THE PERIPHERAL ARM OF HOMEOSTATIC COLLAPSE

Michal Schwartz's Protective Autoimmunity Framework as the Systemic Upstream of the TGF-β–Maintained Microglial Niche, with Implications for the Perineuronal Net as a Seventh Convergence Axis in Alzheimer's Disease

A Companion Synthesis to the Homeostatic Microglial Collapse and Convergent Synaptic Collapse Theses

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Abstract

The Homeostatic Collapse Model of microglial contribution to Alzheimer's disease, developed in a companion thesis from twelve primary research programs, argues that the attack and failure phenotypes of disease-associated microglia are alternative projections of a single upstream event: the age-dependent collapse of the TGF-β/SMAD–maintained homeostatic signature defined by Butovsky and colleagues. The model supplies a unified account of parenchymal microglial dysfunction but is conspicuously silent on the systemic immune compartment. In parallel, a recent re-reading of the Oskar Fischer Prize corpus has identified an emerging seventh convergence axis organized around extracellular matrix and perineuronal net integrity, with the microglial digestion of aggrecan and tenascin-R around parvalbumin-positive interneurons occupying the position of a single effector step that is simultaneously an act of attack and an act of protective withdrawal. Neither of these syntheses has yet engaged with the body of work developed by Michal Schwartz and colleagues over three decades, which holds that Alzheimer's disease is fundamentally a disorder of brain–immune communication driven by peripheral T-cell exhaustion, choroid-plexus gateway closure, and a consequent failure to recruit monocyte-derived macrophages whose clearance functions are distinct from, and in several respects complementary to, those of resident microglia. In this paper we integrate Schwartz's Protective Autoimmunity framework, including her 2025 identification of CD38 as an immunometabolic checkpoint and her 2026 *Neuron* perspective on the evolutionary brain–immune interface, into the Homeostatic Collapse Model and into the emerging perineuronal net axis. We argue that Schwartz supplies three elements the parenchymal model lacks: first, a second upstream driver of homeostatic collapse operating through the peripheral T-cell compartment and the choroid-plexus interferon gateway; second, a non–TREM2-dependent salvage arm in the form of MSR1■ CCR2■ monocyte-derived macrophages whose recruitment is gated by systemic rather than parenchymal signals; and third, a testable mechanistic bridge from meningeal Th17 immunity through matrix metalloproteinase induction to the perineuronal net–parvalbumin interneuron axis. We further argue that the apparent contradiction between Schwartz's protective and Weaver's pathogenic accounts of adaptive immunity in the Alzheimer's disease brain is resolved, not dissolved, by the Homeostatic Collapse framing: peripheral exhaustion and uncontrolled parenchymal autoimmunity are not competing explanations but sequential phases of the same immunological trajectory, with homeostatic collapse marking the transition point. The integrated model, which we term

the Dual-Compartment Homeostatic Collapse Model, predicts that effective Alzheimer's disease therapeutics will operate simultaneously on the parenchymal TGF-β niche and the peripheral immunometabolic gate, and that the combined preservation of the perineuronal net and of the choroid-plexus interferon-γ tone offers a compound biomarker of therapeutic success more sensitive than amyloid or tau burden alone.

1. Introduction: The Missing Peripheral Arm

The Homeostatic Collapse Model, as developed in the companion *Homeostatic Microglial Collapse* thesis, makes a powerful argument for the conceptual unification of the attack and failure frameworks of microglial biology in Alzheimer's disease. It does so by treating the TGF-β/SMAD–maintained homeostatic signature defined by Butovsky and colleagues as the single upstream event whose loss is necessary, and in many cases sufficient, to generate the diverse downstream phenotypes catalogued under the disease-associated microglia, lipid-droplet-accumulating microglia, and dystrophic microglia classifications. The model's explanatory reach is considerable: it resolves the TREM2 paradox by locating TREM2 at the collision point between failed and successful salvage; it reinterprets the Crapser CSF1R-depletion results without requiring microglia to be gratuitously destructive; and it identifies the perineuronal net as the substrate at which attack and failure become mechanistically indistinguishable. Yet for all its integrative ambition, the model remains a model of the **parenchymal compartment**. It treats the TGF-β niche as a locally generated property of the neural and vascular parenchyma, traces homeostatic collapse to intrinsic oxidative drift, iron accumulation, and the cumulative signaling failures described by von Bernhardi, and it considers border-associated macrophage populations only briefly, in the context of the developmental ontogeny work of Prinz and Kierdorf. The peripheral immune compartment — the circulating T and B lymphocytes, the splenic and nodal reservoirs, the bone-marrow-derived monocyte pool, and the systemic cytokine environment in which the brain is embedded — appears nowhere in the model as a causal driver.

This omission is not accidental. The parenchymal framing reflects the historical development of microglial biology as a branch of neuroscience rather than of immunology, and it reflects the operational convenience of treating the brain as an immune-privileged organ whose myeloid cells can be analyzed in isolation from the larger immunological context in which they exist. But it is, increasingly, untenable. The last decade has produced a continuous stream of evidence that systemic immune events modulate brain function and pathology in ways that cannot be captured by purely parenchymal models: meningeal T-cell populations regulate cognition, peripheral inflammation alters microglial transcriptional states, the choroid plexus functions as a dynamic immune interface rather than a passive barrier, and the bone marrow supplies monocytes to the central nervous system under conditions of injury and disease. Ignoring this compartment in a synthesis of microglial pathogenesis produces a model that is internally consistent but externally incomplete, and that is therapeutically impoverished in precisely the direction that the parenchymal-only framing cannot remedy.

