesion-derived receptor search is negative and tissue localization is better explained by cytokine, stromal, or mechanical mechanisms, the provisional endotype should be revised rather than the microbial search space expanded without limit.

A related literature groups several seronegative, tissue-restricted, HLA class I-associated diseases under the term MHC-I-opathy. Its genuine contributions are the clinicogenetic clustering, emphasis on HLA-ERAP interactions, and recognition that allele-specific tissue patterns require explanation [75] [76]. We use those observations but not the grouping as an organizing or competing framework. Barrier dysfunction, mechanical stress, innate activation, peptide-specific memory, and peptide-independent HLA biology remain alternatives whose ordering may differ among endotypes. The present architecture predicts that the family will partition when lesion-derived receptors, natural ligands, and amplification pathways are measured rather than assumed. Supplementary Figure S2 presents these boundary cases and states what evidence would resolve or refine their classification.

7. A lesion-anchored experimental program

The model becomes useful only when it determines what to do at the lesion. Figure 4 therefore moves in a deliberate order: define the niche; recover expanded receptors; define the restricting HLA and candidate ligand; test competing ligand classes; verify natural target-cell presentation and same-receptor recognition; and map local regulation and threshold variables. Candidate microbial and self or drug-modified pHLA multimers are then used to re-interrogate cells from the original lesion. Dual-binding cells can be isolated for paired-chain TCR sequencing, receptor reconstruction, functional testing, and orthogonal biophysical or structural confirmation. This closed-loop sequence converts strong HLA associations into mechanistic endotypes rather than a list of plausible pathways; Supplementary Figure S3 provides the expanded class I and class II workflow.

The strategic move is to begin with the receptor rather than with a long candidate-autoantigen list. In drug hypersensitivity, the lesion may contain oligoclonal cytotoxic cells whose restricting HLA and functional dependence can be measured directly [26]. In MS and other spontaneous diseases, the same logic is harder to execute but minimizes antigen-selection bias. Lesion- or CSF-enriched clonotypes are prioritized first; only then does the search move outward to cognate pHLA surfaces, microbial mimics, altered-self ligands, or native self-targets. The analytical setup should record the risk HLA, phenotype and target cell, exact microanatomical site, direct versus indirect mechanism, candidate organism and antigen phase, relevant T-cell geography, natural self-pHLA density, and patient modifiers before ranking candidates. Scalable receptor synthesis and screening make that sequence increasingly practical, although throughput does not substitute for physiological validation.

Tissue access determines the force of both positive and negative findings. SJS/TEN blister fluid and affected skin allow direct study of the pathologic compartment; CSF, gut biopsy, and synovium provide partial access; CNS parenchyma and pancreatic islets are rarely available at the initiating stage. A negative result from an adequately sampled acute lesion means something different from a negative result in peripheral blood or a late, treated compartment. Supplementary Table S2B and Supplementary Table S3 therefore pair each proposed architecture with its sampling context and the observation that would disconfirm or reassign it.

The workflow also forces prespecified branching. A candidate receptor may support direct mimicry, infection-remodeled self-presentation, drug- or PTM-modified self, native self-recognition, antibody- or Fc-mediated injury, a peptide-independent HLA mechanism, or a pathway outside the framework. These alternatives should be specified before screening begins, with criteria for assigning or rejecting each branch. Negative findings should move the analysis among these prespecified mechanisms rather than trigger an indefinitely broader candidate search. Animal and reduced systems can test defined components of the circuit, but no current model reproduces all of the human receptor polymorphisms, natural persistent infection, decades of intermittent reactivation, and simultaneous satisfaction of several independent conditions in combination.

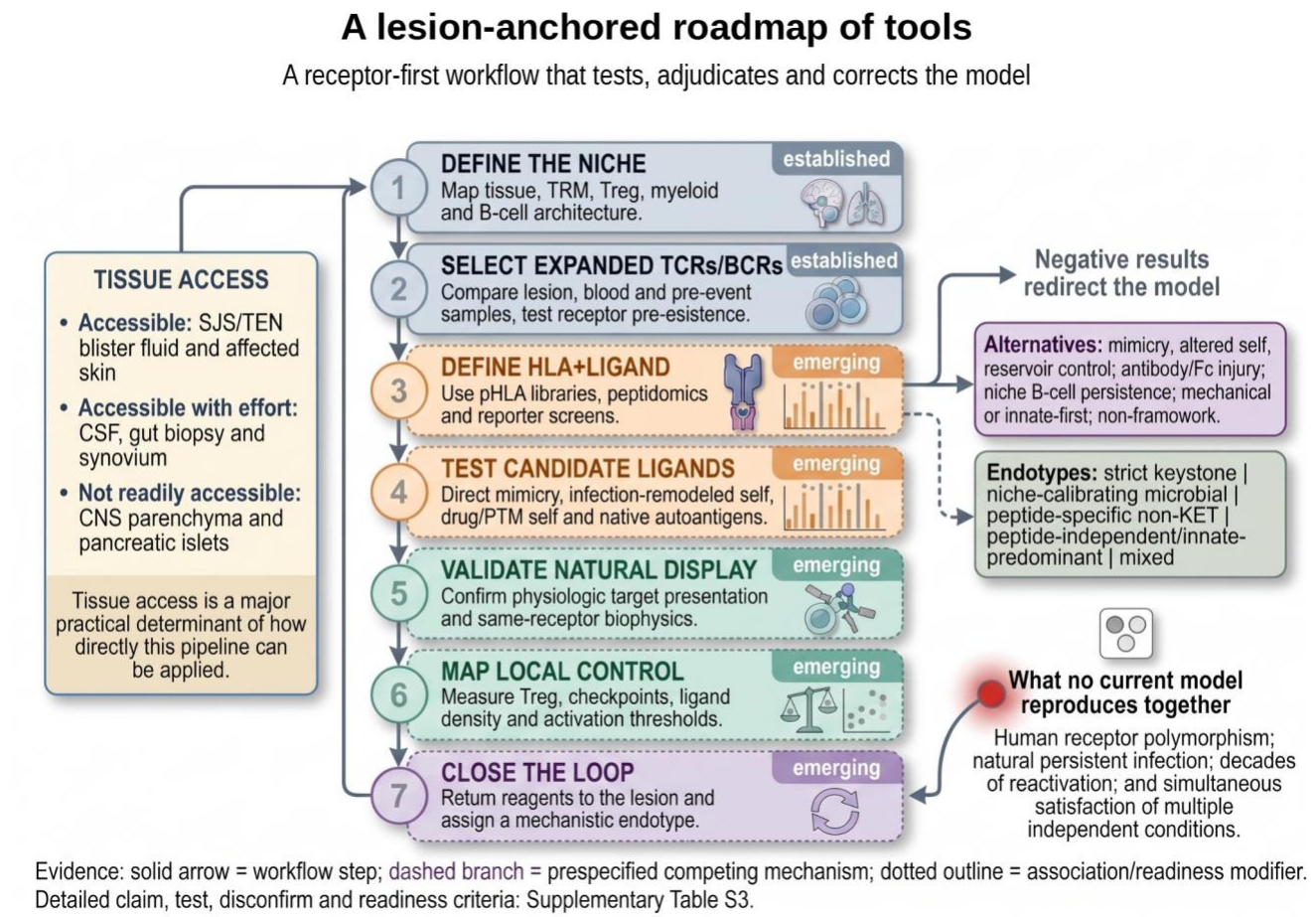


Figure 4. A lesion-anchored roadmap of tools. The workflow begins by defining the tissue niche and resident or recruited immune architecture. Expanded paired TCR and BCR sequences are then prioritized by comparing lesion, blood, and pre-event samples where available. High-resolution HLA typing, immunopeptidomics, pHLA libraries, and reporter systems are used to define restriction and candidate ligands. Candidate receptors are tested against direct microbial-self mimicry, infection-remodeled self-presentation, drug- or PTM-modified self, and native autoantigens. Any proposed circuit requires natural target-cell processing and presentation under physiologically plausible conditions. Same-receptor recognition should be confirmed functionally and, where feasible, by surface plasmon resonance, single-molecule binding studies, and structural analysis such as crystallography or cryo-EM. Local inhibitory receptors, Treg, ligand density, checkpoint tone, and activation thresholds are then measured. Candidate microbial and self or drug-modified pHLA multimers are used to re-probe cells from the original lesion; dual-binding cells can be isolated for paired-chain sequencing, receptor reconstruction, and functional confirmation. Negative findings redirect adjudication among prespecified alternatives rather than justify an indefinitely expanding candidate list. Tissue access determines how directly each step can be tested. Current reduced systems can test defined components but do not reproduce human receptor polymorphism, natural persistent infection, decades of reactivation, and multigate causality in combination.

Box 1. Six discriminating tests

1. Lesion-derived dual recognition. Recover lesion- or CSF-enriched clonotypes and test them against same-allele persistent-organism epitopes, candidate modified-self ligands, and native self pHLA. Repeated failure of an adequately powered, prespecified panel across several diseases would weigh against a broad strict-keystone claim.

2. Recall versus de novo priming. Determine whether the earliest lesion-reactive clonotypes are present before exposure or detectable immediately after onset. Very early same-receptor recall supports pre-existing competence; a consistent requirement for prolonged new priming would argue against it.

3. ERAP-to-peptidome coherence. For each HLA and substrate, test ERAP allotype, the naturally presented peptidome, cognate receptor activation, and viral-burden or disease phenotype as one chain. Direction need not be uniform across alleles; absence of any coherent HLA- and substrate-specific chain would weaken the source-control argument.

4. Niche map versus stress map. Compare lesion localization with candidate antigen-presentation niches and biomechanical-stress maps. If mechanical load predicts lesions after accounting for natural ligand display and receptor occupancy, the current weighting of niche memory should be reduced.

5. Within-person allele partition. In individuals carrying more than one relevant HLA allele, test whether disease site and effector arm track the allele whose restricted memory occupies that niche. This directly tests protective antigen-source control versus contributory tissue execution in one host.

