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Review

Neuroimmune State Configurations at the Amyloid–Tau Interface in Alzheimer's Disease: A Testable Framework

Kai Zhang[1#], Yuanyuan Zhang[1#], Xindi Jiang[1], Xiu Chen[1*]

[1]Department of Neurology, Affiliated Hospital of Nantong University, Medical School of Nantong University, Nantong, China.

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ABSTRACT: Neuroimmune mechanisms are central to Alzheimer's disease (AD), but a single continuum of "more inflammation" does not explain why similar amyloid-β (Aβ) and tau burdens are associated with different clinical trajectories, tissue responses, and treatment risks. We present a testable neuroimmune-state framework that integrates, rather than replaces, the AT(N) system, cellular-phase models, and transcriptional descriptions of disease-associated microglia and reactive astrocytes. The framework treats neuroimmune states as multidimensional, regionally heterogeneous configurations defined by pathological substrate, cellular program, biological target, vascular and aging context, and measurable patient-level readouts. We distinguish four meanings of the amyloid–tau interface: a biomarker interface, a spatial tissue interface, a cellular-state interface, and a clinical-progression interface. We then examine the hypothesis of phagocytic target switching, in which clearance pathways that support plaque compaction or debris removal may, under selected tau- and complement-rich conditions, contribute to removal of stressed but potentially functional synapses. We explicitly separate evidence from longitudinal human studies, cross-sectional biomarkers, human genetics, postmortem tissue, animal models, and in vitro systems. Current biomarkers cannot yet assign patients to validated discrete neuroimmune states; proposed state readers should therefore be probabilistic, allow regional coexistence and parallel vascular–immune trajectories, and be tested for incremental value beyond established AD biomarkers and co-pathologies. Finally, we organize immune-directed interventions by clinical evidence level and frame stage matching as a research strategy rather than a treatment algorithm. The model is useful only if its predictions can be prospectively supported or falsified.

Keywords: Alzheimer's disease, neuroimmunity, amyloid–tau interface, immunomodulation, microglia, biomarkers

Introduction

Alzheimer's disease (AD) is biologically anchored by amyloid-β (Aβ) deposition and tau pathology, but these proteinopathies alone do not account for the marked heterogeneity of cognitive decline, regional vulnerability, and treatment response. Many people remain Aβ-positive for years, whereas the emergence and spread of tau, synaptic failure, and neurodegeneration more closely track clinical progression. This gap has shifted the field from a neuron-centered account toward a multicellular view involving microglia, astrocytes, vascular and brain-border compartments, and peripheral immune signals.

Immune involvement in AD is already well established. Recent syntheses have reviewed innate and adaptive immunity, glial biology, blood–brain barrier (BBB) and lymphatic pathways, systemic aging, and therapeutic opportunities [1–3]. The remaining problem is not whether neuroimmune activity occurs, but how its function depends on pathological substrate, anatomical niche, target identity, and host context.

Immune molecules are not intrinsically pathological. Complement proteins, cytokines, chemokines, major histocompatibility complex (MHC) molecules, and

***Correspondence should be addressed to:** Dr. Xiu Chen, Department of Neurology, Affiliated Hospital of Nantong University, Medical School of Nantong University, Nantong, China. Email: ycchenxiu1990@163.com. #These authors contributed equally to this work.

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immune-derived trophic signals participate in synaptic remodeling, neurogenesis, learning, memory, and brain-border surveillance [4]. This physiological background is compatible with the cellular-phase concept of AD [5], the AT(N) biomarker framework [6], and revised criteria that place inflammatory/immune and vascular processes alongside Aβ, tau, and neurodegeneration [7].

This Review proposes a working framework, not a replacement disease classification. Neuroimmune states are treated as multidimensional and partially overlapping configurations that may coexist across brain regions, recur, or follow alternative trajectories. The framework links pathological substrate to tissue response, patient-level readouts, and experimentally testable therapeutic hypotheses. Its intended contribution is therefore integrative: it asks when a cellular state is likely to be protective, compensatory, maladaptive, or merely correlated with injury.

The amyloid–tau interface is used as an organizing problem because human spatial studies identify regionally structured cellular changes around Aβ and tau pathology [8], astrocyte reactivity modifies the association between Aβ and tau [9], and glial imaging becomes more informative when interpreted with tau burden [10]. However, these observations do not establish a universal, discrete, or irreversible sequence. Figure 1 and Tables 1–3 therefore depict a state space with uncertainty, overlap, feedback, and parallel vascular–immune trajectories rather than a deterministic left-to-right progression.

Table 1. Evidence calibration and falsifiability of the principal propositions.

Major proposition	Evidence class and strongest support	What is currently supported	Main limitation	Falsifiable or competing test
Aβ containment is a distinct useful construct	Human genetics and tissue; animal mechanism [23–41]	Plaque-facing microglial sensing, lipid handling, clustering, and compaction can limit local injury in models and are genetically disease-relevant.	No validated patient classifier; protective and harmful functions may coexist.	At matched Aβ/tau burden, a prespecified containment profile must predict lower subsequent injury or slower progression.
The amyloid–tau interface organizes neuroimmune change	Human spatial tissue and biomarkers [8–10,44–58]	Aβ, tau, glial, and clinical signals show regional and temporal coupling.	Biomarker, spatial, cellular, and clinical interfaces are not equivalent; most data are cross-sectional.	Interface levels should show partial correspondence and incremental prediction beyond A/T/N alone.
Phagocytic target switching contributes to synaptic loss	Animal and in vitro mechanism; human mechanistic inference [61–77,131]	Complement, phosphatidylserine, and glial pathways can clear synapses or living neurons in models.	No longitudinal demonstration that the same human microglia switch targets.	Show target-specific engulfment of viable/recoverable synapses beyond irreversible injury; otherwise reject "mis-clearance."
Adaptive immunity amplifies selected tissue states	Human CSF/postmortem associations; models [78–93]	Clonal and brain-border T-cell engagement occurs in subsets and can modify pathology in models.	Antigen specificity and causal direction are largely unknown; B-cell evidence is limited.	Adaptive signals should identify a reproducible subgroup and add outcome information beyond general injury.
Aging and vascular trajectories condition the state space	Human biomarker, vascular, genetic and cohort evidence [3,19,81,94–101,132]	Aging, BBB dysfunction, CAA, systemic inflammation, and mixed pathologies alter glial and clinical readouts.	Many markers are nonspecific; parallel and downstream effects are difficult to separate.	Model aging/vascular profiles separately and test whether they explain independent variance and treatment risk.
State matching improves therapeutic development	Clinical trials plus preclinical studies [41–43,99,100,123–130]	Intervention effects and toxicity depend on disease stage and vascular context; pathway engagement alone is insufficient.	No validated state-based treatment algorithm or biomarker thresholds.	Prospectively test treatment-by-state interactions; no interaction means the added framework has limited value.

Note: Evidence classes are not combined into a numerical score. Human longitudinal or trial evidence, cross-sectional biomarkers, postmortem tissue, genetics, animal models, in vitro systems, and mechanistic inference support different claims and should not be treated as interchangeable.