The work of Michal Schwartz and colleagues, developed over more than two decades beginning with the protective autoimmunity observations of the late 1990s and extending through the recent CD38 immunometabolic checkpoint work and the 2026 *Neuron* perspective reframing the brain as "a garden sustained by immune cells," constitutes the single most sustained and mechanistically explicit attempt to situate Alzheimer's disease within a systemic immunological framework. Schwartz's program is unusual in the corpus of Alzheimer's disease hypotheses in that it treats the peripheral immune system not as a confounding variable or an amplifier of parenchymal events but as an indispensable positive contributor to central nervous system homeostasis, whose age-dependent exhaustion is itself a cause of

neurodegeneration and whose restoration is itself a therapeutic target. This framing places Schwartz in substantial tension with many of the other frameworks catalogued in the Oskar Fischer corpus, and it has generated documented contradictions with the Weaver framework in particular, where adaptive immune activity in the Alzheimer's disease brain is treated as pathogenic rather than protective. Yet it is precisely this tension that makes Schwartz the necessary integrand for the Homeostatic Collapse Model: she supplies the missing compartment, and the tensions she generates with other frameworks are in fact the productive surfaces at which a more complete synthesis becomes possible.

This paper undertakes that integration. It proceeds in four stages. First, we summarize Schwartz's framework with sufficient mechanistic specificity to make its integration with the parenchymal model possible. Second, we identify three specific points of contact at which the peripheral arm modifies or extends the Homeostatic Collapse Model: the systemic contribution to the upstream driver of homeostatic collapse; the monocyte-derived macrophage arm as a non-TREM2-dependent salvage pathway; and the CD38 immunometabolic checkpoint as a shared metabolic gating substrate linking peripheral T-cell exhaustion to parenchymal microglial failure. Third, we develop an extended mechanistic bridge from Schwartz's meningeal Th17 observations through matrix metalloproteinase induction to the perineuronal net–parvalbumin interneuron axis, thereby connecting the peripheral arm to the emerging seventh convergence axis on extracellular matrix integrity. Fourth, we address the Schwartz–Weaver contradiction and argue that the Homeostatic Collapse framing resolves it through a temporal and compartmental decomposition rather than by adjudicating between competing claims.

2. Schwartz's Framework in Brief

A short reconstruction of the Protective Autoimmunity framework is necessary to make the integration tractable. Schwartz's central claim is that the adult central nervous system, contrary to the classical immune-privilege doctrine, requires continuous positive input from the peripheral adaptive immune system in order to maintain neural function, support repair after injury, and sustain the cognitive capacities associated with a healthy aging brain. The mechanistic substrate of this input is the choroid plexus blood–cerebrospinal fluid barrier, which under physiological conditions supports the controlled, gated trafficking of peripheral immune cells into the central nervous system under the influence of interferon-γ secreted by circulating T cells. Schwartz's laboratory has shown, across a long sequence of papers spanning the choroid plexus, the meninges, and the bone marrow, that this gateway closes progressively with age under the influence of systemic T-cell exhaustion, and that its closure produces a central nervous system deprived of the positive immune input it needs to sustain repair and homeostasis. The therapeutic inference Schwartz draws from this framework is that transient blockade of the PD-1/PD-L1 immune checkpoint, by rejuvenating exhausted peripheral T cells and restoring their capacity to secrete interferon-γ, produces a corresponding re-opening of the choroid plexus gateway, a wave of CCR2-dependent monocyte recruitment across the blood–cerebrospinal fluid barrier, differentiation of these recruited monocytes into MSR1■ macrophages within the central nervous system parenchyma, and clearance of amyloid and tau aggregates that resident microglia have proven incapable of handling.

Several features of this framework distinguish it from other immune theories of Alzheimer's disease and are critical for its integration with the Homeostatic Collapse Model. The first is the distinction between resident microglial inflammation and recruited monocyte-derived macrophage inflammation. Schwartz argues consistently that these are not two varieties of a single pro-inflammatory state but two qualitatively different cellular programs: resident microglia, when chronically activated, produce destructive inflammation with impaired resolution, while recruited monocyte-derived macrophages,

when appropriately licensed by the choroid plexus gateway, produce resolving inflammation with competent clearance. This distinction is grounded in the developmental ontogeny of the two cell populations — yolk-sac-derived microglia versus bone-marrow-derived monocytes — and in their distinct transcriptional programs, their distinct lipid-handling capacities, and their distinct susceptibility to exhaustion in the face of chronic amyloid exposure. The second is the focus on the immunometabolic substrate of immune exhaustion. Schwartz's 2025 *Nature Communications* paper on CD38 establishes that the cognitive deficits in Alzheimer's disease mouse models can be rescued by anti-CD38 treatment, which abrogates meningeal Th17 immunity, restores NAD■ pools in the immune compartment, and re-establishes metabolic fitness in a way that parallels, mechanistically, the TREM2-dependent metabolic program of the Colonna framework but operates on the peripheral immune compartment rather than on the parenchymal microglial one. The third is the evolutionary framing developed in the 2026 *Neuron* perspective, in which Schwartz argues that the brain–immune relationship is not an exception to immunological principles but a specialized instance of a general pattern in which tissue homeostasis depends on continuous immune surveillance and input. On this view, immune privilege is not absence of immune interaction but controlled licensing of it, and the aged and diseased brain suffers not from excessive immune interaction but from the collapse of the licensing system that controls it.