6. Family partition. Apply the lesion-first workflow across selected class I-associated diseases. Uniform positive or uniform negative results would both challenge the predicted heterogeneity; the framework expects mechanistic partition rather than preservation of one umbrella category.

8. From mechanism to intervention

The framework yields five intervention propositions that require prospective validation. The first is reduction of antigen burden. In class I drug hypersensitivity, the exposure can be removed. In infectious or post-infectious disease, the analogous lever may be reduction of pathogen load, control of reactivation, or interruption of a tissue process that increases modified-self display. When the relevant ligand falls below the activation threshold, the pathologic circuit would be predicted to diminish even if the receptive clonotype persists.

The second proposition is restoration of local regulation. Checkpoint tone, inhibitory receptors, Treg abundance, and cytokine context do not identify the target, but they can determine whether a recognizable target becomes clinically dangerous. Blockade of regulation can therefore reveal pre-existing immune competence, whereas restoration of restraint may suppress disease without removing the causal clonotype or source antigen. The model predicts a meaningful distinction between interventions that silence a circuit and those that eliminate it.

The third proposition is direct targeting of the receptor-ligand circuit. Lesion-defining clonotypes could be tracked with pHLA multimers or functionally equivalent reagents, used as pharmacodynamic biomarkers, or, where specificity is sufficiently narrow, targeted selectively. In peptide-defined class I disease, tolerogenic or competitive strategies might be built around the same HLA-restricted surface that drives pathology. In antibody-executed disease, the corresponding target is the autoantibody, Fc effector mechanism, or receptor-modulating interaction.

The fourth proposition is mechanism-based stratification. HLA already functions as an effective exclusion tool in abacavir hypersensitivity and several severe cutaneous adverse reactions. Moving from exclusion toward positive prediction would require evidence of the relevant ligand, receptor context, tissue niche, and threshold state. Perfect prediction is unlikely, but the practical question becomes more specific: not merely who carries the allele, but who currently satisfies the necessary conditions.

The fifth proposition is therapeutic vaccination directed at the keystone or inciting organism. A vaccine might reduce antigenic stimulation by improving reservoir control or broaden the antiviral repertoire away from a dominant cross-reactive clonotype. Candidate vaccines should be screened to remove epitopes predicted to cross-recognize the relevant self pHLA. Observational and natural-experiment studies

associating live or recombinant zoster vaccination with lower subsequent dementia risk provide clinical motivation, but they do not establish that VZV causes dementia or validate a KET mechanism [77] [78].

9. Limits, alternatives and what would change our minds

The architecture has two layers that should not be conflated. The first is the general decomposition into three HLA functions, three temporal stages, and a four-condition gate. The second is the stricter source hypothesis that entrenched memory often derives from persistent, human-adapted, niche-structured organisms. The first layer can remain useful when the second fails in a disease. Several antigen-defined spontaneous diseases may prove peptide-specific yet non-keystone, mixed, or dominated by altered-self rather than mimicry.

The classification is a heuristic spectrum, not a taxonomy. "Associated" is not equivalent to receptor-level "restricted" in most spontaneous diseases, and predictive values are not intrinsic properties of class I or class II biology. They depend on prevalence, exposure, phenotype definition, ancestry, and the allele or haplotype tested. Tissue access and disease stage further constrain what can be inferred from a positive or negative experiment.

Falsifiability requires that negative findings change the model. If lesion-derived receptors fail to recognize persistent-organism ligands and fail to recognize plausible altered or native self-targets under natural presentation conditions, the proposed peptide-centered endotype should be downgraded. If antibody transfer or a peptide-independent HLA mechanism reproduces the disease, the architecture should shift accordingly. If mechanical stress, barrier dysfunction, or cytokine amplification predicts lesion distribution better than the inferred niche-memory map, those variables should receive greater causal weight.

The framework is compatible with an essential role for danger and innate activation but assigns those signals to specific stages. Inflammation and costimulation can be required when memory is first licensed and can amplify tissue injury later; they need not select the target at recall. Very early drug reactions and drug-unexposed responsive repertoires make that distinction concrete in the class I anchor. The model would be weakened if every well-resolved case instead required a fresh danger event to create both competence and target selection at the moment of injury.

Diseases that remain difficult to assign should remain provisionally classified until the decisive experiment is performed. Narcolepsy type 1, vitiligo, selected type 1 diabetes or celiac endotypes, and autoantibody-defined SLE subgroups are informative because they expose where simple classification fails. Their value is that they identify what remains to be measured and how the proposed models may need to be refined: exact receptor restriction, natural target-cell presentation, proximal executor, and the relation between tissue access, amplification, and initiating specificity. Antibody-positive autoimmune nodopathies are not included here when antibody causally disrupts the node or paranode; those endotypes belong in the antibody-executed group.

10. Conclusion

HLA associations point toward mechanism but become explanatory only when the relevant receptor, ligand, tissue niche, and local threshold are identified. Drug hypersensitivity and MS reveal different parts of that logic. Drug hypersensitivity shows that a defined perturbation can create or reveal a class I surface that recruits pre-existing competence without obligate de novo priming, a new danger event, or a concurrent class II, B-cell, or antibody arm at tissue injury. MS shows that specificity, control of a persistent antigen source, and tissue execution can be distributed across different HLA alleles and then converge in a permissive CNS niche.

Together, these anchors support a general architecture. HLA biology can be partitioned into specificity and focusing, antigen-source control, and tissue execution. Disease evolution can be partitioned into imprinting and licensing, tissue recall, and local amplification. Clinical injury requires coincidence of compatible receptor-HLA context, a relevant ligand at sufficient density, natural presentation in the appropriate tissue niche, and permissive local regulation. This architecture remains useful even when the

strict keystone-source hypothesis is not met because it still organizes how to test direct mimicry, altered self-presentation, native self-recognition, antibody execution, and non-peptide alternatives.

The practical consequence is a receptor-first, lesion-anchored program in which every mechanistic claim has a named disconfirming result. Rather than treating HLA association as an endpoint, the framework converts association into a shortlist of competing mechanisms and a method for deciding among them.

Acknowledgments

We are grateful to our colleagues and collaborators across immunology, structural biology, virology, biostatistics, and clinical medicine for generous discussions and for sharing insights, unpublished observations, and critical perspectives that helped shape this Review. We particularly thank members of our respective research groups and long-standing collaborators for feedback over multiple iterations of these ideas.

Funding

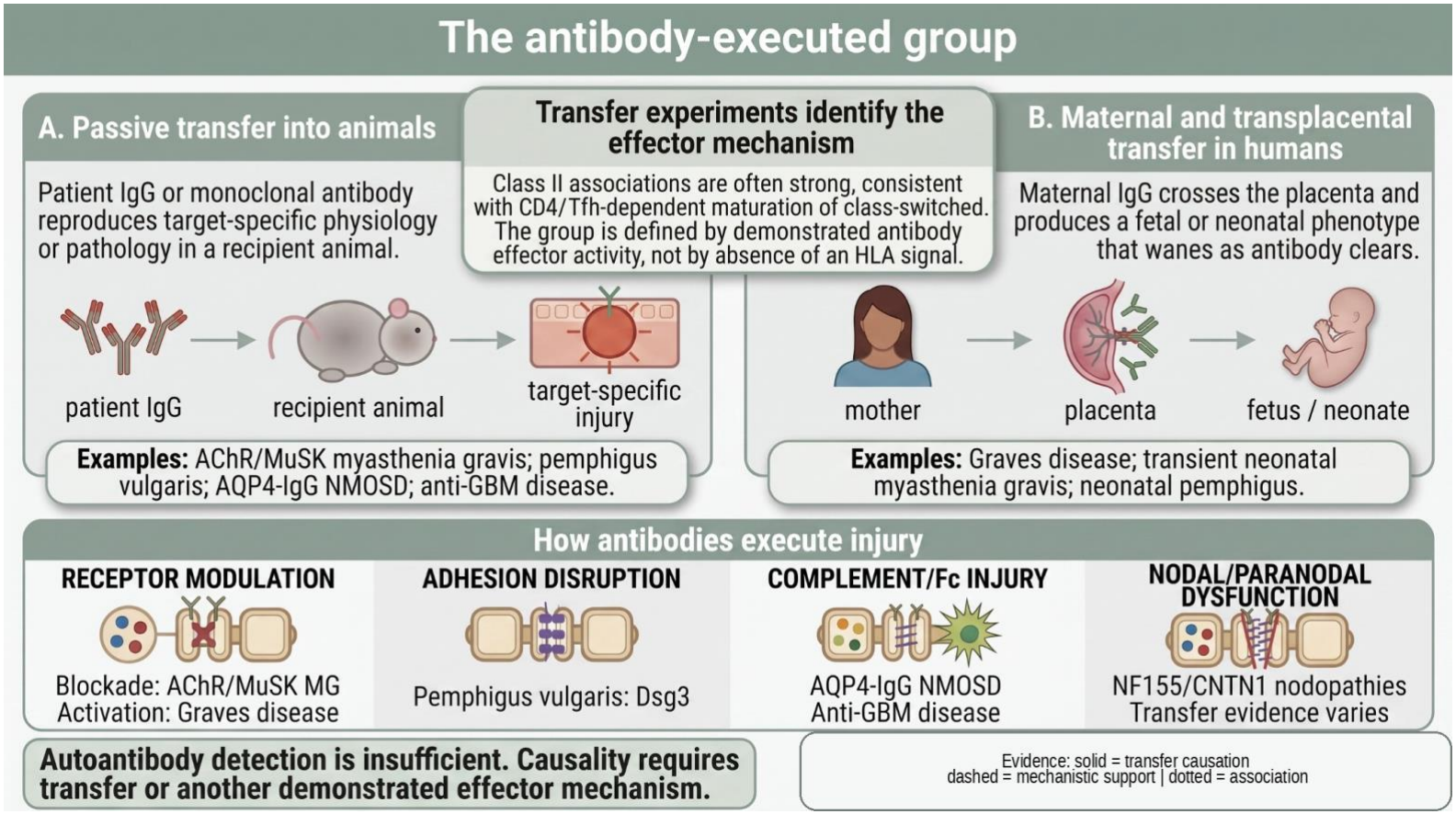
The conceptual and supporting work reflected in this Review was supported in part by the National Institutes of Health (NIH) under awards AI154659, P50GM115305, P30AI110527, 1R35HL140016, 5R01AI060460, U54AG089326, P01HL174442, P30CA068485, R01AI077505, 1R01AI147765, 1R01AI142093, and R00HG011367. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Competing interests