Review approach and evidence assessment

This is a conceptual narrative Review rather than a systematic review or clinical guideline. References were selected to represent influential mechanistic studies, recent human spatial and single-cell datasets, longitudinal and cross-sectional biomarker studies, human genetics, animal and in vitro experiments, and therapeutic trials. No formal risk-of-bias score or meta-analysis was performed.

To avoid treating unlike evidence as equivalent, major claims are calibrated to seven evidence classes: longitudinal human studies and clinical trials; cross-sectional human biomarker studies; human postmortem or spatial tissue studies; human genetics; animal models; in vitro or organoid systems; and mechanistic inference across levels. Transcriptional states are not assumed to establish phagocytic function, neurotoxicity, or therapeutic responsiveness. Table 1 summarizes the evidence supporting the principal propositions and the observations that would weaken them.

Figures 1–4 are conceptual review schematics that were manually redrawn by the authors for the revised manuscript. All scientific concepts, labels, relationships, and visual elements were defined and verified by the authors. The figures contain no original experimental data, and no generative-AI-generated visual content is included in the revised manuscript.

OpenAI ChatGPT (GPT-5.6 Sol; accessed 24 September 2026) was used solely to assist with English-language polishing and final formatting checks. Representative prompt: "Polish the English for grammar, clarity, readability, and formatting consistency without changing the scientific meaning, citations, or structure." The authors independently verified all scientific content, citations, interpretations, and final wording and take full responsibility for the manuscript.

1. From neuroinflammation to a testable neuroimmune-state framework

The term neuroinflammation is often used to collapse diverse processes into one intensity scale. A more precise description asks four questions: what pathological substrate is present, which cellular program is engaged, what biological target is being acted upon, and what consequence follows for tissue function. A rise in a glial marker may represent successful containment, compensation, failed repair, or injury amplification depending on these dimensions.

Physiological immune functions illustrate why direction cannot be inferred from activation alone. Complement signaling contributes to developmental synapse elimination [11], microglia refine circuits through activity- and complement-dependent engulfment [12], and microglial brain-derived neurotrophic factor supports learning-dependent synapse formation [13]. Neuronal MHC class I also participates in activity-dependent plasticity [14]. Border-associated immunity has similarly context-dependent roles in neurogenesis, learning, social behavior, and memory [15–18].

Aging modifies this baseline. Type I interferon signaling at the choroid plexus can impair brain function [19], and meningeal lymphatic vessels connect central nervous system (CNS) fluid and antigen drainage to cervical lymph nodes [20]. These changes occur before or independently of AD pathology and should not be labeled an Aβ-containment state unless an Aβ anchor is present.

The proposed framework therefore differs from disease-associated microglia (DAM), reactive-astrocyte, and cellular-phase models mainly in scale and testability. Those models describe cellular programs or disease phases; the present framework requires that a proposed state also specifies pathological context, target, spatial location, patient readout, and competing explanation. Its value must be judged by whether these additions improve prediction or intervention testing beyond existing human-data-focused frameworks and models centered on apolipoprotein E (APOE) and triggering receptor expressed on myeloid cells 2 (TREM2) [21,22].

2. Aβ-positive containment: a local configuration, not a universal stage

An Aβ-positive containment configuration is a plausible, but not obligatory, early tissue response. Plaque-associated microglia can remodel lipid and phagocytic programs, cluster around deposits, compact fibrillar Aβ, and restrict peri-plaque exposure to toxic Aβ species. The term "containment" denotes this locally protective relationship; it does not imply that the entire brain or patient is in a uniformly protective state.

Human genetics places microglial sensing and adaptation at the center of Aβ handling. Rare TREM2 variants increase risk of late-onset AD [23,24], and coding variants in PLCG2, ABI3, and TREM2 implicate microglial innate-immune pathways [25]. Disease-associated microglia and the TREM2–APOE pathway link lipid metabolism, phagocytosis, survival, and immune sensing [26,27]. TREM2 can act as a lipid sensor, bind apolipoproteins, and mediate Aβ-associated responses [28–30].

Spatial organization is critical. Microglia can form a barrier around plaques that limits Aβ42 hotspots [31], whereas TREM2 haploinsufficiency impairs barrier formation, reduces plaque compaction, and worsens axonal dystrophy [32]. TREM2 deficiency has different effects across models and disease stages [33–35], showing why plaque burden alone is an inadequate measure of

benefit. Plaque architecture, neuritic damage, microglial position, and tau context are also required.

Human tissue further demonstrates heterogeneity rather than a single activation state. APOE and TREM2 variants alter amyloid-responsive microglial populations [36], CD33 inhibits microglial Aβ uptake [37], and PLCG2 variants can produce different functional phenotypes [25,38]. These findings support calibrated sensing and target-selective clearance, not generalized immune activation.

TREM2-directed intervention illustrates both the appeal and the limitations of the containment hypothesis. TREM2 antibodies increase microglial proliferation or metabolic activity and reduce pathology in animal models [39,40]. Gallo and colleagues reported that the synthetic TREM2-binding sulfolipid SULF A enhanced Aβ phagocytosis, plaque-associated microglial recruitment, and behavioral outcomes in primary murine microglia and Tg2576 mice without a conventional inflammatory signature [41]. This study strengthens the biological plausibility of inflammation-sparing microglial support, but it remains a murine preclinical study and does not validate a patient state or therapeutic window.

Clinical translation remains unresolved. A first-in-human study of the TREM2 agonistic antibody AL002 established feasibility and pharmacodynamic engagement [42], whereas a phase 2 trial did not establish clinical efficacy [43]. TREM2 activation may therefore be beneficial only in selected pathological and temporal contexts, and soluble TREM2 (sTREM2) cannot be treated as a direct measure of a protective state. It may reflect receptor shedding, microglial abundance, survival, turnover, or activation.

3. Four levels of the amyloid–tau interface

The term amyloid–tau interface is potentially useful only if its different meanings are separated. We distinguish four related levels that may occur at different times and need not coincide in the same person or region.

Biomarker interface. This level refers to movement from Aβ positivity with absent or low tau toward measurable tau pathology, assessed with amyloid and tau positron emission tomography (PET), cerebrospinal fluid (CSF) biomarkers, or plasma phosphorylated tau. Aβ-positive, tau-positive cognitively unimpaired individuals have a higher risk of subsequent decline than Aβ-positive, tau-negative individuals [44], and tau PET is strongly associated with cognitive progression [45]. These observations define risk, not an immune mechanism.

Spatial tissue interface. This level refers to local proximity among plaques, tau-positive neurites or neurons, glial cells, synapses, and vascular structures. Spatial transcriptomics and in situ sequencing identify plaque-associated multicellular programs [46], while multiregion and multimodal atlases show substantial regional heterogeneity [47–49]. Spatial adjacency supports a candidate interaction but cannot by itself establish direction or causality.

Cellular-state interface. This level refers to changes in microglial, astrocytic, neuronal, oligodendroglial, or vascular-cell programs in tissue containing Aβ and tau. Single-cell and single-nucleus studies demonstrate broad cell-type-specific dysregulation [50–55]. A human spatial study identified microglial programs associated with an Aβ–tau inflection point and with dementia or resilience [8]. These data provide a conceptual anchor, but a transcriptional state does not establish actual phagocytosis, antigen presentation, neurotoxicity, or reversibility.

