UNIFIED COLLAPSE · CHAPTER 1

The Homeostatic–Matrix–Synaptic–Propagation Axis (HMS+P)

A Unified Synthesis of Convergent Synaptic Collapse, Homeostatic Microglial Collapse, Perineuronal Net Degradation, and Templated Propagation in Alzheimer's Disease — gated by Lipid Availability and APOE Isoform

Integrating twenty-six research programs across four prior ONS theses, with the cross-axis revision from *Templated Misfolding as the Fourth Substrate* (HMSP, May 2026) and the lipid/APOE gate (§4.8) embedded throughout. This chapter supersedes the April-2026 trilayer Chapter 1 (*The Homeostatic–Matrix–Synaptic Axis*).

Prepared under the Organic Network Synthesis methodology
AdultCognitiveDisease.com
Ben Gustafsson
April 2026 · revised May 2026

Chapter 1 — The Homeostatic–Matrix–Synaptic–Propagation Axis (HMS+P)

Abstract

Four prior analyses conducted under the Organic Network Synthesis (ONS) methodology have each reframed a major pillar of Alzheimer's disease pathogenesis as a convergence phenomenon rather than a linear cascade. The *Convergent Synaptic Collapse* (CSC) thesis integrated eight frameworks — Ramsden's lipid peroxidation, Small's retromer dysfunction, Gouras's inside-out amyloid pathology, Moosmann's chronic excitatory insufficiency, Rappoport's allostatic load, Huang's monomer dose-response, Margolis's synaptic confinement, and the Shatz–Stevens complement axis — into a four-phase model in which sporadic Alzheimer's disease emerges from the simultaneous, parallel failure of endosomal, excitatory-homeostatic, cytoskeletal-proteostatic, and neuroimmune systems converging on the synapse. The *Homeostatic Microglial Collapse* thesis integrated twelve additional research programs — Butovsky's homeostatic signature, Keren-Shaul and Amit's DAM taxonomy, Colonna's TREM2 biology, the Stevens and Shatz pruning pathways, Crapser's perineuronal net depletion work, Lemke's TAM receptor clearance axis, Marschallinger's LDAM state, the Prinz–Kierdorf border-associated macrophage ontogeny, Streit's dystrophy, von Bernhardi's TGF-β/SMAD collapse, and the de Vries resilience neuropathology — into a model in which the apparent dichotomy between microglial "attack" and "failure" resolves as two projections of a single upstream event: the collapse of the TGF-β-maintained homeostatic microglial state. The *Perineuronal Net Integrity* thesis integrated the Crapser, de Vries, Fawcett, Auer, and van 't Spijker programs into a self-reinforcing PNN Integrity–Microglial Activation Cycle positioning the matrix surrounding parvalbumin-positive interneurons as the single mechanical substrate on which amyloid pathology, microglial collapse, and inhibitory circuit failure jointly act. The *Convergent Propagation Collapse* thesis, completed in early 2026 in the Bu–Prusiner–Walker monograph and its companion synucleinopathy literature, integrated Prusiner's prion synthesis, Walker and Jucker's experimental seeding program, Bu's identification of LRP1 as the master neuronal receptor for templated tau and α-synuclein uptake, Diamond's strain-faithful propagation framework, and the Lee–Trojanowski–Luk α-synucleinopathy program into an account of how pathology advances across the cortical network through receptor-mediated trans-synaptic spread.

This synthesis asks what remains when these four analyses are themselves subjected to the convergence operation that each individually performed on its constituent literatures. The answer is that the CSC synaptic framework, the Homeostatic Collapse microglial framework, the PNN matrix framework, and the Propagation framework are not four independent pillars that happen to meet in the Alzheimer's brain but four views of a single tetralayered event in which (i) a shared upstream

collapse — the failure of TGF-β-maintained homeostatic signaling — simultaneously unleashes post-homeostatic microglia, licenses matrix degradation around parvalbumin interneurons, and reactivates developmental synaptic pruning programs; and (ii) a parallel upstream gate — LRP1-mediated lipid availability, set by APOE isoform — modulates the threshold at which each substrate's collapse becomes self-sustaining and licenses LRP1-mediated receptor-bridged propagation as the substrate-level mechanism by which pathology advances. We name the integrated framework the Homeostatic–Matrix–Synaptic–Propagation (HMS+P) Collapse Model.