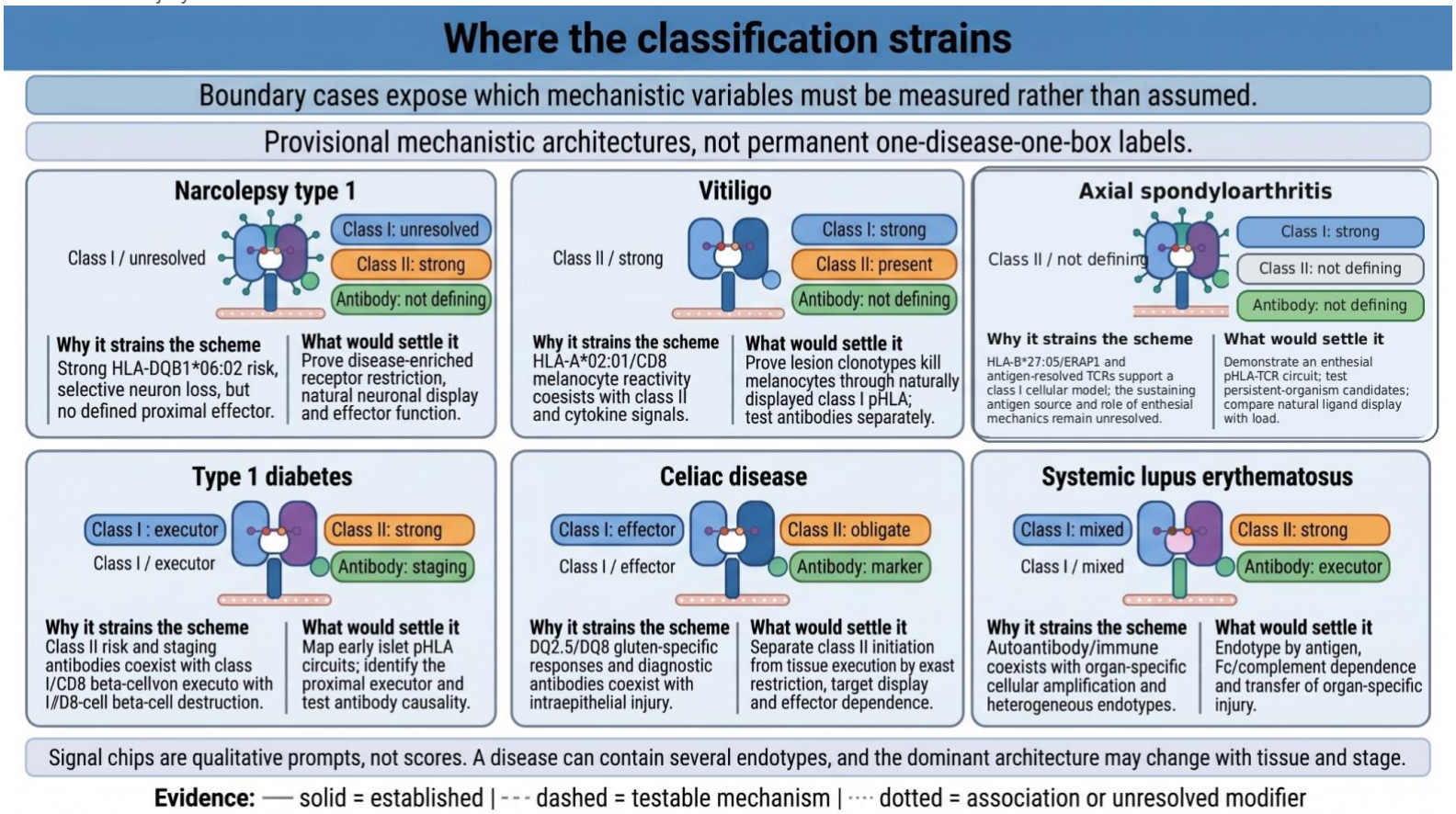
S.A.M. and E.J.P. are named inventors on U.S. provisional patent application No. 63/945,526, filed December 19, 2025, entitled “Methods and Systems for Identifying Disease-Relevant T-Cell Epitopes and Modified Self or Viral Mimics Using Tissue-Derived T-Cell Receptors,” which is assigned to Vanderbilt University. The authors declare no other competing interests.

Supplementary Material

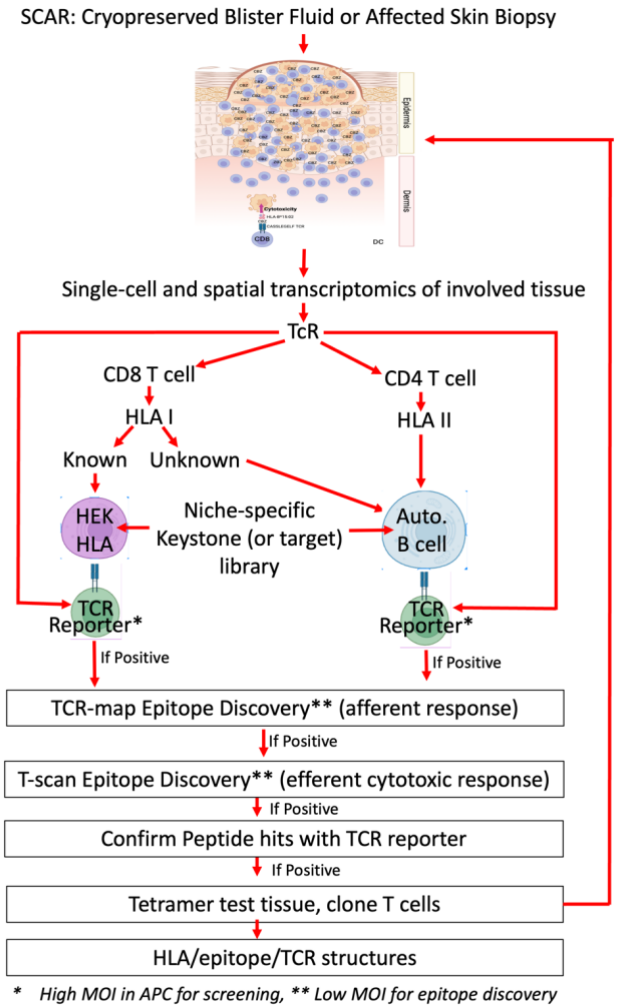
Supplementary Figures



Supplementary Figure S1. The antibody-executed group. Antibody-executed disease is defined by evidence that the autoantibody produces target-specific dysfunction or injury. Panel A shows passive transfer into animals, including AChR- and MuSK-associated myasthenia gravis, pemphigus vulgaris, AQP4-IgG-positive neuromyelitis optica spectrum disorder, and anti-GBM disease. Panel B shows maternal and transplacental transfer in humans, including fetal or neonatal Graves disease, transient neonatal myasthenia gravis, and neonatal pemphigus. The lower register summarizes receptor blockade or activation, adhesion disruption, complement- or Fc-dependent injury, and nodal or paranodal dysfunction. Antibody-positive autoimmune nodopathies are included when NF155-, CNTN1-, or related antibodies directly disrupt nodal or paranodal function, while acknowledging that transfer evidence varies by antigen and subclass. Class II associations may be strong because class-switched autoantibody responses require CD4 and Tfh organization; the defining feature of this group is the demonstrated effector mechanism, not absence of HLA or cellular biology. Autoantibody detection alone is insufficient for classification as antibody-executed disease. Supporting primary studies are refs. [48-50] and [79,80] for passive transfer, refs. [81-83] for maternal transfer, and refs. [84,85] for autoimmune nodopathies.



Supplementary Figure S2. Where the classification strains. The three headings are provisional mechanistic architectures rather than mutually exclusive disease categories. Narcolepsy type 1, vitiligo, axial spondyloarthritis, type 1 diabetes, celiac disease, and systemic lupus erythematosus are presented as boundary cases because HLA class, cellular effectors, antibody findings, tissue access, and proximal execution do not collapse into one axis. Axial spondyloarthritis is provisionally assigned to the class I-associated, cellular-predominant architecture; its boundary question concerns the sustaining antigenic source and the relative roles of antigen-specific recognition and enthesial amplification, not evidence for an obligatory class II arm. SLE is shown only as a reminder that autoantibody-clinical endotypes must be considered separately because they have distinct HLA associations and effector mechanisms. Each card states why the disease strains the classification and the observation that would most directly settle, reassign, or refine it. Signal chips are qualitative prompts rather than scores, and the dominant architecture may differ among endotypes, tissues, and disease stages. Solid borders denote established features, dashed borders denote testable mechanisms, and dotted borders denote associations or unresolved modifiers.



Supplementary Figure S3. Expanded lesion-to-mechanism workflow for class I- and class II-restricted receptor discovery in SCAR and related immune-mediated disease. Cryopreserved blister fluid or lesional skin is profiled by single-cell and spatial transcriptomics to identify expanded paired TCRs. CD8 candidates are tested in matched class I reporter systems or autologous APCs when restriction is unknown; CD4 candidates are tested in autologous B-cell or other class II APC systems. Positive ligands are mapped by TCR-map, T-Scan, or equivalent libraries and confirmed with reconstructed TCR reporters. Paired microbial and self or drug-modified pHLA multimers can then identify dual-binding cells in the original lesion, followed by paired-chain sequencing, functional testing, surface plasmon resonance or single-molecule binding measurements, and, where feasible, crystallography or cryo-EM. Re-interrogation of the original material closes the loop between candidate ligand and pathology.