Clinical-progression interface. This level refers to the period in which tau spread, neurodegeneration, or cognitive decline accelerates. It is a patient-level outcome and may be influenced by reserve, vascular disease, co-pathology, and systemic health. Resistance denotes lower pathology than expected for a given exposure; resilience denotes better cognition than expected for the amount of pathology; brain reserve and cognitive reserve describe structural and functional capacities that modify clinical expression. These constructs should not be used interchangeably.

Glial measurements reinforce the need for contextual interpretation. Microglial activation and tau can propagate along related anatomical patterns [10], yet microglial activation has also been associated with less subsequent tau accumulation in nondemented people with AD pathology [56]. Disease-associated astrocytes occur in AD and aging [57], plasma glial fibrillary acidic protein (GFAP) rises early with Aβ pathology [58], and astrocyte reactivity modifies the relationship between Aβ and tau [9]. The same glial signal can therefore have different meanings at different interface levels.

States may coexist within a patient and even within one anatomical region. Plaque-facing microglia may retain containment functions while neighboring tau-rich circuits show complement activation and synaptic vulnerability. Other patients may exhibit a dominant vascular–immune trajectory or mixed pathologies without a clear transition through all proposed configurations. Figure 1 therefore uses adjacent domains, reciprocal arrows, and parallel pathways. Human genetics and cross-dataset single-cell or spatial resources can help test whether these dimensions generalize across cohorts [59,60].

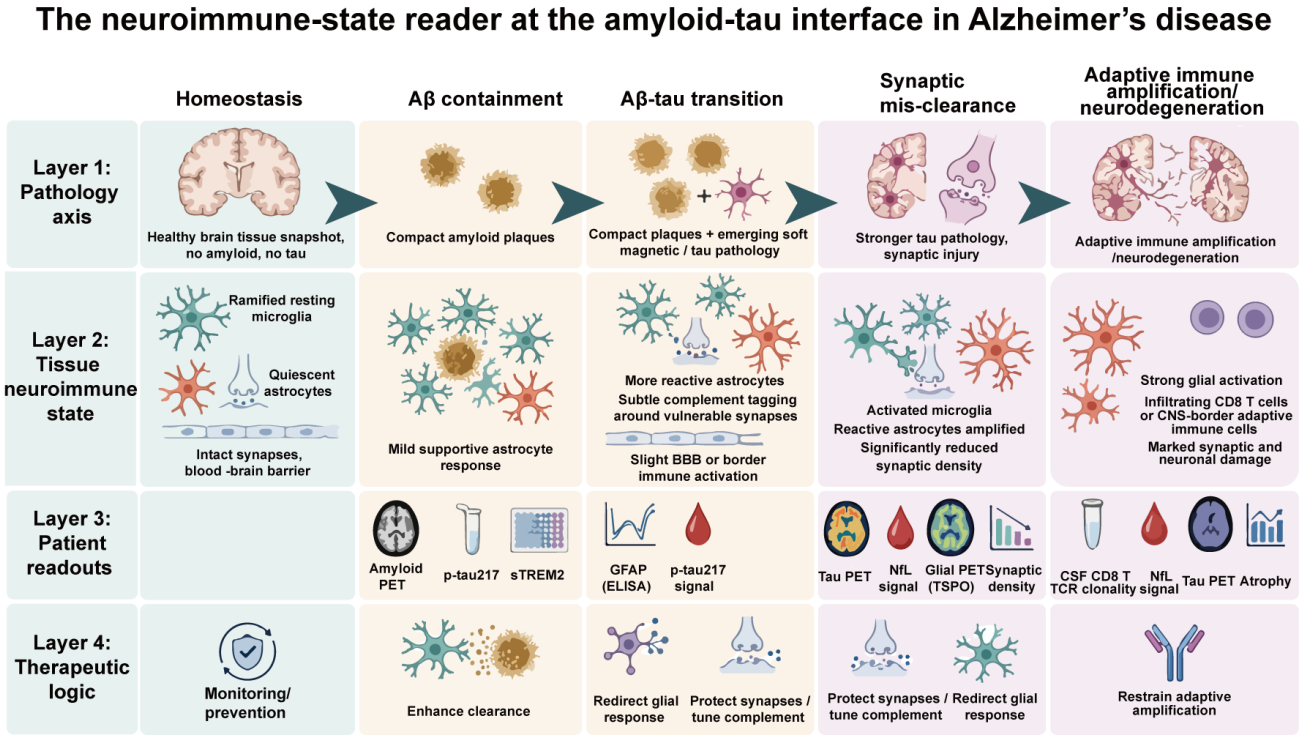


Figure 1. A multidimensional neuroimmune-state framework at the amyloid–tau interface. Neuroimmune configurations are represented as overlapping and potentially reversible domains rather than a deterministic sequence. Aβ containment, Aβ–tau coupling, synaptic vulnerability, and adaptive immune engagement can coexist across regions and are conditioned by aging, sex, genotype, vascular/CAA pathology, systemic inflammation, and co-pathologies. The amyloid–tau interface has biomarker, spatial tissue, cellular-state, and clinical-progression meanings that may be asynchronous. Solid arrows indicate better-supported relationships; dashed and reciprocal arrows indicate hypotheses, feedback, or alternative trajectories. Patient-level readouts are research measurements that require validation and do not currently define treatment eligibility.

The strongest test of the interface model is not whether each component is associated with AD, but whether combining interface levels adds predictive information beyond Aβ, tau, neurodegeneration, age, vascular injury, and co-pathology. Failure to improve prediction would argue that the framework is descriptive rather than clinically informative.

4. Phagocytic target switching and synaptic mis-clearance

Phagocytic target switching is the most specific mechanistic hypothesis in this Review. It proposes that clearance systems can have opposite tissue consequences because the identity and viability of the target change. During plaque containment, microglial and complement pathways may support aggregate compaction, uptake, and debris removal. In a tau- and complement-rich niche, stressed synapses, dystrophic neurites, or living neurons may also display recognition signals and become vulnerable to engulfment.

We use synaptic mis-clearance to mean removal of a synapse or neuritic structure that remains viable or potentially functional, or whose dysfunction might otherwise be reversible. Removal of irreversibly destroyed debris is not mis-clearance. This distinction is essential because current human studies rarely establish the prior functional state of an engulfed structure.

Complement-mediated synapse loss provides the clearest mechanistic precedent. Complement and microglia mediate early synapse loss in AD mouse models [61], and C3 deficiency can protect synapses and cognition despite increased plaque burden [62]. Astrocyte-derived C3 and microglial complement receptors also participate in Aβ handling [63,64], whereas C1q and C3aR signaling contribute to synaptic injury in tauopathy models [65,66]. These findings show branch-, receptor-, cell-, and stage-specific effects rather than a uniformly harmful complement cascade.