These three features together generate the framework within which Schwartz's work can be integrated into the Homeostatic Collapse Model. The resident-versus-recruited distinction provides a non-TREM2 salvage arm that the parenchymal model does not currently contain. The CD38 immunometabolic checkpoint provides a shared metabolic substrate linking the peripheral and parenchymal compartments. The evolutionary framing provides the conceptual warrant for treating TGF-β niche maintenance as a two-compartment system rather than a purely local one, with the parenchymal TGF-β signal dependent on peripheral immune inputs for its own maintenance.

3. Peripheral T-Cell Exhaustion as a Second Upstream Driver of Homeostatic Collapse

The Homeostatic Collapse Model traces the loss of the Butovsky homeostatic signature to the intrinsic failure of the TGF-β/SMAD pathway under the cumulative influence of oxidative stress, iron accumulation, and lipid burden. This account is mechanistically compelling within the parenchymal compartment but it is etiologically incomplete: it does not explain why the TGF-β niche should fail on a roughly decadal timescale matched to the clinical onset of late-onset Alzheimer's disease rather than on the faster timescale that would be predicted by intrinsic oxidative chemistry alone, and it does not explain why the homeostatic signature is preserved in some individuals despite comparable levels of amyloid and tau burden. The resilience evidence from de Vries and colleagues, which the companion thesis cites as the strongest human confirmation of the Homeostatic Collapse Model, actually poses a sharper question than the thesis acknowledges: what determines which individuals retain homeostatic microglial identity and which do not, given comparable pathological burdens? The parenchymal model can offer only local oxidative load and local lipid handling as candidate explanations, and these are correlated with but not identical to the systemic factors that have emerged from the epidemiology of cognitive resilience.

Schwartz's framework supplies a more mechanistically precise candidate: peripheral T-cell exhaustion, operating through the choroid plexus interferon-γ gateway, constitutes a second upstream driver of homeostatic collapse whose severity varies substantially across individuals and whose timing is determined by the cumulative history of peripheral immune challenge rather than by intrinsic parenchymal chemistry. On this reading, the TGF-β niche in the parenchyma is not a closed system maintained by local signaling alone but an open system whose maintenance depends on continuous positive input from the peripheral immune compartment. The specific mediating signal is not necessarily

interferon-γ itself but rather the set of choroid-plexus-gated trafficking events that interferon-γ licenses: the passage of regulatory T cell populations into the cerebrospinal fluid, the controlled influx of monocyte-derived macrophages whose clearance of cellular debris reduces the oxidative burden on resident microglia, and the maintenance of a trophic signaling environment at the meningeal and choroid plexus interfaces that shapes parenchymal TGF-β tone. When peripheral T cells become exhausted under the influence of PD-1/PD-L1 upregulation, this entire set of licensing events collapses, and the parenchymal TGF-β niche is left to maintain itself under progressively more hostile local conditions until the intrinsic failure mechanisms described by von Bernhardi tip the signaling balance toward collapse.

This reframing has substantial consequences for the Homeostatic Collapse Model. It converts the model from a single-driver to a dual-driver account, in which homeostatic collapse occurs when the joint effects of peripheral exhaustion and parenchymal oxidative drift exceed the maintenance capacity of the TGF-β/SMAD pathway. It predicts that individuals with preserved peripheral immune function should tolerate higher parenchymal pathological burdens without homeostatic collapse — a prediction that maps cleanly onto the cognitive resilience phenotype described by de Vries. It predicts that interventions targeting the peripheral compartment should be capable of rescuing parenchymal homeostasis even in the absence of direct effects on the parenchymal microglia themselves — a prediction that is consistent with Schwartz's pre-clinical results with anti-PD-L1 and anti-CD38 treatment. And it predicts that individuals with chronic peripheral immunological stressors — infections, autoimmune disease, systemic inflammatory conditions, immunosenescence — should exhibit accelerated homeostatic collapse and earlier clinical disease, a prediction that is broadly consistent with the epidemiology of Alzheimer's disease risk associated with systemic inflammatory comorbidities.

4. Monocyte-Derived Macrophages as a Non-TREM2 Salvage Arm

The second major contribution that Schwartz's framework makes to the Homeostatic Collapse Model concerns the identity of the clearance machinery available to the central nervous system under conditions of parenchymal microglial failure. The parenchymal model, in its treatment of the TAM receptor tyrosine kinase work of Lemke and colleagues, identifies TAM-mediated phagocytosis as the major protective clearance pathway and treats TREM2 as the metabolic gate on whether this program succeeds or fails. But this treatment assumes that the only cells available to execute clearance are resident microglia, and it accordingly interprets every therapeutic failure as a failure of resident microglial function. Schwartz's framework challenges this assumption directly. She argues, on the basis of both mouse genetic studies and human neuropathological evidence, that the monocyte-derived macrophages recruited from the peripheral bone marrow under conditions of choroid plexus gateway opening constitute a distinct clearance compartment whose function differs from that of resident microglia in three critical ways.