Supplementary Tables

Supplementary Table S1. Feature matrix across three mechanistic archetypes

Feature	Class I-associated, cellular-predominant immunopathology	Class II-associated autoimmunity with variable class I and antibody arms	Antibody-executed disease
Core definition	Tissue injury is organized around a class I-presented target and cellular effector arm. Drug hypersensitivity supplies the cleanest receptor-level anchor; axial spondyloarthritis is provisionally included as class I-associated cellular-predominant disease, while its sustaining antigenic source remains unresolved.	Class II presentation organizes specificity and CD4 programs, with variable B-cell, antibody and class I contributions to control or tissue execution.	The group is defined by demonstrated antibody effector activity, not by absence of HLA association or cellular participation.
Dominant HLA architecture	Usually a strong class I allele association; ERAP, TAP, tapasin, KIR or other class I-pathway modifiers may refine risk.	Usually strong class II risk with independent class I alleles that can protect, impair antigen-source control or contribute to tissue execution.	Class II associations are present and often strong because class-switched autoantibody maturation requires CD4/Tfh help.
HLA functions most visible	Specificity/focusing and tissue execution are directly accessible in drug reactions; antigen-source control may remain an upstream determinant.	Specificity/focusing, antigen-source control and tissue execution can be distributed among different alleles and point in opposite directions.	Specificity/focusing of the helper and B-cell response is central; proximal execution is mediated by the antibody target and effector system.
Inflammatory costimulation during imprinting	May be required when durable memory is first licensed. Prior pathogen exposure, vaccination or another immunizing context is a candidate source.	Usually contributes to initial CD4 and B-cell programming; timing and context of persistent infection may alter the resulting repertoire.	Required for maturation of the class-switched autoantibody response, although the initiating tolerance defect may be unknown.
New danger event at tissue recall	Not necessarily obligatory if competent memory and naturally presented target already coincide. Inflammation and tissue stress can amplify presentation and lower restraint.	Not necessarily obligatory for already licensed memory, but local B-cell, myeloid, endothelial and cytokine programs often amplify recall.	Not obligatory once circulating antibody reaches an accessible target; complement, Fc cells, target access or inflammatory priming may still be required.
CD4 contribution during priming	Can contribute to CD8 memory formation in some settings, but is not an obligate element of class I-mediated drug hypersensitivity.	Usually central to specificity, Tfh support, B-cell organization, epitope spreading or direct cytotoxic/inflammatory CD4 programs.	Required for class-switched, affinity-matured autoantibody generation.
CD4 requirement at proximal tissue injury	Not obligatory. No disease-antigen-specific class II response or concurrent CD4 or B-cell arm is required in the direct class I drug-hypersensitivity anchor.	Variable: direct CD4 injury, B-cell organization, class I execution or mixed mechanisms can dominate.	Usually not required at the moment of injury once sufficient autoantibody and the relevant effector system are present.
Proximal tissue-damaging effector	CD8 T cells, often including TRM or tissue-positioned memory; innate and cytokine cells amplify the lesion.	CD4 T cells, CD8 T cells, B cells, antibody/complement, myeloid cells or mixed combinations depending on endotype.	Autoantibody acting through receptor blockade/activation, adhesion disruption, complement, Fc receptors or related target-specific mechanisms.
Disease-defining autoantibody	Absent, minimal or not required.	Often present, but may be a staging biomarker, associated marker, amplifier or causal executor only in a subset.	Present and causally linked to the proximal mechanism.
NPV and PPV pattern	A narrowly defined risk HLA can have very high NPV but low PPV because ligand, receptor, niche and regulation must also align. Drug-HLA PPV ranges approximately 0.12% to 55%, with most pairs below 10%.	No single allele usually excludes disease because several class II and class I combinations converge. Predictive values are endpoint-, ancestry- and prevalence-dependent.	HLA genotype is not the primary diagnostic predictor. Antigen-specific antibody status, titre, subclass, Fc function and target access are more proximal.
Peptide-processing modifier	Often prominent: ERAP1/2, TAP, tapasin and allele-specific loading shape the class I surface.	Class II processing and HLA-DM/DO biology may shape specificity; class I processing can independently modify reservoir control or execution.	Can influence upstream helper specificity, but is less often the proximal determinant once a causal antibody has formed.
Tissue restriction of injury	Usually strong and determined by target-cell expression, pHLA display, resident repertoire, trafficking and local amplification.	Variable but often organ-specific; class II focusing can be systemic while class I or antibody execution remains tissue-restricted.	Determined chiefly by antigen distribution, antibody access and availability of complement or Fc-bearing effectors.

Feature	Class I-associated, cellular-predominant immunopathology	Class II-associated autoimmunity with variable class I and antibody arms	Antibody-executed disease
CD8 TRM or tissue-positioned CD8 cells in lesion	Demonstrated in SJS/TEN and psoriasis; likely relevant in other class I-associated diseases but not uniformly established.	Common in MS, type 1 diabetes and celiac lesions, but may be executor, surveillance population or secondary recruit.	Not defining and may be absent or secondary.
Identified ligand, modification or trigger	Drug-dependent pHLA, altered repertoire, native self, PTM-self or microbial/self mimic; examples include carbamazepine pHLA, abacavir-altered self and ADAMTSL5.	Native or altered self, infection-remodeled self and exogenous antigens; examples include EBNA1-ANO2, EBV-remodeled myelin display, gluten, citrullinated self and beta-cell peptides.	Defined native cell-surface or extracellular target, for example AChR, AQP4, desmoglein 3, TSH receptor or alpha3(IV) collagen.
Candidate memory-source interpretation	Can be Tier A strict keystone, Tier B niche-calibrating microbial or Tier C peptide-specific non-KET. The source must be prespecified rather than rescued after a negative search.	Tier A is plausible in EBV-associated MS; many other diseases are currently Tier C or unresolved.	A microbial source is not required to establish the proximal antibody mechanism, although it may contribute to the origin of tolerance loss.
Innate, cytokine or mechanical amplification	IL-17, TNF, myeloid, stromal, barrier and mechanical programs can alter gain and persistence. They do not by themselves identify the antigenic target, and may dominate some endotypes.	Often substantial and endotype-dependent. Tissue inflammation can change antigen presentation, reservoir persistence, trafficking and regulatory set-points.	Complement, Fc receptors, innate effector cells and target access are integral to many antibody-executed mechanisms.
Transfer-experiment evidence	Not defining; receptor transfer or engineered TCR systems test cellular causality.	Variable and usually indirect unless an antibody-executed endotype is present.	Central: passive transfer into animals or maternal/transplacental transfer in humans can reproduce target-specific physiology or pathology.
Dominant mechanistic readouts	Lesion pHLA, expanded paired TCRs, cytotoxic phenotype, natural target-cell presentation, same-receptor recognition and tissue killing.	Antigen-specific CD4/CD8 responses, B-cell and antibody features, reservoir burden, class I control, lesion or CSF receptor-pHLA coherence and tissue state.	Target-specific antibody, complement/Fc dependence, receptor modulation, transfer activity and response to selective antibody depletion or neutralization.
Decisive experiment	Recover lesion-enriched receptor(s), define exact class I pHLA, show natural presentation and physiologic function, and determine whether a prespecified microbial source is recognized by the same receptor.	Separate class II focusing, class I control and tissue execution with exact receptor-HLA-ligand mapping, temporal sampling and tissue validation.	Remove or transfer the antigen-specific antibody and show loss or reproduction of target-specific pathology under appropriate effector conditions.
Representative examples	T cell-mediated drug hypersensitivity; HLA-C*06:02-positive psoriasis; HLA-B*27:05 axial and ocular endotypes; Behçet disease and birdshot remain less receptor-resolved.	Multiple sclerosis, type 1 diabetes, celiac disease, ACPA-positive rheumatoid arthritis, and narcolepsy type 1 as a boundary case.	AChR- or MuSK-positive myasthenia gravis, AQP4-IgG NMOSD, pemphigus vulgaris, Graves disease and anti-GBM disease.

Note: The columns describe mechanistic archetypes, not mutually exclusive disease bins. "Associated" is reserved for disease-level HLA relationships; "restricted" is used only when receptor-level restriction is demonstrated.

Supplementary Table S2A. Provisional mechanistic architectures across selected HLA-associated diseases and endotypes