"Eat-me" signals offer a candidate mechanism for target ambiguity. Tau-bearing living neurons can expose phosphatidylserine and undergo microglial engulfment [67], and local phosphatidylserine exposure mediates developmental pruning [68]. In AD models, TREM2-dependent engulfment of hyperactive phosphatidylserine-positive synapses can reduce neuronal hyperactivity [69],

whereas the R47H TREM2 variant alters synaptosome and neuronal phagocytosis [70]. Whether these events are compensatory or harmful depends on the functional state of the target and the circuit-level outcome.

Aging and astrocytes modify this process. CD22 blockade restores aspects of homeostatic microglial phagocytosis in aged mice [71], but increasing phagocytosis without target specificity could be unsafe in tau-rich tissue. Astrocytes and microglia jointly mediate C1q-dependent synapse elimination [72], whereas neuronal pentraxin 2 restrains complement activity and microglia-mediated synapse loss [73]. Downstream complement effectors such as C5a receptor 1 (C5aR1) may offer more selective experimental targets [74–77].

Current evidence does not demonstrate that the same human microglial cell or clone longitudinally changes from plaque-directed clearance to removal of viable synapses. The model is an inference assembled from human spatial associations, postmortem tissue, and mechanistic animal or in vitro experiments. Alternative explanations include simultaneous but distinct microglial subpopulations, independent Aβ- and tau-induced programs, or generalized tissue injury that increases both phagocytic markers and synapse loss.

The target-switching hypothesis would be strengthened by longitudinal or lineage-resolved evidence linking target identity, phagocytic program, and functional consequence in the same tissue context. It would be weakened if synaptic engulfment were fully explained by irreversible degeneration, if the responsible cells were unrelated to plaque-associated populations, or if target-specific measures did not predict decline beyond nonspecific injury markers.

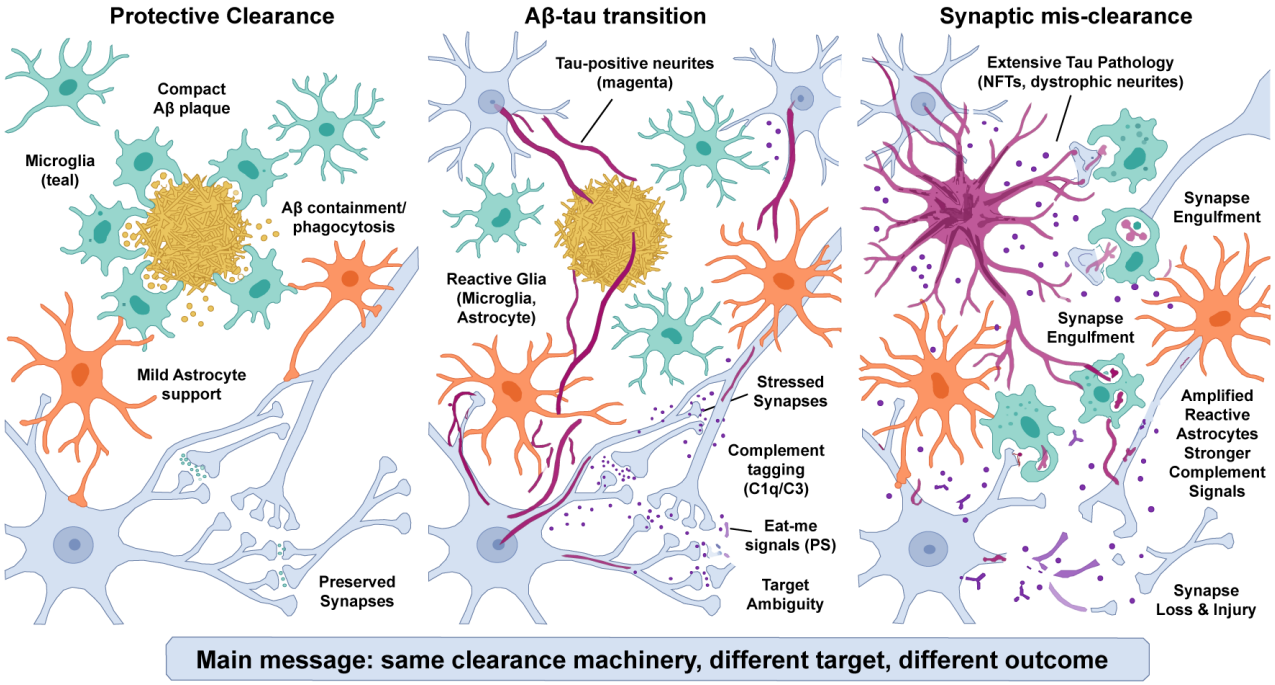


Figure 2. Phagocytic target switching as a testable hypothesis. Clearance pathways can have different consequences depending on target identity and viability. Plaque-associated phagocytosis and debris removal may support local containment, whereas complement tagging, phosphatidylserine exposure, astrocyte–microglia interactions, and tau-associated stress may create ambiguity between irreversibly damaged structures and synapses that remain functional or recoverable. "Synaptic mis-clearance" is restricted to inappropriate removal of the latter. Human studies have not yet shown longitudinal switching by the same microglial cells; the figure therefore distinguishes established mechanisms in models from the proposed human trajectory.

5. Adaptive immune amplification: subgroup biology, not proof of autoimmunity

Adaptive immune amplification refers to organized recruitment, persistence, clonal expansion, or effector signaling of adaptive immune cells in relation to CNS tissue injury. It is not synonymous with any T-cell presence, and it does not by itself establish that AD is an autoimmune disease.

Human data support organized T-cell engagement in selected patients. Clonally expanded CD8+ T cells patrol the CSF in AD [78], extravascular T cells in AD brain correlate more closely with tau than amyloid pathology [79], and clonally expanded tissue-resident CD8+ T cells occur in leptomeningeal and brain-border compartments across human degenerative brain diseases [80]. These findings do not establish antigen specificity or pathogenicity.

Brain-border routes provide anatomical plausibility. Meningeal lymphatics drain CNS macromolecules and influence aging-related cognitive decline and AD-like pathology [81], Aβ is enriched in human cervical lymph nodes [82], and the choroid plexus can regulate immune surveillance and repair [83]. In tauopathy models, microglia-mediated T-cell infiltration drives neurodegeneration [84], and a humanized three-dimensional model links infiltrating CD8+ T cells to microglial activation and CXCL10–CXCR3 signaling [85].

Adaptive responses can be protective or harmful. Manipulating regulatory T cells has produced opposite or context-dependent effects in AD models [86,87], CXCR6+ programmed cell death protein 1 (PD-1)+ brain-resident CD8+ T cells limit pathology in one model [88], and clonally expanded CD8+ T cells have stage-specific effects on amyloid pathology [89]. Aβ-reactive T cells are detectable in older people and AD [90], and Aβ-specific regulatory T cells can attenuate pathology in mice [91].

The evidence base is more T-cell-rich than B-cell-rich. B cells, plasma cells, immunoglobulins, immune complexes, and antibody-dependent mechanisms could contribute through meningeal or perivascular compartments, but human evidence linking defined B-cell clonotypes or humoral specificity to the proposed amyloid–tau states is currently insufficient for a parallel mechanistic section. We therefore treat humoral immunity as an important evidence gap rather than assume absence of effect.