First, monocyte-derived macrophages are TREM2-independent in their clearance capacity. They utilize the MSR1 scavenger receptor, together with the broader scavenger receptor repertoire of bone-marrow-derived macrophages, to engage amyloid and debris in a manner that does not require the lipid-sensing and metabolic-gating function supplied by TREM2 in resident microglia. This has profound consequences for the interpretation of the TREM2 paradox developed in the companion thesis. Under the parenchymal-only framing, TREM2 loss-of-function variants confer risk because they impair the metabolic gating of successful clearance at the level of the resident microglia. Under the Schwartz framing, TREM2 loss-of-function additionally confers risk by reducing the burden that resident microglia can carry without exhaustion, thereby increasing the demand on the peripheral monocyte-derived arm — a demand that can only be met if the choroid plexus gateway is functional and the peripheral T-cell compartment is not exhausted. TREM2 loss-of-function therefore operates through

a compound mechanism that involves both parenchymal metabolic gating and peripheral clearance demand, and the apparent paradox of TREM2 as a risk allele whose loss impairs activation is resolved when one recognizes that the downstream consequences of impaired parenchymal activation must be compensated by a peripheral arm whose own functional capacity is independently variable across individuals.

Second, monocyte-derived macrophages differ from resident microglia in the transcriptional program they execute during clearance. Schwartz's work and the broader literature on bone-marrow-derived versus yolk-sac-derived macrophages establish that the former produce what she terms "resolving" inflammation, characterized by interleukin-10 output, transforming growth factor-β production, and prompt transition from the pro-inflammatory to the pro-resolution phase of the clearance response. Resident microglia in the post-homeostatic state, by contrast, produce what she terms "destructive" inflammation, in which the pro-inflammatory phase is prolonged and the resolution phase is impaired. The mechanistic basis of this difference is not fully established but likely involves both developmental programming and the cumulative effect of local context on gene expression. Whatever its basis, the distinction matters enormously for the interpretation of the Homeostatic Collapse Model, because it implies that the collateral damage associated with failed salvage attempts is not an inevitable consequence of clearance activity per se but a specific consequence of attempting clearance with cells that have lost the capacity for prompt resolution. Restoration of homeostasis through the peripheral recruitment arm therefore produces clearance without collateral damage, whereas restoration through cell-autonomous rescue of resident microglia carries a higher risk of continued destructive output even if the immediate clearance capacity is restored.

Third, and most importantly for the integration with the perineuronal net axis developed in the next section, monocyte-derived macrophages differ from resident microglia in their enzymatic output during clearance. The matrix metalloproteinase 2 and 9, ADAMTS-4, and cathepsin-S program that the companion thesis identifies as the effector repertoire of post-homeostatic microglia at the perineuronal net is characteristic of the resident microglial lineage in its failed-salvage state and is not reproduced to the same degree by bone-marrow-derived macrophages executing competent clearance. This implies that peripheral salvage, where it is available, should spare the perineuronal net in a way that resident salvage does not. If this is correct, then the Crapser perineuronal net rescue by CSF1R-mediated microglial depletion is not simply an ablation of the destructive program but a substitution of the non-destructive peripheral arm for the destructive resident arm, and the therapeutic implication is not that microglia should be depleted but that the balance between resident and recruited clearance should be shifted toward the latter under conditions of parenchymal exhaustion.

5. CD38 and the Immunometabolic Gate

The third contribution that Schwartz's framework makes to the integration is the identification of a shared immunometabolic substrate linking the peripheral and parenchymal compartments. Her 2025 *Nature Communications* paper on CD38 as an immunometabolic checkpoint in Alzheimer's disease mouse models establishes that anti-CD38 treatment rescues cognition in a manner that is mechanistically distinct from anti-PD-L1 treatment: it operates through NAD■ metabolism rather than through T-cell receptor signaling directly, and it abrogates meningeal Th17 immunity specifically rather than generally suppressing T-cell function. The mechanism has several features that make it particularly valuable for the integration with the Homeostatic Collapse Model.

The first is that CD38 is an NAD■-consuming ectoenzyme whose activity depletes the cellular NAD■ pool in a manner that compromises mitochondrial oxidative phosphorylation and cellular metabolic fitness. The Colonna framework developed in the companion thesis identifies metabolic fitness — specifically, the capacity to sustain oxidative phosphorylation during phagocytic engagement — as the gating variable that determines whether TREM2-dependent clearance programs produce successful or failed outcomes. CD38 blockade, by restoring NAD■ pools, directly restores the metabolic capacity that the Colonna framework identifies as rate-limiting. This means that CD38 and TREM2 are not parallel but serial elements of the same metabolic gating system, and that CD38 blockade should produce functional rescue of the downstream TREM2-dependent program even in the absence of direct TREM2 manipulation. The therapeutic implication, which Schwartz's results begin to validate, is that immunometabolic rescue at the NAD■ level may succeed where TREM2 agonism fails, because it addresses the substrate availability problem that TREM2 agonism presumes is already solved.

The second is that CD38 is expressed across both the peripheral and parenchymal immune compartments. Peripheral T cells, meningeal Th17 cells, monocyte-derived macrophages, and resident microglia all express CD38, and all are susceptible to NAD■ depletion under the influence of CD38 upregulation in the aged and diseased state. This means that anti-CD38 treatment is, functionally, a simultaneous intervention on both compartments of the Dual-Compartment Homeostatic Collapse Model. It rescues peripheral T-cell function, restoring the choroid plexus interferon-γ gateway; it rescues monocyte-derived macrophage metabolic fitness, enabling competent recruited clearance; and it rescues resident microglial metabolic fitness, enabling the TREM2-dependent program to produce successful rather than failed salvage outcomes. No other intervention described in the Oskar Fischer corpus operates simultaneously on both compartments in this way, and the CD38 pathway accordingly occupies a privileged position in the integrated therapeutic landscape implied by the dual-compartment model.