No.	Disease or endotype	Major HLA context and proposed function	Proximal tissue-damaging effector	Autoantibody role	Candidate ligand and memory-source interpretation
1	Carbamazepine-associated SJS/TEN	HLA-B*15:02, strongest in Han Chinese and several Southeast Asian populations. Class I tissue execution is demonstrated; the source of specificity and focusing remains under investigation.	Lesion-expanded cytotoxic CD8 T cells, including tissue-resident or tissue-positioned cells, recognize drug-dependent pHLA on keratinocytes and drive epithelial injury.	Absent or not required.	Carbamazepine-dependent recognition of peptide-loaded HLA-B*15:02 is supported. HSV/VZV-restricted memory is a prespecified Tier A candidate, but same-receptor microbial and keratinocyte dual recognition is not yet established. [86] [22] [15]
2	Abacavir hypersensitivity	HLA-B*57:01. Altered self-presentation and class I tissue recognition are established. The foreign antigen that originally focused the relevant memory repertoire is unresolved.	Broad private, oligoclonal or polyclonal CD8 responses to an abacavir-altered self repertoire. Both memory-derived and naive-derived responses can be generated; very early onset supports memory recall in at least some patients.	Absent or not required.	Abacavir alters the HLA-B*57:01 F-pocket and presented self repertoire. The original foreign priming source is unknown. Dominant EBV-specific TCRs tested by Sooda et al. did not recognize abacavir plus self-peptide, providing a bounded negative rather than a global exclusion. [14] [23] [27]
3	HLA-C*06:02-positive plaque psoriasis	HLA-C*06:02, prominent in early-onset plaque psoriasis. ERAP1 determines autoantigen generation and abundance. The best-supported function is tissue execution through class I presentation.	HLA-C*06:02-restricted lesional CD8 T-cell recognition of melanocytes, with IL-17A, TNF, keratinocyte, dendritic-cell and broader inflammatory amplification. Direct melanocyte killing is not the sole established mechanism.	Not disease-defining.	ADAMTSL5 is an established native self ligand, therefore Tier C. The same lesional TCR can recognize several environmental or microbial peptides, creating an emerging Tier B candidate branch, but no strict Tier A source has been shown. [44] [51] [87]
4	HLA-B*27:05-positive axial spondyloarthritis	HLA-B*27:05, especially in European-ancestry disease, with ERAP1 epistasis. The provisional assignment is class I-associated, cellular-predominant disease; peptide-independent HLA biology remains a competing mechanism.	A disease-associated TCR-defined CD8 compartment, with IL-17, TNF, myeloid, stromal and biomechanical amplification. These amplifiers do not establish an obligatory class II arm.	Absent or not disease-defining.	HLA-B*27:05-bound bacterial and self peptides, including YeiH-related circuits, provide a Tier B candidate. Persistent human-adapted intracellular sources, including herpesviruses, remain to be tested. [16] [70] [71]
5	Multiple sclerosis	HLA-DRB1*15:01: specificity and focusing. HLA-A*02:01: protective antigen-source control. HLA-A*03:01 and HLA-B*07:02: higher antigen-pressure or candidate effector contexts, with distinct evidence for each.	Endotype-dependent combinations of class II-restricted CD4 cells, CD8 cells, B cells, antibody-secreting cells, microglia and myeloid cells. The proximal executor is not uniform.	No universal disease-defining autoantibody. Oligoclonal IgG, EBV-directed antibody properties and a minority preclinical autoantibody endotype may be biomarkers or amplifiers rather than universal executors.	EBV meets Tier A source criteria. Direct EBNA1-ANO2 cross-recognition and EBV-induced remodeling of the HLA-DRB1*15:01 self-peptidome are supported. Direct CNS self-cross-reactivity of implicated class I clonotypes remains unproven. [32,33] [30,31,34,35] [36]
6	Type 1 diabetes	HLA-DQA1*03:01-DQB1*03:02 (DQ8) and HLA-DQA1*05:01-DQB1*02:01 (DQ2.5) principally shape class II specificity and focusing. Class I presentation contributes to beta-cell tissue execution.	Beta-cell-reactive CD8 T cells, with class II-restricted CD4 help and inflammatory amplification within islets.	Multiple islet autoantibodies are powerful staging and progression biomarkers. They are not established as the universal proximal beta-cell-damaging effector.	Insulin and other beta-cell self peptides are established candidate antigens. No persistent microbial imprinting source is established, making the current assignment Tier C, peptide-specific non-KET or mixed. [52] [45] [55]
7	Celiac disease	HLA-DQA1*05:01-DQB1*02:01 (DQ2.5) or HLA-DQA1*03:01-DQB1*03:02 (DQ8) provides obligate class II specificity and focusing in most conventional celiac disease.	Gluten-specific CD4 T cells organize the response; intraepithelial CD8 and unconventional lymphocytes execute epithelial injury through class I and NKG2D-dependent pathways.	Anti-transglutaminase 2 and anti-endomysial antibodies are disease-defining diagnostic markers but are not the sole proximal executors of villous injury.	Recurrent dietary gluten, modified by transglutaminase 2-mediated deamidation, is the disease antigen. This is an established antigen-specific non-KET architecture, not evidence for a persistent microbial source. [57] [58]

No.	Disease or endotype	Major HLA context and proposed function	Proximal tissue-damaging effector	Autoantibody role	Candidate ligand and memory-source interpretation
8	ACPA-positive rheumatoid arthritis	HLA-DRB1*04:01 and related shared-epitope alleles primarily shape class II specificity toward post-translationally modified self. Population and endotype differences remain substantial.	Citrullinated-antigen-specific CD4 cells, B cells, macrophages, fibroblast-like synoviocytes, osteoclasts and other inflammatory cells act in a mixed synovial program.	ACPA and rheumatoid factor can precede disease, stratify risk, form immune complexes and amplify inflammation. They are not sufficient universal executors of the entire arthritis phenotype.	Citrullinated tenascin-C, collagen, alpha-enolase and other modified self proteins are Tier C ligands. A specific persistent microbial memory source is not established. [61] [62] [88]
9	Narcolepsy type 1	HLA-DQB1*06:02 confers an exceptionally strong class II association. Class II specificity and focusing are likely; any class I tissue-execution contribution remains incompletely resolved.	Hypocretin-neuron-antigen-reactive CD4 and CD8 T cells have been detected, but direct in vivo neuronal killing by a defined receptor-pHLA circuit has not been demonstrated.	No reproducible disease-defining autoantibody.	Hypocretin-neuron self antigens are candidates. No persistent or niche-calibrating microbial source has been established, making this a declared boundary architecture. [67] [68] [69]
10	Early-onset, AChR-positive myasthenia gravis	The HLA-B*08:01-DRB1*03:01-DQB1*02:01 8.1 ancestral haplotype is associated with early-onset AChR-positive disease in European populations. HLA-DRB1*03:01 is the more plausible specificity and focusing element; HLA-B*08:01 may primarily mark the haplotype.	AChR-specific IgG causes receptor loss, complement activation and neuromuscular transmission failure.	Causal executor, supported by purified-antibody and passive-transfer studies.	Acetylcholine receptor is the defined autoantigen. No microbial source is required to classify the proximal mechanism, although the origin of helper and B-cell tolerance loss remains unresolved. [89] [48]
11	AQP4-IgG-positive neuromyelitis optica spectrum disorder	HLA-DRB1*03:01 is a recurrent but ancestry-dependent class II risk association. Its most plausible role is specificity and focusing of the AQP4-directed humoral response.	AQP4-IgG drives astrocyte injury through complement-dependent and Fc-cell-dependent mechanisms, with secondary inflammation and demyelination.	Causal executor, demonstrated in passive-transfer systems.	Aquaporin-4 is the defined autoantigen. No persistent microbial source is required for the proximal antibody-executed classification. [90] [49]
12	Pemphigus vulgaris	HLA-DRB1*04:02 and HLA-DQB1*05:03 are recurrent class II risk alleles across several populations and shape desmoglein-specific CD4 help.	Anti-desmoglein 3, with or without anti-desmoglein 1, disrupts keratinocyte adhesion through direct binding and signaling-dependent mechanisms.	Causal executor, supported by passive transfer of patient IgG and monoclonal antibodies.	Desmoglein 3 and desmoglein 1 are defined autoantigens. No persistent microbial source is required for the proximal mechanism. [91] [50]
13	Systemic lupus erythematosus, autoantibody-defined endotypes	HLA-DRB1 associations differ among autoantibody and clinical subphenotypes. SLE should not be treated as one HLA-defined mechanism.	Autoantibody or immune-complex injury in some endotypes, with organ-specific CD4, CD8, myeloid, complement and stromal amplification.	Potential causal executor in defined nephritic, antiphospholipid or other endotypes; marker or absent in others.	Nuclear antigens and phospholipid-binding proteins are defined targets, but no single memory source or cellular circuit explains all SLE. [72] [73] [74]

Source labels used in the working table: Tier A, strict keystone source; Tier B, broader niche-calibrating microbial source; Tier C, native self, modified self, or another ligand without a demonstrated microbial imprinting history. These labels are provisional and endotype-specific.

Supplementary Table S2B. Tissue access, evidence tier, and observations that would falsify or reassign each architecture