Checkpoints or other adaptive immune interventions require especially strict selection. PD-1 blockade improved pathology in some mouse studies [92] but failed to alter cerebral Aβ burden in several other amyloid models [93]. CSF immune profiling, T-cell receptor (TCR) or B-cell receptor (BCR) clonality, and interferon (IFN)/C-X-C motif chemokine ligand (CXCL) signatures are research readouts; they are not validated indications for checkpoint treatment in AD.

6. Aging-conditioned baseline, parallel vascular–immune trajectories, and co-pathologies

Aging, vascular pathology, and co-pathologies are not peripheral annotations to the model. They shape the baseline state before Aβ or tau appears, create parallel routes to glial activation and neurodegeneration, and alter the specificity of nearly every proposed biomarker.

Aging-conditioned baseline. Normal aging can produce immunosenescence, inflammaging, myeloid skewing, senescent glial programs, impaired efferocytosis, altered lipid handling, and declining meningeal lymphatic function [3,19,57,71,81,94]. These changes are not an Aβ-containment state because they do not require Aβ pathology. They may, however, change the probability that a subsequent Aβ response is protective, insufficient, or maladaptive.

Age-associated clonal hematopoiesis illustrates why simple "more inflammation" assumptions can fail. In large human cohorts, clonal hematopoiesis was associated with lower AD risk, and donor-derived mutant cells were identified in the brain with microglia-like transcriptional features [95]. The observation is not a general endorsement of clonal hematopoiesis, which has other health risks; it demonstrates that age-related myeloid remodeling can have mutation- and context-specific associations.

Sex is another biological variable rather than a nuisance covariate. Sex-related differences in immune aging, APOE effects, glial programs, vascular risk, and biomarker trajectories may alter both baseline state and transition probabilities. Studies and trials should therefore report sex-stratified effects when adequately powered and test interactions rather than merely adjust for sex.

Parallel vascular–immune trajectory. BBB breakdown permits blood-derived proteins, cells, and mediators to alter the CNS environment [96] and can be associated with cognitive dysfunction partly independently of classical Aβ or tau changes [97]. APOE4-related pericyte injury and BBB dysfunction predict cognitive decline [98]. Cerebral amyloid angiopathy (CAA), microhemorrhage, fibrinogen leakage, impaired perivascular clearance, and vascular inflammation can directly activate glia and injure synapses; they need not occur downstream of a neuronal Aβ–tau transition.

This vascular trajectory is particularly important for anti-Aβ antibodies. CAA and microvascular fragility influence antibody distribution, perivascular clearance, and amyloid-related imaging abnormalities (ARIA). ARIA in aducanumab and lecanemab studies [99,100] should therefore be interpreted as an immune–vascular interaction, not only a treatment toxicity added after the core disease model. Magnetic resonance imaging (MRI) microbleeds, superficial siderosis, edema, anticoagulant exposure, and APOE genotype are safety variables, not neuroimmune-state labels by themselves.

Co-pathologies and frailty. In older adults, AD neuropathologic change commonly coexists with vascular lesions, Lewy body disease, TAR DNA-binding protein 43 (TDP-43)/limbic-predominant age-related TDP-43 encephalopathy (LATE), hippocampal sclerosis, and other pathologies. Community autopsy studies show that mixed pathologies account for a large proportion of dementia [101]. Systemic inflammation, infection, renal dysfunction, cancer, medication exposure, and frailty can also alter GFAP, neurofilament light chain (NfL), chemokines, immune-cell profiles, and cognition.

Consequently, a rise in GFAP, NfL, translocator protein (TSPO) signal, or inflammatory markers cannot be assigned to an amyloid–tau neuroimmune transition without differential interpretation. At minimum, studies should characterize vascular injury, major co-pathologies where possible, systemic inflammatory conditions, age, sex, APOE genotype, and clinical reserve. The framework applies most directly to late-onset AD; autosomal-dominant or other early-onset forms may have different immune and vascular baselines despite shared Aβ and tau pathology.

Microbiota, infection, diet, trauma, and other exposures can shape systemic inflammation, vascular integrity, and glial priming through immune, metabolic, and neural pathways [102–105]. Because confounding and reverse causality remain substantial, these factors are best treated as modifiers or alternative explanations rather than independent substitutes for AD pathology.

7. Operationalizing a patient-level state reader

A patient-level neuroimmune-state reader is currently a research construct, not a validated classifier. No reproducible, platform-independent thresholds define containment, interface, mis-clearance, or adaptive amplification. State assignment should therefore be probabilistic, multidimensional, and accompanied by an uncertainty estimate.

The first layer consists of pathological anchors. Amyloid PET or CSF Aβ42/40 establishes Aβ status; tau PET and plasma or CSF phosphorylated tau characterize tau emergence and distribution; NfL, structural imaging, and other measures describe injury. Aβ and tau positivity predict decline more strongly than Aβ alone [44,45]. Plasma phosphorylated tau at threonine 217 (p-tau217) has high diagnostic performance [106,107], and phosphorylated tau at threonine 231 (p-tau231) or p-tau217 can detect early Aβ-associated changes [108,109]. These markers define AD biology but do not specify an immune state.

The second layer consists of supportive tissue-response measurements. Plasma or CSF GFAP provides an astrocytic signal linked to Aβ and Aβ–tau coupling [9,58]. CSF sTREM2 is associated with early microglial response, tau-related neurodegeneration, clinical trajectory, and metabolic changes [110–113]. Chitinase-3-like protein 1 (YKL-40) provides a broader astroglial or inflammatory readout [114,115]. None is sufficiently specific to assign a state alone.

The third layer measures biological consequence. Plasma or CSF NfL tracks axonal injury and longitudinal progression [116,117] but is not AD-specific. Synaptic markers, complement fragments, and imaging of atrophy or metabolism may help determine whether a tissue response is associated with preserved function or escalating injury. A containment hypothesis requires evidence of limited neuritic injury, not simply a high microglial marker.

Imaging of glia must be interpreted target by target. TSPO PET differs across ligands, binding genotypes, quantification methods, cellular sources, and disease stages. TSPO signal can arise from microglia, astrocytes, and vascular elements and should not be called a unitary "microglial PET" measure. Studies show potentially protective, dynamic, or tau-associated patterns [10,118–120], but no tracer currently assigns the proposed states in routine practice.

The fourth layer assesses adaptive and modifier axes. CSF immune-cell profiling and TCR clonality can identify organized immune engagement [78,80], but low cell counts, sampling variability, and uncertain antigen specificity limit interpretation. APOE genotype, MRI vascular markers, BBB measures, systemic inflammatory burden, age, sex, renal function, infection, and co-pathologies modify both biology and assay specificity.

Operationally, a study should report a state profile rather than force a single label: for example, Aβ-positive/tau-low with plaque-associated glial response and stable injury markers; Aβ-positive/tau-emerging with astrocytic and regional glial signals; tau-positive with rising injury and complement or synaptic vulnerability; or adaptive immune engagement superimposed on one of these profiles. Different profiles may coexist across regions, and a parallel vascular profile should be reported separately.