The third is that CD38 is directly targetable with pharmacological agents, including monoclonal antibodies originally developed for multiple myeloma and small-molecule inhibitors of the ectoenzyme activity. This contrasts sharply with the therapeutic classes identified in the companion thesis as most promising for homeostatic restoration — TGF-β pathway agonists, SMAD7 inhibitors, oxidative stress reducers targeted to microglia — none of which have matured clinical candidates in the Alzheimer's disease indication. CD38 is therefore not only mechanistically privileged but also practically tractable, and the integrated model predicts that anti-CD38 trials in early-stage Alzheimer's disease, designed with perineuronal net integrity and choroid plexus interferon-γ tone as compound biomarkers, should produce detectable benefit on a timescale consistent with a disease-modifying rather than symptomatic intervention.

6. The Th17–MMP–PNN Axis: Bridging to the Seventh Convergence

The emerging seventh convergence axis in the Oskar Fischer corpus is organized around extracellular matrix and perineuronal net integrity, with the PNN cluster — aggrecan, tenascin-R, matrix metalloproteinase 2 and 9, cathepsin-S, and ADAMTS-4 — forming the strongest bottom-up case for a new convergence axis beyond the six originally identified in the Convergent Synaptic Collapse synthesis. The companion Homeostatic Microglial Collapse thesis identifies the perineuronal net as the substrate at which attack and failure become mechanistically indistinguishable, because the enzymatic release that digests aggrecan and tenascin-R around parvalbumin-positive interneurons is simultaneously an act of matrix destruction and an act of protective withdrawal. The thesis proposes perineuronal net integrity as the most tractable molecular readout of therapeutic success in restoring homeostasis, and the de Vries resilience evidence is cited as the strongest human confirmation of this proposal. But the thesis does not

identify the upstream drivers of the MMP-2, MMP-9, ADAMTS-4, and cathepsin-S program that executes perineuronal net degradation. It treats this effector repertoire as a generic consequence of post-homeostatic collapse, without specifying the signaling inputs that determine its magnitude, its spatial distribution, or its therapeutic manipulability.

Schwartz's framework, when read alongside the broader literature on Th17 immunity and matrix metalloproteinase induction, supplies a specific and testable candidate. Her 2025 CD38 paper establishes that meningeal Th17 immunity is a critical driver of cognitive dysfunction in Alzheimer's disease mouse models, and that its abrogation through CD38 blockade rescues cognition. The molecular connection between Th17 immunity and the matrix metalloproteinase program at the perineuronal net is well-established in the broader inflammation literature: interleukin-17, the signature cytokine of Th17 cells, is among the most potent known inducers of MMP-9 and ADAMTS family proteases in tissue macrophages, and Th17-driven inflammation in non-central-nervous-system tissues is characterized by ECM remodeling programs that closely parallel those observed at the perineuronal net in Alzheimer's disease. If meningeal Th17 immunity drives, through interleukin-17 signaling to parenchymal microglia at the border of the meningeal compartment, the induction of the MMP-2, MMP-9, ADAMTS-4, and cathepsin-S program that executes perineuronal net degradation, then the Schwartz CD38 intervention is mechanistically equivalent, at the perineuronal net, to the Crapser CSF1R depletion intervention: both abrogate the enzymatic program that degrades the matrix, but they do so through different upstream handles, with the CD38 intervention operating on the Th17 driver and the CSF1R intervention operating on the microglial executor.

This is a strong claim, and it deserves to be stated with its full weight. If the Th17–MMP–PNN axis is correct, then the Schwartz framework provides a peripheral handle on the seventh convergence axis that the parenchymal Homeostatic Collapse Model cannot supply. It predicts that interleukin-17 blockade — a therapeutic class already in clinical use for psoriasis and ankylosing spondylitis — should preserve perineuronal net integrity in Alzheimer's disease in a manner comparable to microglial depletion but without the collateral effects of ablating the microglial compartment entirely. It predicts that meningeal Th17 cell burden should correlate with perineuronal net degradation across individuals with comparable amyloid and tau burdens, providing a mechanistic basis for the inter-individual variation captured by the cognitive resilience phenotype. And it predicts that the combination of anti-CD38 peripheral rescue with TGF-β pathway restoration in the parenchyma should produce superadditive preservation of the perineuronal net–parvalbumin interneuron axis, because the two interventions operate on different stages of the same effector program: CD38 blockade reduces the Th17-driven induction of the enzymatic program, while TGF-β restoration prevents the homeostatic collapse that licenses its execution.

The Th17–MMP–PNN bridge is, to our knowledge, not explicitly developed in either the Schwartz corpus or the perineuronal net literature, and its status is therefore that of a predicted connection generated by the integration rather than an established one. It is for this reason testable: a direct measurement of meningeal Th17 cell burden, interleukin-17 levels in cerebrospinal fluid, and perineuronal net integrity in the same human post-mortem cohort would either confirm or refute the bridge, and the resilient cohort described by de Vries and colleagues provides an immediately available population in which such a measurement could be performed.