No.	Accessible disease material	Evidence tier and provisional mechanistic architecture	Observation that would falsify or reassign the architecture
1	Acute blister fluid, lesional skin, keratinocytes, blood and archived culprit-drug samples.	Established class I-restricted tissue-execution mechanism. The proposed strict-keystone imprinting source remains a hypothesis.	Failure of adequately sampled lesion-enriched TCRs to recognize any naturally processed carbamazepine-dependent HLA-B*15:02 ligand would reject the proximal circuit. Drug-self recognition without microbial dual recognition would reassign the endotype to peptide-specific non-KET.
2	Blood and archived PBMCs; patch-test tissue may be available. The clinically relevant source cell and target tissue are not established.	Established altered-repertoire mechanism with a demonstrated pre-existing memory component. The original microbial or foreign imprinting source remains unresolved.	A prespecified source-cell and Tier A/B microbial panel with no same-receptor dual recognition in confirmed cases would reject the microbial-imprinting branch, not the altered-self mechanism. Consistent absence of pre-existing memory in the earliest cases would weaken recall dominance.
3	Lesional and nonlesional skin are highly accessible for spatial, single-cell, immunopeptidomic and functional analysis.	Established peptide-specific non-KET endotype in HLA-C*06:02-positive disease; an environmental or Tier B imprinting branch is emerging.	Failure of lesion-dominant HLA-C*06:02-restricted clonotypes to recognize naturally presented ADAMTSL5 across the defined endotype, or persistence after selective circuit disruption, would favor a cytokine-dominant or mixed architecture.
4	Sacroiliac and enthesial tissue is poorly accessible. Peripheral synovium, gut biopsy, blood and occasional surgical tissue provide indirect access.	Mechanistically supported class I-associated, cellular-predominant endotype with cytokine, stromal and biomechanical amplification; the strict KET source is unproven.	No coherent HLA-B*27:05 pHLA-TCR circuit in adequate lesion-adjacent tissue, with biomechanical load predicting lesions independently of ligand presentation, would favor peptide-independent or innate-predominant disease. Identification of a persistent-organism/self dual-recognition circuit would strengthen a KET-type model.
5	CSF is accessible with effort; brain, meningeal and early lesion-border tissue is rarely accessible.	Mechanistically supported mixed class II/class I architecture with a strict Tier A antigen source. The exact proximal executor is endotype-dependent and incompletely resolved.	Adequately powered early-lesion and CSF studies showing no coherent EBV/self or EBV-induced altered-self circuits, together with a sufficient EBV-independent mechanism, would weaken the EBV-linked architecture. A reproducible EBV-independent subgroup would support partition.
6	Blood is readily accessible; pancreatic islets and early insulitic tissue are not. Organ-donor tissue provides a limited window.	Mechanistically supported mixed class II-initiation/class I-execution architecture, currently peptide-specific non-KET unless an imprinting source is demonstrated.	Absence of antigen-specific CD8-pHLA circuits in adequately sampled early islets, combined with purified autoantibody reproducing beta-cell destruction, would force reassignment toward antibody execution.
7	Duodenal biopsy is accessible with effort and can be sampled before and after controlled gluten exposure.	Established class II antigen-specific initiation with mixed epithelial execution. This is an antigen-specific non-KET architecture.	Conventional celiac disease without HLA-DQ2.5/DQ8-restricted gluten-specific CD4 responses or relevant gluten processing would invalidate the architecture. Purified transglutaminase 2 antibody transferring enteropathy would reassign it.
8	Synovial fluid and ultrasound-guided synovial biopsy are accessible; preclinical mucosal sites are harder to obtain.	Mechanistically supported class II/PTM mixed endotype. Autoantibodies are staging signals and potential amplifiers rather than sufficient universal executors.	Failure to recover PTM-specific shared-epitope-restricted receptors from early ACPA-positive synovium despite adequate coverage would weaken specificity. Reproduction of full persistent synovitis and erosion by isolated antibody would support antibody execution.
9	Blood and CSF are accessible; the lateral hypothalamus and early neuronal lesion are not.	Associated to mechanistically supported class II-led boundary architecture. Cellular execution remains unproven.	Failure to recover disease-enriched HLA-DQB1*06:02-restricted or class I-restricted receptors against hypocretin-neuron antigens, together with evidence for nonimmune neuron loss, would reassign the disease outside the cellular architecture.
10	Serum and circulating B cells are readily accessible. Thymus may be available after thymectomy.	Established antibody-executed endotype.	Removal of AChR-specific IgG failing to remove pathogenic activity, or purified antigen-specific IgG consistently failing to reproduce receptor dysfunction in validated systems, would require revision.
11	Serum and CSF are accessible; acute optic-nerve and spinal-cord lesions are not routinely sampled.	Established antibody-executed endotype with complement and Fc dependence.	Selective depletion or neutralization of AQP4-IgG failing to remove pathogenicity, or purified AQP4-IgG failing to reproduce target-specific astrocyte injury with adequate target access and effector systems, would require revision.
12	Lesional and perilesional skin or mucosa, serum and circulating B cells are readily accessible.	Established antibody-executed endotype.	Failure of purified desmoglein-specific IgG to disrupt adhesion or transfer disease after confirming target binding and exposure, or persistence after selective removal of anti-desmoglein activity, would imply reassignment or an additional endotype.
13	Blood, serum and urine are accessible; skin or kidney biopsy is available in selected active endotypes.	Endotype-specific class II/antibody and mixed cellular architectures. Classification should follow autoantibody and clinical phenotype rather than the umbrella SLE label.	Analyze each autoantibody-clinical endotype separately. Demonstrate whether isolated antibody transfers organ-specific injury or whether lesion-derived class I or class II TCR circuits dominate; failure of either model should reassign that endotype.

Supplementary Table S3. Lesion-anchored roadmap: claim, test, disconfirming observation, and readiness

Step	Claim tested	Test	Disconfirming observation	Readiness at 13 Aug 2026
1. Define the niche	The disease-relevant tissue contains a coherent local immune and antigen-presentation architecture rather than only nonspecific inflammation.	Map active disease tissue by histology, multiplex imaging, spatial transcriptomics, scRNA-seq, paired TCR/BCR sequencing and phenotyping of TRM, Treg, B cells, myeloid and target cells. Pair with stage and anatomical location.	Adequate early-lesion sampling shows no reproducible lesion-enriched clonotypes, no coherent spatial relation to target cells or pHLA display, and only diffuse bystander recruitment.	Established for accessible skin, gut and synovium; emerging for CSF and rare surgical tissue; not readily available for early CNS parenchyma and pancreatic islets.
2. Prioritize expanded receptors and test pre-existence	Expanded lesion-derived receptors are mechanistically informative and, for a recall model, at least some disease-driving clonotypes pre-exist overt tissue injury.	Compare lesion with blood using bulk and single-cell paired TCRalpha/beta and BCR sequencing. Use archived pre-event samples when available; phenotype naive, stem-like memory, effector-memory and TRM states; reconstruct prioritized receptors.	No reproducible lesion enrichment despite adequate depth, or disease-driving clonotypes consistently appear only after injury with naive phenotypes and de novo priming requirements.	Sequencing and reconstruction established; paired pre-event samples and reliable temporal inference emerging.
3. Map restricting HLA and cognate ligand	The prioritized receptor recognizes a defined ligand in an exact HLA context at physiologically plausible abundance.	High-resolution HLA typing; single-HLA reporter cells; immunopeptidomics; peptide-HLA libraries; T-Scan or related functional screens; tetramers; minimal epitope mapping; class I and class II peptide-length and processing constraints.	Recognition cannot be assigned to one HLA or ligand, occurs only with nonspecific activation, or requires concentrations and peptide pulsing far above plausible natural display.	Established for many class I systems; emerging for class II, PTMs and low-abundance tissue ligands.
4. Test mimicry, altered self and native autoantigens	The receptor recognizes a prespecified Tier A or Tier B microbial target and a tissue ligand, or recognizes infection-induced altered self, drug/PTM-altered self or a native autoantigen.	Search in prespecified order: strict keystone candidates, broader niche-calibrating microbial epitopes, then native or modified self. Use structural modeling, alanine scanning, PTM mapping, drug-state libraries, infection-remodeled immunopeptidomes, dual multimers and cross-recognition assays.	No dual recognition or pathogen-induced altered self-presentation after adequate source, peptide and receptor coverage. A coherent native-self or modified-self circuit without microbial imprinting reassigns the endotype to peptide-specific non-KET rather than being relabeled as strict KET.	Emerging. Candidate-based studies are feasible; unbiased human source-space coverage and class II screens remain limiting.
5. Verify natural processing and same-receptor recognition	The candidate ligand is generated and presented by the relevant target cell under physiological conditions, and the same receptor recognizes both proposed surfaces.	Endogenous expression or infection/drug exposure in disease-relevant cells; immunopeptidomic confirmation; CRISPR perturbation of source protein, processing and HLA; functional cytotoxicity or cytokine assays; surface plasmon resonance, single-molecule binding studies, and, where feasible, crystallography or cryo-EM.	The candidate appears only after peptide pulsing, is not naturally processed, requires nonphysiologic density or affinity, or the microbial and tissue ligands are recognized by different receptors.	Established for selected class I drug and autoantigen systems; emerging for low-abundance tissue ligands, class II and dual biophysical confirmation.
6. Map regulation, amplification and thresholds	Local inhibitory control, antigen density, cytokines, innate cells and mechanical or barrier context determine whether a target-selective response becomes tissue injury.	Titrate ligand density; perturb PD-1/PD-L1, CTLA-4, Treg and other checkpoints; measure IL-17, TNF and myeloid programs; test barrier or mechanical inputs; compare regulated and active lesions; model target selection separately from amplification.	Injury is independent of predicted regulatory or amplification variables, or tissue localization follows mechanical/barrier stress after accounting for ligand presentation and cognate receptor occupancy.	Checkpoint, cytokine and antigen-density assays established; integrated human niche and mechanical models emerging.
7. Close the loop and adjudicate the endotype	The candidate circuit maps back to the original lesion, explains a defined endotype and predicts a selective intervention or longitudinal biomarker.	Re-probe the original lesion with paired microbial and self or drug-modified pHLA multimers and single-cell methods; isolate dual-binding cells for paired-chain TCR sequencing and reconstruction; demonstrate target-cell injury; test receptor or antibody depletion/blockade; relate circuit abundance to activity and relapse; assign the endotype.	Candidate-specific cells are absent from the original lesion, circuit abundance does not track activity, or selective interruption does not alter the predicted tissue phenotype despite adequate target engagement.	Emerging. Closed-loop demonstrations exist in selected diseases; prospective endotype-specific intervention remains uncommon.

Readiness assessments are dated 13 August 2026 and are operational judgments, not permanent platform ratings.

References

1 Wucherpfennig, K. W. & Strominger, J. L. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell* **80**, 695–705 (1995). https://doi.org/10.1016/0092-8674(95)90348-8

2 Levitsky, V., de Campos-Lima, P. O., Frisan, T. & Masucci, M. G. The clonal composition of a peptide-specific oligoclonal CTL repertoire selected in response to persistent EBV infection is stable over time. *Journal of immunology* **161**, 594–601 (1998).