The minimal useful panel remains unknown. A proposed panel must show reproducibility across cohorts and platforms, longitudinal stability or interpretable dynamics, tissue correspondence, and incremental prediction beyond Aβ, tau, neurodegeneration, vascular injury, age, sex, and co-pathology. Blood-biomarker consensus reviews similarly emphasize interpretation with established AD biomarkers and clinical context [121]. Until those criteria are met, Table 2 should be read as a design template for research cohorts rather than a clinical scoring system.

8. Stage-matched immunomodulation as an evidence-tiered research strategy

Combination and stage-matched immunomodulation have been proposed as next-generation research directions [122], but current evidence does not support a clinical algorithm that selects TREM2 agonism, complement modulation, glial redirection, or adaptive immune therapy from a biomarker panel. The therapeutic discussion should instead separate established approaches, human

investigational programs, and preclinical or conceptual strategies.

Table 2. Research-oriented operational profiles and validation requirements.

Research profile	Required pathological anchors	Supportive readouts (not defining alone)	Coexistence/alternative trajectory	Key confounders and validation requirement
Aβ-positive containment candidate	Confirmed Aβ positivity; absent/low regional tau; limited injury progression.	Plaque-associated glial signal, GFAP, sTREM2, plaque morphology, stable NfL [31,32,56–58,110–113].	May coexist with tau-rich or vascular-fragile regions.	Age, APOE, assay platform, CAA. Must predict slower tau/injury at matched Aβ burden.
Aβ–tau coupling candidate	Aβ positivity plus emerging/increasing tau by PET or fluid biomarker.	GFAP, regional glial PET, dynamic sTREM2, early injury markers [9,10,44,45,56–58,108–113].	Biomarker and tissue interfaces may be asynchronous.	Reserve, co-pathology, regional sampling. Must improve prediction beyond A/T/N.
Synaptic-vulnerability / mis-clearance candidate	Tau-associated region plus evidence of synaptic injury or complement engagement.	Complement fragments, synaptic markers, NfL, glial imaging, phosphatidylserine-related assays [62–77,131].	Can coexist with useful debris clearance and plaque containment.	Irreversible degeneration can mimic mis-clearance. Requires evidence of target viability and functional consequence.
Adaptive immune-engagement candidate	Underlying AD pathology plus organized CSF/brain-border immune signal.	CSF immune profiling, TCR/BCR clonality, IFN/CXCL signatures [78–85].	May overlay any Aβ/tau profile; not necessarily pathogenic.	Infection, cancer, autoimmune disease, low CSF cell counts. Requires antigen and functional validation.
Parallel vascular/CAA profile	CAA, microbleeds, BBB dysfunction, or perivascular injury characterized independently.	MRI markers, BBB measures, APOE genotype, vascular inflammation, ARIA monitoring [96–100].	May run parallel to or amplify Aβ–tau configurations.	Anticoagulation, hypertension, small-vessel disease. Must predict vascular outcomes or treatment toxicity independently.
Aging/systemic modifier profile	Age and systemic context explicitly characterized.	Inflammaging, immune phenotyping, clonal hematopoiesis, frailty, infection and metabolic markers [3,94,95,132].	Changes baseline probabilities rather than defining AD pathology.	Sex, comorbidities, medications, renal function. Requires external validation and interaction testing.

Note: These profiles are probabilistic research constructs. No universal biomarker thresholds or validated clinical assignment rules currently exist. Regional coexistence and parallel vascular trajectories should be reported rather than forced into one label.

Clinically established or efficacy-supported approaches. Anti-Aβ antibodies provide proof that modifying an immune-mediated clearance process can alter AD biomarkers and modestly slow decline in selected early symptomatic patients. Lecanemab and donanemab produced clinical and biomarker effects in phase 3 trials, with earlier phase 2 donanemab evidence supporting biomarker activity [123–125], whereas gantenerumab lowered amyloid without clear clinical benefit [126]. These results demonstrate biological modifiability, not restoration of a complete tissue state.

Anti-Aβ therapy also shows why vascular context cannot be separated from immune intervention. ARIA, microhemorrhage, edema, and other safety concerns require MRI and clinical monitoring [99,100]. Amyloid status, disease stage, CAA burden, APOE genotype, and vascular fragility currently have more immediate treatment relevance than unvalidated neuroimmune-state labels.

Therapies evaluated in humans without established clinical efficacy. Broad anti-inflammatory prevention with naproxen or celecoxib did not improve cognition [127]. AL002 showed first-in-human pharmacodynamic engagement [42] but did not establish efficacy in phase 2 [43]. These examples argue against

assuming that pathway engagement or biomarker change identifies a successful therapeutic state.

Preclinical or conceptual strategies. TREM2 antibodies and BBB-transported TREM2 activation can enhance microglial proliferation or metabolism in models [39,40], and SULF A provides additional preclinical evidence for inflammation-sparing Aβ clearance [41]. Complement, C5aR1, NLR family pyrin domain containing 3 (NLRP3), and IL-12/IL-23 interventions alter pathology in animal models [75,77,128–130]. These strategies should be described with their evidence level, proposed window, pharmacodynamic readout, and principal safety concern.

"Glial redirection" should mean a demonstrated change in a specified glial program and function, such as target-selective phagocytosis, metabolic fitness, cytokine output, or synapse interaction. A fall in a generic inflammatory marker is not sufficient. Likewise, adaptive immune treatment should require evidence that a defined immune population and pathway contribute causally to injury, rather than the presence of T cells or a chemokine signal alone.

Table 3. Evidence-tiered framework for immune-directed interventions.

Intervention class	Development level	Proposed research window or hypothesis	Candidate research stratifiers / pharmacodynamic readouts	Principal risk or interpretive limit
Anti-Aβ antibodies	Clinical efficacy supported in selected early AD [123–126].	Reduce Aβ pathology in appropriately selected early symptomatic disease; test whether tissue/vascular profiles modify benefit.	Aβ confirmation, tau burden, cognition, MRI/CAA markers, APOE, plasma p-tau and GFAP.	ARIA, vascular fragility, modest clinical effect, and incomplete restoration of tissue function [99,100].
Broad anti-inflammatory drugs	Human trials without demonstrated cognitive benefit [127].	Useful mainly as evidence that nonspecific suppression is unlikely to match heterogeneous biology.	Systemic inflammation, target engagement, vascular and infection status.	May suppress protective functions; negative trials do not exclude selective immune targets.
TREM2 agonism / microglial support	First-in-human and phase 2 experience; no established efficacy [42,43].	Test impaired plaque-facing microglial fitness in Aβ-anchored profiles rather than assume universal benefit.	Aβ/tau context, sTREM2 interpreted cautiously, microglial PET where validated, NfL and safety markers.	Stage dependence, receptor shedding/turnover, excess activation, and failed translation from models.
SULF A and other inflammation-sparing microglial modulators	Preclinical [41].	Enhance target-selective Aβ clearance while preserving neuronal and inflammatory homeostasis.	TREM2 engagement, plaque-associated recruitment, Aβ uptake, cytokine/metabolic profile.	Murine evidence only; target specificity, exposure, and human efficacy unestablished.
Complement or phagocytic-effector modulation	Preclinical / conceptual [62–77,128,131].	Protect viable synapses while retaining useful aggregate and debris clearance.	Complement branch markers, synaptic measures, tau context, NfL, infection monitoring.	Global blockade may impair host defense and debris clearance; target viability is difficult to measure.
Inflammasome or cytokine modulation	Preclinical / early translational concept [129,130].	Test defined inflammatory amplification rather than generic glial activation.	Pathway-specific pharmacodynamics, GFAP/YKL-40, NfL, systemic immune monitoring.	Model dependence, infection risk, and uncertain patient subgroup.
Adaptive immune / checkpoint strategies	Preclinical and conflicting [92,93].	Restrict to mechanistically defined adaptive amplification with causal evidence.	CSF immune profiling, clonality, antigen specificity, IFN/CXCL signaling.	Autoimmunity, infection, neurotoxicity, and no validated AD indication.