7. Resolving the Schwartz–Weaver Contradiction

The integration of Schwartz's framework into the Homeostatic Collapse Model must address the documented contradiction, recorded in the Oskar Fischer corpus connections registry, between

Schwartz's protective and Weaver's pathogenic accounts of adaptive immunity in the Alzheimer's disease brain. Schwartz argues that adaptive immune activity, properly licensed through the choroid plexus gateway, is protective and that its loss drives disease. Weaver argues that adaptive immune activity, triggered by electrophysiological mimicry between neural proteins and autoantigens, is pathogenic and that its presence drives disease. Both frameworks command experimental support; both generate coherent therapeutic programs; and neither can be simply absorbed by the other without loss of mechanistic content.

The Homeostatic Collapse framing, however, suggests that the contradiction is apparent rather than real, because it treats Schwartz and Weaver as describing different temporal phases and different compartmental locations of the same immunological trajectory. In the pre-collapse phase, when the peripheral immune compartment is functional and the choroid plexus gateway is appropriately gated, adaptive immune activity is predominantly protective in the Schwartz sense: it supplies trophic input to the parenchymal TGF-β niche, it licenses monocyte-derived macrophage recruitment for competent clearance, and it maintains the meningeal and cerebrospinal fluid immune environment that supports homeostasis. In the post-collapse phase, when the peripheral compartment has become exhausted and the choroid plexus gateway has closed, adaptive immune activity in the parenchymal compartment becomes predominantly pathogenic in the Weaver sense: it is dysregulated, mislocalized, and deployed against substrates that the homeostatic system no longer protects. Schwartz and Weaver are therefore not describing incompatible accounts of adaptive immunity but sequential phases of the same process, and the transition between them is marked by homeostatic collapse.

This framing has the substantial advantage of preserving the experimental content of both frameworks while dissolving the apparent contradiction. It predicts that pre-symptomatic interventions designed to sustain protective adaptive immunity will produce benefit, consistent with Schwartz, while late-stage interventions designed to suppress pathogenic adaptive immunity will also produce benefit, consistent with Weaver. It predicts that the same patient may require opposite interventions at different disease stages, a prediction that is consistent with the general experience of failed trials in which a single intervention applied uniformly across a heterogeneous patient population produces inconsistent effects. And it predicts that the biomarker signatures distinguishing protective from pathogenic adaptive immunity should be detectable and should correlate with the homeostatic collapse transition, providing a staging tool that current clinical practice does not possess.

The Schwartz–Weaver contradiction, on this view, is not a point at which the Homeostatic Collapse Model struggles but a point at which its explanatory power is most fully on display. The model absorbs both frameworks by recognizing that they describe different phases of the same trajectory, and it thereby transforms a standing contradiction in the field into a staged therapeutic program with distinct interventions appropriate to distinct disease phases.

8. The Dual-Compartment Homeostatic Collapse Model

The integration of Schwartz's framework with the parenchymal Homeostatic Collapse Model produces what we term the Dual-Compartment Homeostatic Collapse Model. The model's central claim is that microglial homeostasis in Alzheimer's disease is not a property of the parenchymal compartment alone but a two-compartment system in which the parenchymal TGF-β/SMAD niche and the peripheral immune-metabolic compartment are coupled through the choroid plexus interferon-γ gateway, the monocyte-derived macrophage recruitment arm, and the shared CD38/NAD■ immunometabolic substrate. Homeostatic collapse in this model is a joint event that occurs when the two compartments

have both exceeded their individual maintenance thresholds, and it produces a coordinated degradation of clearance capacity, trophic support, and matrix integrity whose downstream manifestations include the disease-associated microglial states, the perineuronal net degradation program, and the cognitive deficits associated with parvalbumin-positive interneuron dysfunction.

The model makes a series of specific claims that distinguish it from the parenchymal-only Homeostatic Collapse Model. First, the timing of homeostatic collapse in any individual is determined not only by intrinsic parenchymal oxidative drift but also by the cumulative history of peripheral immune challenge, including infectious exposure, autoimmune events, and systemic inflammatory comorbidities. Second, the cognitive resilience phenotype described by de Vries is produced by individuals in whom both compartments retain their maintenance capacity despite comparable pathological burdens, and it is more fully captured by biomarkers that integrate peripheral T-cell function, choroid plexus gateway patency, and perineuronal net integrity than by any single parenchymal measure. Third, effective therapeutics must operate simultaneously on both compartments or must address the point of coupling between them; interventions that operate on only one compartment will produce partial rescue with ceiling effects determined by the residual capacity of the other. Fourth, the CD38 immunometabolic checkpoint, the interleukin-17 pathway in meningeal Th17 cells, and the TGF-β/SMAD pathway in parenchymal microglia are the three most promising therapeutic handles because they operate on the coupling points between the compartments rather than within a single compartment alone. Fifth, the perineuronal net–parvalbumin interneuron axis is the most tractable compound biomarker of therapeutic success because its integrity is sensitive to both the parenchymal enzymatic program and the peripheral Th17 induction signal, and its preservation therefore requires success in both compartments.

9. Therapeutic Predictions

The Dual-Compartment Homeostatic Collapse Model generates a set of therapeutic predictions that are specific enough to be operationalized in trial design and distinct enough from existing therapeutic programs to be distinguishable from them empirically.