3 Hislop, A. D., Annels, N. E., Gudgeon, N. H., Leese, A. M. & Rickinson, A. B. Epitope-specific evolution of human CD8(+) T cell responses from primary to persistent phases of Epstein-Barr virus infection. *The Journal of experimental medicine* **195**, 893–905 (2002). https://doi.org/10.1084/jem.20011692

4 Masopust, D., Vezys, V., Marzo, A. L. & Lefrancois, L. Preferential localization of effector memory cells in nonlymphoid tissue. *Science* **291**, 2413–2417 (2001). https://doi.org/10.1126/science.1058867

5 Zhu, J. *et al.* Immune surveillance by CD8alphaalpha+ skin-resident T cells in human herpes virus infection. *Nature* **497**, 494–497 (2013). https://doi.org/10.1038/nature12110

6 Stevens, J. G. & Cook, M. L. Latent herpes simplex virus in spinal ganglia of mice. *Science* **173**, 843–845 (1971). https://doi.org/10.1126/science.173.3999.843

7 Taylor-Wiedeman, J., Sissons, J. G., Borysiewicz, L. K. & Sinclair, J. H. Monocytes are a major site of persistence of human cytomegalovirus in peripheral blood mononuclear cells. *J Gen Virol* **72 (Pt 9)**, 2059–2064 (1991). https://doi.org/10.1099/0022-1317-72-9-2059

8 McGeoch, D. J., Cook, S., Dolan, A., Jamieson, F. E. & Telford, E. A. Molecular phylogeny and evolutionary timescale for the family of mammalian herpesviruses. *J Mol Biol* **247**, 443–458 (1995). https://doi.org/10.1006/jmbi.1995.0152

9 Hertz, T. *et al.* Mapping the landscape of host-pathogen coevolution: HLA class I binding and its relationship with evolutionary conservation in human and viral proteins. *Journal of virology* **85**, 1310–1321 (2011). https://doi.org/10.1128/JVI.01966-10

10 Bouneaud, C., Kourilsky, P. & Bousso, P. Impact of negative selection on the T cell repertoire reactive to a self-peptide: a large fraction of T cell clones escapes clonal deletion. *Immunity* **13**, 829–840 (2000). https://doi.org/10.1016/s1074-7613(00)00080-7

11 Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M. & Toda, M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *Journal of immunology* **155**, 1151–1164 (1995).

12 Belkaid, Y., Piccirillo, C. A., Mendez, S., Shevach, E. M. & Sacks, D. L. CD4+CD25+ regulatory T cells control Leishmania major persistence and immunity. *Nature* **420**, 502–507 (2002). https://doi.org/10.1038/nature01152

13 Magliozzi, R. *et al.* Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain* **130**, 1089–1104 (2007). https://doi.org/10.1093/brain/awm038

14 Ostrov, D. A. *et al.* Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proc Natl Acad Sci U S A* **109**, 9959–9964 (2012). https://doi.org/10.1073/pnas.1207934109

15 Gibson, A. *et al.* Multiomic single-cell sequencing defines tissue-specific responses in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Commun* **15**, 8722 (2024). https://doi.org/10.1038/s41467-024-52990-3

16 Evans, D. M. *et al.* Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet* **43**, 761–767 (2011). https://doi.org/10.1038/ng.873

17 Burrows, S. R., Khanna, R., Burrows, J. M. & Moss, D. J. An alloresponse in humans is dominated by cytotoxic T lymphocytes (CTL) cross-reactive with a single Epstein-Barr virus CTL epitope: implications for graft-versus-host disease. *The Journal of experimental medicine* **179**, 1155–1161 (1994). https://doi.org/10.1084/jem.179.4.1155

18 Amir, A. L. *et al.* Allo-HLA reactivity of virus-specific memory T cells is common. *Blood* **115**, 3146–3157 (2010). https://doi.org/10.1182/blood-2009-07-234906

19 Mallal, S. *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *The New England journal of medicine* **358**, 568–579 (2008). https://doi.org/10.1056/NEJMoa0706135

20 Daly, A. K. *et al.* HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* **41**, 816–819 (2009). https://doi.org/10.1038/ng.379

21 Pavlos, R. *et al.* T cell-mediated hypersensitivity reactions to drugs. *Annu Rev Med* **66**, 439–454 (2015). https://doi.org/10.1146/annurev-med-050913-022745

22 Pan, R. Y. *et al.* Identification of drug-specific public TCR driving severe cutaneous adverse reactions. *Nat Commun* **10**, 3569 (2019). https://doi.org/10.1038/s41467-019-11396-2
23 Lucas, A. *et al.* Abacavir-reactive memory T cells are present in drug naive individuals. *PloS one* **10**, e0117160 (2015). https://doi.org/10.1371/journal.pone.0117160
24 Cardone, M. *et al.* A transgenic mouse model for HLA-B*57:01-linked abacavir drug tolerance and reactivity. *The Journal of clinical investigation* **128**, 2819–2832 (2018). https://doi.org/10.1172/JCI99321
25 Phillips, E. J. & Mallal, S. A. Active suppression rather than ignorance: tolerance to abacavir-induced HLA-B*57:01 peptide repertoire alteration. *The Journal of clinical investigation* **128**, 2746–2749 (2018). https://doi.org/10.1172/JCI121525
26 Mallal, S., Asiaee, A. & Phillips, E. Keystone Epitope Theory: Implications for Hypersensitivity, Autoimmunity, and Transplantation. *Pathog Immun* **11**, 16–38 (2026). https://doi.org/10.20411/pai.v11i2.1016
27 Sooda, A. *et al.* Abacavir inhibits but does not cause self-reactivity to HLA-B*57:01-restricted EBV specific T cell receptors. *Commun Biol* **5**, 133 (2022). https://doi.org/10.1038/s42003-022-03058-9
28 Almeida, C. A. *et al.* Virus-specific T-cell clonotypes might contribute to drug hypersensitivity reactions through heterologous immunity. *The Journal of allergy and clinical immunology* **144**, 608–611 e604 (2019). https://doi.org/10.1016/j.jaci.2019.05.009
29 Bjornevik, K. *et al.* Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* **375**, 296–301 (2022). https://doi.org/10.1126/science.abj8222
30 Nyeo, S. S. *et al.* Population-scale sequencing resolves determinants of persistent EBV DNA. *Nature* **650**, 664–672 (2026). https://doi.org/10.1038/s41586-025-10020-2
31 Schmidt, A. *et al.* Host control of persistent Epstein-Barr virus infection. *Nature* **653**, 444–454 (2026). https://doi.org/10.1038/s41586-026-10274-4
32 Thomas, O. G. *et al.* Anoctamin-2-specific T cells link Epstein-Barr virus to multiple sclerosis. *Cell* **189**, 585–602 e538 (2026). https://doi.org/10.1016/j.cell.2025.12.032
33 Wang, J. *et al.* EBV infection and HLA-DR15 jointly drive multiple sclerosis by myelin peptide presentation. *Cell* **189**, 569–584 e514 (2026). https://doi.org/10.1016/j.cell.2025.12.046
34 Mack, S. J. *et al.* High resolution HLA analysis reveals independent class I haplotypes and amino-acid motifs protective for multiple sclerosis. *Genes Immun* **20**, 308–326 (2019). https://doi.org/10.1038/s41435-017-0006-8
35 Reijm, S. *et al.* Multiple sclerosis-associated HLA demarcates EBV-specific CD8(+) T cells with an exhausted and brain residency phenotype. *iScience* **29**, 115744 (2026). https://doi.org/10.1016/j.isci.2026.115744
36 Hayashi, F. *et al.* Antigen specificity of clonally enriched CD8(+) T cells in multiple sclerosis. *Nat Immunol* **27**, 490–502 (2026). https://doi.org/10.1038/s41590-025-02412-3
37 Engelenburg, H. J. *et al.* B-cell abundance in perivascular cuffs associates with local lesion activity in multiple sclerosis. *Acta Neuropathol Commun* **14** (2026). https://doi.org/10.1186/s40478-025-02208-4
38 Kermode, A. G. *et al.* Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis. Pathogenetic and clinical implications. *Brain* **113 (Pt 5)**, 1477–1489 (1990). https://doi.org/10.1093/brain/113.5.1477
39 Gaitan, M. I. *et al.* Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions. *Ann Neurol* **70**, 22–29 (2011). https://doi.org/10.1002/ana.22472
40 Behrens, M. *et al.* Proinflammatory Epstein-Barr Virus Antibody Functions Track with Disease Activity in Multiple Sclerosis. *Ann Neurol* (2026). https://doi.org/10.1002/ana.78285
41 Ramagopalan, S. V. *et al.* Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. *PLoS Genet* **5**, e1000369 (2009). https://doi.org/10.1371/journal.pgen.1000369
42 Hedström, A. K. *et al.* Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis. *Brain* **134**, 653–664 (2011). https://doi.org/10.1093/brain/awq371
43 Simon, K. C. *et al.* Combined effects of smoking, anti-EBNA antibodies, and HLA-DRB1*1501 on multiple sclerosis risk. *Neurology* **74**, 1365–1371 (2010). https://doi.org/10.1212/WNL.0b013e3181dad57e
44 Arakawa, A. *et al.* Melanocyte antigen triggers autoimmunity in human psoriasis. *The Journal of experimental medicine* **212**, 2203–2212 (2015). https://doi.org/10.1084/jem.20151093
45 Pinkse, G. G. *et al.* Autoreactive CD8 T cells associated with beta cell destruction in type 1 diabetes. *Proc Natl Acad Sci U S A* **102**, 18425–18430 (2005). https://doi.org/10.1073/pnas.0508621102