Note: Candidate windows and biomarkers are research hypotheses, not clinical recommendations.

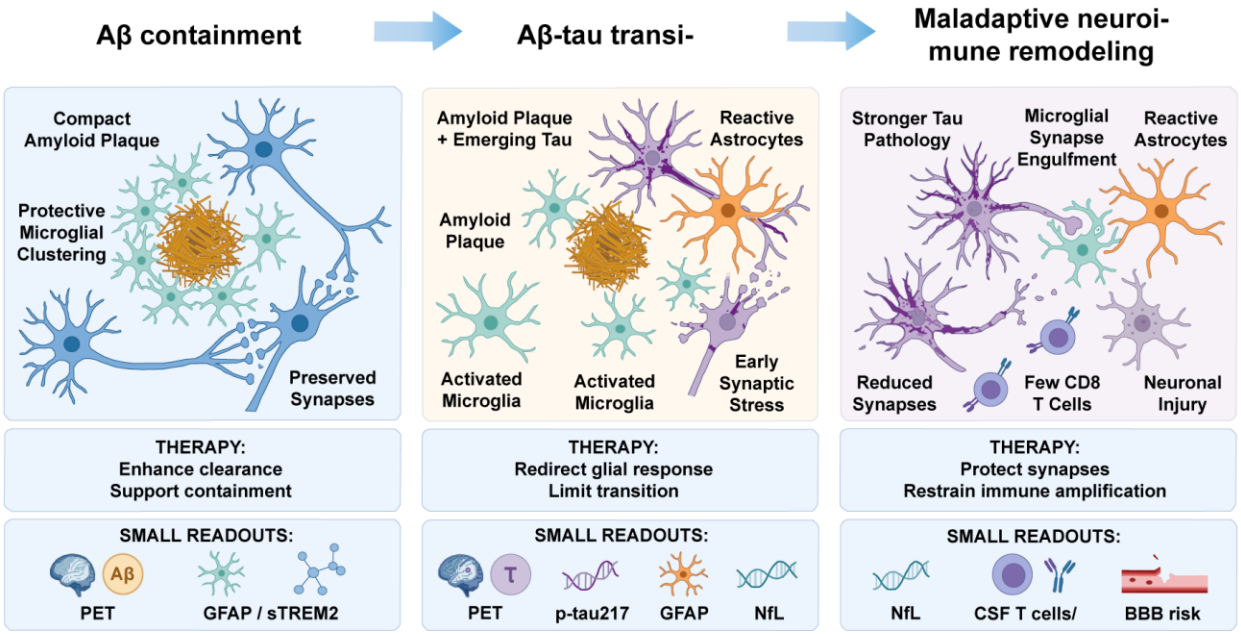


Figure 3. Evidence-tiered framework for testing stage-matched immunomodulation. The figure is a research framework, not a clinical treatment algorithm. Clinically established or efficacy-supported approaches, interventions evaluated in humans without established efficacy, and preclinical or conceptual strategies are separated. Each intervention should be linked to a mechanistic hypothesis, pathological and vascular context, pharmacodynamic readout, and principal safety concern. Candidate neuroimmune profiles are used to test heterogeneity of treatment effect prospectively; they do not currently justify selection of TREM2, complement, glial, or adaptive immune therapies in clinical practice.

Figure 3 therefore presents a trial-design framework. A candidate intervention is paired with a mechanistic hypothesis, an evidence tier, a proposed pathological context, a pharmacodynamic measure, and a predefined safety risk. State variables are used to test heterogeneity of treatment effect, not to prescribe therapy.

A stage-matched model would gain credibility if an intervention showed different benefit or harm across prospectively defined Aβ, tau, vascular, and tissue-response profiles. It would lose credibility if the proposed state variables did not modify treatment response or if simpler pathological and safety markers performed equally well.

9. Falsifiable predictions and state-stratified trial design

The framework is scientifically useful only if it can fail. Several prospective predictions distinguish it from a model that retrospectively assigns every beneficial or harmful immune finding to a different state.

Prediction 1: containment has incremental prognostic value. Among people with similar Aβ burden and low tau, a prespecified containment profile should predict slower tau emergence, less neuritic injury, or slower cognitive decline. If it does not add information beyond Aβ, tau, APOE, age, and vascular markers, the containment construct should be reduced.

Prediction 2: interface levels are related but non-equivalent. Biomarker, spatial, cellular-state, and clinical-progression interfaces should show measurable but incomplete correspondence. A model that assumes they are interchangeable is falsified if their timing and regional distribution are discordant.

Prediction 3: target switching is target-specific. Tau- and complement-associated regions should show increased tagging and engulfment of viable or potentially recoverable synapses beyond what is explained by irreversible degeneration. If engulfment only follows terminal structural damage, "mis-clearance" is not supported.

Prediction 4: adaptive amplification defines a subgroup. Clonal or organized adaptive immune engagement should be enriched in selected tau-, injury-, or brain-border-active profiles rather than being universal in Aβ-positive disease. Lack of association with tissue context or outcome would weaken its placement in the framework.

Prediction 5: vascular and aging trajectories are partially independent. Vascular/CAA and aging-conditioned profiles should explain variance in glial and injury markers that is not captured by the Aβ–tau axis. If

they merely track the same latent disease severity, separate trajectory labels add little.

Prediction 6: state variables modify treatment effect. In trials, prespecified state profiles should identify differential pharmacodynamic response, efficacy, or toxicity. This should be tested with interaction analyses and external validation, not post hoc subgroup narratives.

A practical trial pipeline would pair human spatial tissue maps with longitudinal fluid and imaging cohorts, derive parsimonious profiles, validate them against tissue and outcome, and then embed them as stratification or interaction variables in trials. Figure 4 emphasizes this evidence-to-trial loop and includes an explicit route for model revision when predictions fail.