The first prediction is that anti-CD38 treatment, administered to early-stage Alzheimer's disease patients with mild cognitive impairment and documented amyloid positivity, should produce disease modification measurable in the composite of perineuronal net integrity on advanced imaging or post-mortem validation, cerebrospinal fluid interferon-γ tone, and cognitive progression over eighteen to twenty-four months. The mechanism is the dual rescue of peripheral T-cell metabolic fitness and parenchymal microglial metabolic fitness through NAD■ restoration, which should produce benefit through both compartmental arms simultaneously. The existing oncology experience with daratumumab and isatuximab provides the pharmacological template, and the critical design question is whether cerebrospinal fluid drug exposure is sufficient to engage the meningeal Th17 compartment.

The second prediction is that interleukin-17 blockade, using agents already approved for psoriasis and ankylosing spondylitis, should preserve perineuronal net integrity in Alzheimer's disease patients in a manner comparable to the effects of CSF1R-mediated microglial depletion but without the systemic and central effects of ablating the microglial compartment. The mechanism is the abrogation of the Th17 driver of the matrix metalloproteinase 9 and ADAMTS-4 program that executes perineuronal net degradation. The critical design question is whether the meningeal Th17 compartment is accessible to peripherally administered interleukin-17 antagonists and whether the effect is sufficient to produce detectable perineuronal net preservation within the timescale of a clinical trial.

The third prediction is that the combination of transient anti-PD-L1 treatment, applied as Schwartz's original protocol describes, with a TGF-β pathway agonist targeted to the parenchymal microglial compartment, should produce superadditive benefit compared to either intervention alone. The mechanism is the rescue of peripheral T-cell function through checkpoint blockade combined with the direct restoration of parenchymal TGF-β/SMAD signaling through the agonist, operating on both compartments simultaneously. The critical design question is whether the TGF-β agonist can be targeted to the parenchymal microglial compartment with sufficient specificity to avoid the systemic effects of generalized TGF-β activation.

The fourth prediction is that the timing of interventions must be matched to disease phase under the Schwartz–Weaver decomposition. Pre-symptomatic and early-symptomatic patients should receive Schwartz-class interventions designed to sustain protective adaptive immunity, including PD-L1 blockade and CD38 blockade. Late-symptomatic patients should receive Weaver-class interventions designed to suppress pathogenic adaptive immunity in the parenchymal compartment, including potentially interleukin-17 blockade and complement inhibition. The transition point is marked by homeostatic collapse, which in current practice is not measurable but which the model predicts should be detectable through a compound biomarker integrating peripheral T-cell function, choroid plexus gateway patency, and perineuronal net integrity.

The fifth prediction is that existing amyloid-lowering therapies, when combined with dual-compartment homeostatic restoration, should produce disease modification that substantially exceeds the modest effect sizes observed with amyloid-lowering alone. The mechanism is the reduction of the substrate burden that drives homeostatic collapse, combined with the restoration of the homeostatic maintenance capacity on which successful clearance depends. The critical design question is the sequencing and dosing of the combination, and the model predicts that homeostatic restoration should precede or accompany amyloid lowering rather than follow it, because restoring clearance capacity before reducing substrate burden produces the largest reduction in collateral damage per unit of clearance activity.

10. Testable Predictions and Experimental Program

Beyond the therapeutic predictions, the Dual-Compartment Homeostatic Collapse Model generates a set of mechanistic predictions that can be tested in existing experimental systems and human cohorts. These predictions are the operational content of the model and are the basis on which it can be confirmed or refuted.

The first testable prediction is that the cognitive resilience cohort described by de Vries and colleagues should exhibit preserved peripheral T-cell function, measured through PD-1 expression, interferon-γ production capacity, and meningeal Th17 burden, to a degree that distinguishes them from symptomatic Alzheimer's disease patients with comparable parenchymal pathology. This prediction can be tested in existing post-mortem cohorts with stored peripheral blood or lymphoid tissue, or prospectively in longitudinal cohorts with banked samples. A positive result would establish peripheral immune function as a component of the resilience substrate that the parenchymal-only model does not currently acknowledge.

The second testable prediction is that meningeal Th17 cell burden should correlate with perineuronal net degradation across individuals with comparable amyloid and tau burdens. This prediction can be tested directly in existing post-mortem cohorts by quantifying Th17 cells in meningeal tissue and perineuronal net integrity in the underlying cortex. A positive correlation would establish the Th17–MMP–PNN bridge and would provide the first direct evidence for a peripheral handle on the seventh convergence

axis.

The third testable prediction is that anti-CD38 treatment in 5xFAD mice should preserve perineuronal net integrity to a degree comparable to CSF1R-mediated microglial depletion, but without the ablation of the resident microglial compartment. This prediction can be tested in an existing mouse model with an available pharmacological agent, and a positive result would confirm that the CD38 immunometabolic checkpoint operates through the Th17–MMP–PNN axis predicted by the model.

The fourth testable prediction is that interleukin-17 blockade in 5xFAD mice should preserve perineuronal net integrity and parvalbumin-positive interneuron function. This prediction can be tested directly and provides the most immediate empirical test of the Th17–MMP–PNN bridge.

The fifth testable prediction is that the combination of peripheral PD-L1 blockade and parenchymal TGF-β restoration in the same mouse model should produce preservation of perineuronal net integrity, parvalbumin interneuron function, and cognitive performance that exceeds either intervention alone. This combination test is the experimental operationalization of the dual-compartment model and is the single most discriminating experiment that can be performed to distinguish the Dual-Compartment Homeostatic Collapse Model from the parenchymal-only version.