46 Mazzarella, G. *et al.* Gliadin activates HLA class I-restricted CD8+ T cells in celiac disease intestinal mucosa and induces the enterocyte apoptosis. *Gastroenterology* **134**, 1017–1027 (2008). https://doi.org/10.1053/j.gastro.2008.01.008
47 Seitz, V. *et al.* Specific T-cell receptor beta-rearrangements of gluten-triggered CD8(+) T-cells are enriched in celiac disease patients' duodenal mucosa. *Clin Immunol* **256**, 109795 (2023). https://doi.org/10.1016/j.clim.2023.109795
48 Tzartos, S., Hochschwender, S., Vasquez, P. & Lindstrom, J. Passive transfer of experimental autoimmune myasthenia gravis by monoclonal antibodies to the main immunogenic region of the acetylcholine receptor. *J Neuroimmunol* **15**, 185–194 (1987). https://doi.org/10.1016/0165-5728(87)90092-0
49 Saadoun, S. *et al.* Intra-cerebral injection of neuromyelitis optica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice. *Brain* **133**, 349–361 (2010). https://doi.org/10.1093/brain/awp309
50 Schulze, K. *et al.* An adult passive transfer mouse model to study desmoglein 3 signaling in pemphigus vulgaris. *J Invest Dermatol* **132**, 346–355 (2012). https://doi.org/10.1038/jid.2011.299
51 Arakawa, A. *et al.* ERAP1 Controls the Autoimmune Response against Melanocytes in Psoriasis by Generating the Melanocyte Autoantigen and Regulating Its Amount for HLA-C*06:02 Presentation. *Journal of immunology* **207**, 2235–2244 (2021). https://doi.org/10.4049/jimmunol.2100686
52 Lee, K. H., Wucherpfennig, K. W. & Wiley, D. C. Structure of a human insulin peptide-HLA-DQ8 complex and susceptibility to type 1 diabetes. *Nat Immunol* **2**, 501–507 (2001). https://doi.org/10.1038/88694
53 Mallone, R. *et al.* CD8+ T-cell responses identify beta-cell autoimmunity in human type 1 diabetes. *Diabetes* **56**, 613–621 (2007). https://doi.org/10.2337/db06-1419
54 Skowera, A. *et al.* CTLs are targeted to kill beta cells in patients with type 1 diabetes through recognition of a glucose-regulated preproinsulin epitope. *The Journal of clinical investigation* **118**, 3390–3402 (2008). https://doi.org/10.1172/JCI35449
55 Ziegler, A. G. *et al.* Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *Jama* **309**, 2473–2479 (2013). https://doi.org/10.1001/jama.2013.6285
56 Anderson, A. M. *et al.* Beta cell reactivity defines disease-relevant pancreatic CD8 T cells in type 1 diabetes. *bioRxiv* (2026). https://doi.org/10.64898/2026.06.08.729940
57 Tollefsen, S. *et al.* HLA-DQ2 and -DQ8 signatures of gluten T cell epitopes in celiac disease. *The Journal of clinical investigation* **116**, 2226–2236 (2006). https://doi.org/10.1172/JCI27620
58 Bodd, M. *et al.* Direct cloning and tetramer staining to measure the frequency of intestinal gluten-reactive T cells in celiac disease. *Eur J Immunol* **43**, 2605–2612 (2013). https://doi.org/10.1002/eji.201343382
59 Petersen, J. *et al.* T cell receptor cross-reactivity between gliadin and bacterial peptides in celiac disease. *Nat Struct Mol Biol* **27**, 49–61 (2020). https://doi.org/10.1038/s41594-019-0353-4
60 Feitsma, A. L. *et al.* Identification of citrullinated vimentin peptides as T cell epitopes in HLA-DR4-positive patients with rheumatoid arthritis. *Arthritis Rheum* **62**, 117–125 (2010). https://doi.org/10.1002/art.25059
61 Rantapaa-Dahlqvist, S. *et al.* Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* **48**, 2741–2749 (2003). https://doi.org/10.1002/art.11223
62 Sharma, R. K. *et al.* Biased TCR gene usage in citrullinated Tenascin C specific T-cells in rheumatoid arthritis. *Sci Rep* **11**, 24512 (2021). https://doi.org/10.1038/s41598-021-04291-8
63 Namekawa, T., Wagner, U. G., Goronzy, J. J. & Weyand, C. M. Functional subsets of CD4 T cells in rheumatoid synovitis. *Arthritis Rheum* **41**, 2108–2116 (1998). https://doi.org/10.1002/1529-0131(199812)41:12<2108::AID-ART5>3.0.CO;2-Q
64 Jonsson, A. H. *et al.* Granzyme K(+) CD8 T cells form a core population in inflamed human tissue. *Sci Transl Med* **14**, eabo0686 (2022). https://doi.org/10.1126/scitranslmed.abo0686
65 Kirabo, A. *et al.* DC isoketal-modified proteins activate T cells and promote hypertension. *The Journal of clinical investigation* **124**, 4642–4656 (2014). https://doi.org/10.1172/JCI74084
66 Bloodworth, N. *et al.* Posttranslationally modified self-peptides promote hypertension in mouse models. *The Journal of clinical investigation* **134** (2024). https://doi.org/10.1172/JCI174374
67 Mignot, E. *et al.* Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *Am J Hum Genet* **68**, 686–699 (2001). https://doi.org/10.1086/318799
68 Latorre, D. *et al.* T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature* **562**, 63–68 (2018). https://doi.org/10.1038/s41586-018-0540-1

69 Pedersen, N. W. *et al.* CD8(+) T cells from patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. *Nat Commun* **10**, 837 (2019). https://doi.org/10.1038/s41467-019-08774-1
70 Yang, X. *et al.* Autoimmunity-associated T cell receptors recognize HLA-B*27-bound peptides. *Nature* **612**, 771–777 (2022). https://doi.org/10.1038/s41586-022-05501-7
71 Paley, M. A. *et al.* Mucosal signatures of pathogenic T cells in HLA-B*27+ anterior uveitis and axial spondyloarthritis. *JCI Insight* **9** (2024). https://doi.org/10.1172/jci.insight.174776
72 Morris, D. L. *et al.* MHC associations with clinical and autoantibody manifestations in European SLE. *Genes Immun* **15**, 210–217 (2014). https://doi.org/10.1038/gene.2014.6
73 Bang, S. Y. *et al.* Brief Report: Influence of HLA-DRB1 Susceptibility Alleles on the Clinical Subphenotypes of Systemic Lupus Erythematosus in Koreans. *Arthritis Rheumatol* **68**, 1190–1196 (2016). https://doi.org/10.1002/art.39539
74 Diaz-Gallo, L. M. *et al.* Four Systemic Lupus Erythematosus Subgroups, Defined by Autoantibodies Status, Differ Regarding HLA-DRB1 Genotype Associations and Immunological and Clinical Manifestations. *ACR Open Rheumatol* **4**, 27–39 (2022). https://doi.org/10.1002/acr2.11343
75 McGonagle, D., Aydin, S. Z., Gul, A., Mahr, A. & Direskeneli, H. 'MHC-I-opathy'-unified concept for spondyloarthritis and Behcet disease. *Nat Rev Rheumatol* **11**, 731–740 (2015). https://doi.org/10.1038/nrrheum.2015.147
76 Kuiper, J. J. *et al.* EULAR study group on 'MHC-I-opathy': identifying disease-overarching mechanisms across disciplines and borders. *Ann Rheum Dis* **82**, 887–896 (2023). https://doi.org/10.1136/ard-2022-222852
77 Eyting, M. *et al.* A natural experiment on the effect of herpes zoster vaccination on dementia. *Nature* **641**, 438–446 (2025). https://doi.org/10.1038/s41586-025-08800-x
78 Taquet, M., Dercon, Q., Todd, J. A. & Harrison, P. J. The recombinant shingles vaccine is associated with lower risk of dementia. *Nature medicine* **30**, 2777–2781 (2024). https://doi.org/10.1038/s41591-024-03201-5
79 Viegas, S. *et al.* Passive and active immunization models of MuSK-Ab positive myasthenia: electrophysiological evidence for pre and postsynaptic defects. *Exp Neurol* **234**, 506–512 (2012). https://doi.org/10.1016/j.expneurol.2012.01.025
80 Dean, E. G. *et al.* Experimental autoimmune Goodpasture's disease: a pathogenetic role for both effector cells and antibody in injury. *Kidney Int* **67**, 566–575 (2005). https://doi.org/10.1111/j.1523-1755.2005.67113.x
81 Tamaki, H. *et al.* Evaluation of TSH receptor antibody by 'natural in vivo human assay' in neonates born to mothers with Graves' disease. *Clin Endocrinol (Oxf)* **30**, 493–503 (1989). https://doi.org/10.1111/j.1365-2265.1989.tb01420.x
82 Djelmis, J., Sostarko, M., Mayer, D. & Ivanisevic, M. Myasthenia gravis in pregnancy: report on 69 cases. *Eur J Obstet Gynecol Reprod Biol* **104**, 21–25 (2002). https://doi.org/10.1016/s0301-2115(02)00051-9
83 Campo-Voegeli, A. *et al.* Neonatal pemphigus vulgaris with extensive mucocutaneous lesions from a mother with oral pemphigus vulgaris. *Br J Dermatol* **147**, 801–805 (2002). https://doi.org/10.1046/j.1365-2133.2002.04969.x
84 Manso, C., Querol, L., Mekaouche, M., Illa, I. & Devaux, J. J. Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. *Brain* **139**, 1700–1712 (2016). https://doi.org/10.1093/brain/aww062
85 Manso, C. *et al.* Anti-Neurofascin-155 IgG4 antibodies prevent paranodal complex formation in vivo. *The Journal of clinical investigation* **129**, 2222–2236 (2019). https://doi.org/10.1172/JCI124694
86 Chung, W. H. *et al.* Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* **428**, 486 (2004). https://doi.org/10.1038/428486a
87 Ishimoto, T. *et al.* Multiple environmental antigens may trigger autoimmunity in psoriasis through T-cell receptor polyspecificity. *Front Immunol* **15**, 1374581 (2024). https://doi.org/10.3389/fimmu.2024.1374581
88 Ge, C. *et al.* Key interactions in the trimolecular complex consisting of the rheumatoid arthritis-associated DRB1*04:01 molecule, the major glycosylated collagen II peptide and the T-cell receptor. *Ann Rheum Dis* **81**, 480–489 (2022). https://doi.org/10.1136/annrheumdis-2021-220500
89 Salvado, M. *et al.* HLA-DQB1*05:02, *05:03, and *03:01 alleles as risk factors for myasthenia gravis in a Spanish cohort. *Neurol Sci* **43**, 5057–5065 (2022). https://doi.org/10.1007/s10072-022-06102-y
90 Hyun, J. W. *et al.* HLA Association With AQP4-IgG-Positive Neuromyelitis Optica Spectrum Disorder in the Korean Population. *Neurol Neuroimmunol Neuroinflamm* **12**, e200366 (2025). https://doi.org/10.1212/NXI.0000000000200366
91 Gil, J. M. *et al.* Study of the association between human leukocyte antigens (HLA) and pemphigus vulgaris in Brazilian patients. *Int J Dermatol* **56**, 557–562 (2017). https://doi.org/10.1111/ijd.13577