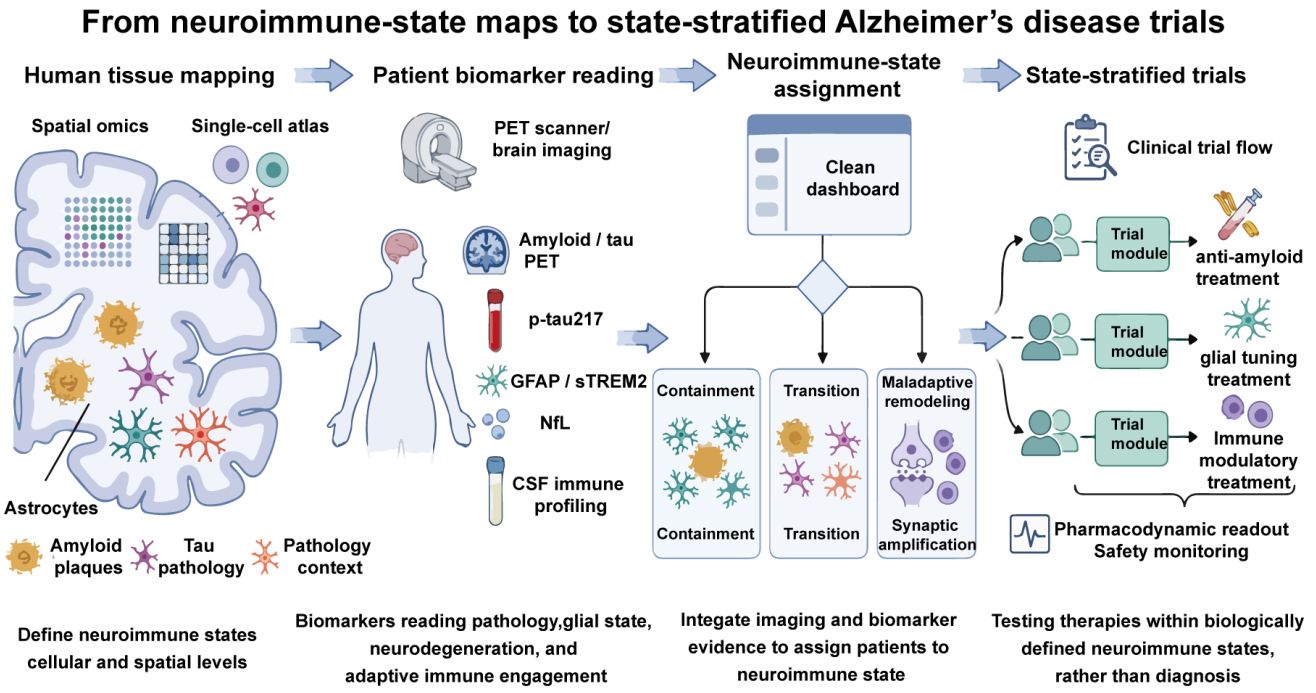


Figure 4. From tissue-state maps to falsifiable, state-stratified trials. Human spatial and single-cell studies can generate candidate tissue configurations, which are translated into parsimonious longitudinal biomarker profiles and validated against tissue, clinical outcomes, and alternative explanations. Prespecified profiles can then be tested as stratification or treatment-interaction variables in trials. Failure to improve prediction, tissue correspondence, treatment response, or safety assessment should lead to model revision or rejection rather than retrospective relabeling.

10. Limitations and competing explanations

The framework has substantial limitations. First, most human cellular evidence is cross-sectional or postmortem. Agonal state, postmortem interval, regional sampling, terminal disease stage, cell loss, and dissociation artifacts can distort apparent cell states. Single-cell transcription does not directly measure function, and spatial proximity does not prove interaction.

Second, patient biomarkers lack cellular and spatial specificity. GFAP, sTREM2, YKL-40, NfL, TSPO PET, chemokines, and immune-cell profiles are influenced by age, sex, genotype, vascular injury, infection, renal function, medication, and non-AD neurodegeneration. Thresholds vary by assay and cohort.

Third, the model is vulnerable to overfitting and circular interpretation. A protective marker could be relabeled maladaptive whenever an outcome is poor. To prevent this, state definitions, thresholds, primary outcomes, and competing explanations must be prespecified and tested in independent cohorts.

Fourth, alternative models remain plausible: immune changes may be downstream reporters of neuronal injury; Aβ and tau may induce partly independent responses without a unifying interface; distinct microglial populations may coexist without longitudinal switching; and vascular or mixed pathologies may dominate the clinical trajectory. These alternatives should be tested directly rather than absorbed into an increasingly broad framework.

Accordingly, neuroimmune-state medicine should be viewed as a hypothesis-generating integration strategy. It should be retained only where it improves measurement, prediction, or trial design beyond established AD pathology, vascular assessment, and conventional clinical variables.

Box 1. Operational glossary for the neuroimmune-state framework

Neuroimmune state

A measurable, context-dependent configuration of immune cells, glia, neurons, vascular interfaces, and soluble mediators. It should specify pathological substrate, cellular program, biological target, spatial location, consequence, and uncertainty; it is not defined by inflammatory intensity alone.

Aβ-positive containment configuration

An Aβ-anchored local response in which plaque-associated sensing, lipid handling, compaction, and clearance are associated with limited peri-plaque injury. It can coexist with maladaptive states elsewhere and is not synonymous with early clinical stage.

Amyloid–tau interface

An umbrella term that must be qualified as biomarker, spatial tissue, cellular-state, or clinical-progression interface. These levels are related but may be asynchronous and are not interchangeable.

Phagocytic target switching

The hypothesis that the target of clearance changes across pathological contexts, for example from aggregates and debris toward stressed synapses or viable neural structures. Longitudinal switching by the same human cells remains unproven.

Synaptic mis-clearance

Inappropriate removal of a synapse or neuritic structure that remains viable, potentially functional, or recoverable. Clearance of irreversibly damaged debris is excluded.

Adaptive immune amplification

Organized recruitment, persistence, clonal expansion, or effector signaling of adaptive immune cells that augments a tissue response. It does not imply autoimmunity or pathogenicity without functional evidence.

Glial redirection

A demonstrated change in a specified glial program and function, such as target selectivity, metabolic fitness, cytokine output, or synapse interaction. A nonspecific reduction in an inflammatory marker is insufficient.

Aging-conditioned baseline

Age-related immune, glial, lymphatic, metabolic, and vascular changes present before or independently of Aβ and tau pathology.

Parallel vascular–immune trajectory

A route in which BBB dysfunction, CAA, microhemorrhage, perivascular clearance failure, and vascular inflammation directly shape glial activity, neurodegeneration, treatment response, or ARIA risk.

Stage-matched immunomodulation

A research strategy that tests whether pathological and tissue-response profiles modify intervention benefit, pharmacodynamic response, or toxicity. It is not a validated treatment algorithm.

Author Contributions

K.Z. and Y.Z. conceived the review, performed the literature synthesis, and drafted the manuscript. X.J. contributed to literature evaluation, figure preparation, and critical revision. X.C. conceived and supervised the work, obtained funding, and critically revised the manuscript. All authors approved the final manuscript.

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OpenAI ChatGPT (GPT-5.6 Sol; accessed 24 September 2026) was used solely to assist with English-language polishing and final formatting checks of the manuscript. Representative prompt: “Polish the English for grammar, clarity, readability, and formatting consistency without changing the scientific meaning, citations, or structure.” All scientific content, interpretations, citations, and final wording were reviewed and approved by the authors, who take full responsibility for the manuscript.

Conflict of Interest Statement

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

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