11. Limitations and Open Questions

The integration developed in this paper is substantial but it is not complete, and several open questions deserve explicit acknowledgment. The first concerns the developmental programming of monocyte-derived macrophages relative to resident microglia. The claim that recruited peripheral cells produce resolving rather than destructive inflammation rests on experimental evidence from mouse models and from peripheral macrophage biology, but the generalization to the central nervous system context in chronic amyloid exposure is not fully established. It remains possible that monocyte-derived macrophages, once recruited to the amyloid-rich parenchyma, undergo the same homeostatic collapse as resident microglia and contribute to rather than resolve pathology. If this is correct, then the peripheral arm is not a stable clearance compartment but a temporary one whose benefit is confined to the window before the recruited cells themselves exhaust, and the therapeutic implication is that repeated rather than sustained peripheral recruitment would be required.

The second open question concerns the specificity of the CD38–NAD■–TREM2 metabolic linkage. The claim that CD38 blockade rescues the downstream metabolic program that TREM2 agonism fails to rescue rests on the mechanistic plausibility of NAD■ pool restoration as a rate-limiting step, but the direct demonstration that CD38 and TREM2 operate as serial rather than parallel elements of the same metabolic gating system has not been performed. This is a straightforward experiment but it has not yet been done, and the model's therapeutic priority for CD38 blockade depends on its outcome.

The third open question concerns the quantitative contribution of the peripheral arm to homeostatic maintenance relative to the parenchymal arm. The dual-compartment framing treats both compartments as necessary but does not specify their relative magnitudes, and it is entirely possible that one compartment dominates in a manner that makes the other therapeutically irrelevant. The epidemiological evidence supporting peripheral immune function as a resilience determinant is suggestive but not quantitative, and the experimental evidence from mouse models does not cleanly distinguish the compartmental contributions.

The fourth open question concerns the translation of the mouse-model findings that anchor Schwartz's framework into the human disease. Her most striking results, including the PD-L1 blockade rescue and

the CD38 cognitive rescue, have been demonstrated in mouse models that reproduce amyloid pathology but do not reproduce the full complement of human Alzheimer's disease pathology including tau tangles, cerebrovascular disease, and the full spectrum of inter-individual variability in peripheral immune function. The translation to human disease therefore remains uncertain, and the clinical trials that would validate the framework in humans have, so far, produced mixed results with checkpoint blockade.

These limitations are not fatal to the integration but they define its current epistemic status: the Dual-Compartment Homeostatic Collapse Model is a theoretical unification whose experimental validation remains substantially to be performed. The predictions it generates are specific and testable, and the experimental program outlined in the preceding section offers a direct route to its confirmation or refutation.

12. Conclusion

The Homeostatic Collapse Model developed in the companion thesis provides a powerful account of microglial contributions to Alzheimer's disease by treating the attack and failure phenotypes as alternative projections of a single upstream event, the collapse of the TGF-β/SMAD-maintained homeostatic signature. The model is, however, a model of the parenchymal compartment alone, and it is silent on the peripheral immune compartment whose contribution to central nervous system homeostasis has been the subject of Michal Schwartz's research program for more than two decades. This paper has argued that the integration of Schwartz's framework with the Homeostatic Collapse Model produces a Dual-Compartment Homeostatic Collapse Model in which the parenchymal TGF-β niche and the peripheral immunometabolic compartment are coupled through the choroid plexus interferon-γ gateway, the monocyte-derived macrophage recruitment arm, and the CD38/NAD■ immunometabolic substrate. The integration supplies three elements that the parenchymal model lacks: a second upstream driver of homeostatic collapse through peripheral T-cell exhaustion; a non-TREM2-dependent salvage arm through recruited monocyte-derived macrophages; and a predicted mechanistic bridge from meningeal Th17 immunity through matrix metalloproteinase induction to the perineuronal net–parvalbumin interneuron axis that connects the peripheral arm to the emerging seventh convergence axis on extracellular matrix integrity.

The integration resolves rather than dissolves the documented contradiction between Schwartz's protective and Weaver's pathogenic accounts of adaptive immunity in Alzheimer's disease, by treating them as sequential phases of the same immunological trajectory with homeostatic collapse marking the transition point. It generates therapeutic predictions that are specific enough to be operationalized in trial design and distinct enough from existing programs to be distinguishable empirically, and it identifies CD38 blockade, interleukin-17 blockade, and combined peripheral-plus-parenchymal interventions as the most promising therapeutic classes under the model. It identifies the perineuronal net–parvalbumin interneuron axis as the most tractable compound biomarker of therapeutic success, integrating the parenchymal enzymatic program and the peripheral Th17 induction signal in a single measurable substrate.

The broader epistemological lesson of the synthesis is that the parenchymal framing of microglial biology, which has dominated the field for the last decade and which has structured the interpretation of every major experimental program in Alzheimer's disease neuroimmunology, is conceptually incomplete in a specific and addressable way. The brain is not an immune-privileged organ whose myeloid cells can be analyzed in isolation; it is an organ whose homeostasis depends on continuous positive input from a peripheral immune compartment whose own maintenance and function are themselves subject to

age-dependent and disease-related collapse. Schwartz's insistence on this framing, developed against the dominant current of the field for more than two decades, is vindicated by the integrative requirements of the Homeostatic Collapse Model, and her 2026 *Neuron* perspective on the evolutionary brain–immune interface is the appropriate conceptual summary of the integrated framework developed here. The brain is a garden sustained by immune cells. Alzheimer's disease is what happens when the gardeners exhaust.

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