Five emergent convergences organize this integration. First, the parvalbumin-positive fast-spiking interneuron ensheathed by its perineuronal net is the single anatomical locus at which all four theses make coincident mechanistic predictions, and the loss of PV+ synaptic coverage is the common final pathway through which the four frameworks each derive cognitive failure. Second, TGF-β/SMAD signaling occupies a position upstream of three of the four frameworks (H, M, S): it maintains the Butovsky homeostatic signature, it is sequestered in latent form within the perineuronal matrix itself, and it restrains the reactivation of developmental complement-mediated pruning. Third, brain lipid availability — gated at the cell membrane by LRP1 and set systemically by APOE isoform — operates as a parallel upstream variable on all four substrates, supplying the cholesterol and sphingolipid pool that maintains synaptic-membrane function, supporting microglial phagocytic capacity, organizing the perinodal interface where PNN attaches to the neuronal membrane, and gating the LRP1-mediated endocytic step on which propagation depends. Fourth, LRP1 is the molecular receptor at which the matrix substrate's exposure of receptor-rich PV+ membranes, the propagation substrate's receptor-mediated uptake, and the lipid availability gate's APOE-particle endocytosis converge — a single transmembrane protein whose ligand promiscuity is the structural basis for the cross-substrate coupling that the HMS+P model articulates. Fifth, cognitive resilience is the human demonstration that preservation of any one of the four layers is insufficient but that joint preservation of all four — homeostatic microglia, intact perineuronal nets, competent PV+ inhibitory circuitry, and an unsaturated propagation receptor pool — is sufficient to sustain cognition at pathological burdens that would otherwise produce dementia, with APOE isoform setting the threshold at which the joint preservation regime is achievable in the first place.

The HMS+P Collapse Model makes specific predictions that none of the four constituent theses could generate alone. It predicts that effective Alzheimer's-disease therapeutics will act not at the level of amyloid, tau, synapse, microglia, matrix, or propagating seed individually but at the level of the TGF-β-maintained homeostatic state in combination with the APOE/LRP1-mediated lipid gate, whose joint collapse generates pathology in all four layers simultaneously. It predicts that perineuronal net integrity around PV+ interneurons is the single most compact biomarker of therapeutic success, because the PNN is the mechanical substrate at which microglial behavior, synaptic pruning, inhibitory circuit competence, and propagation-receptor access meet. It predicts that the repeated clinical failures of monotherapies targeting any single layer — anti-amyloid antibod-

ies, complement inhibitors, TREM2 agonists, NSAIDs — reflect not the inadequacy of their targets but the fact that each target is a downstream projection of an upstream collapse that the monotherapies leave untouched. And it predicts that homeostatic restoration in combination with lipid-gate stabilization — pharmacological reinstatement of the TGF-β/SMAD program that maintains Butovsky-signature microglia, latent PNN-sequestered TGF-β, and complement restraint, coupled with isoform-selective APOE modulation or LRP1-arm-specific intervention — is the therapeutic class most likely to produce durable disease modification, and the class that has been most systematically neglected by the field to date.

> **What remains uncertain:** *Whether the HMS+P+Gate architecture is itself the terminal cross-axis synthesis, or whether subsequent axes — most plausibly Bioenergetic Collapse (oxidative-phosphorylation failure, NAD^+ depletion), Network-Oscillatory Collapse (gamma/theta dysrhythmia), and a Vascular/Cerebrovascular axis whose substrate-status depends on whether VCID's downstream coupling to H, M, S, and P is substrate-irreducible — will require further extension. The four-substrate model with the lipid/APOE gate is defensible at the current state of the literature; the question of architectural closure is not.*

1. Introduction: Four Theses, One Disease

The Organic Network Synthesis methodology approaches complex, deadlocked scientific literatures not by adjudicating between competing frameworks but by searching for the emergent convergences at which apparently incompatible models resolve as projections of a common underlying process. Four prior ONS analyses have now applied this method to the Alzheimer's-disease framework literature with results that, taken individually, reframe substantial portions of the field. The Convergent Synaptic Collapse (CSC) thesis integrated eight synaptic, endosomal, and neuroimmune frameworks into a four-phase model of sporadic AD as parallel homeostatic failure converging on the synapse. The Homeostatic Microglial Collapse thesis integrated twelve microglial research programs into a model in which the long-standing attack/failure dichotomy in microglial biology dissolves once the TGF-β-maintained homeostatic state is recognized as the upstream variable. The Perineuronal Net thesis integrated the matrix biology literature with the de Vries 2024 resilience neuropathology to position PNN integrity as both a mechanistic hub and a resilience substrate. The Convergent Propagation Collapse thesis integrated the Prusiner prion synthesis, the Walker–Jucker seeded-transmission program, the Bu LRP1 receptor identification, the Diamond strain-faithful framework, and the Lee–Trojanowski synucleinopathy program into a substrate-level account of how pathology advances through the cortical network. Each thesis is self-contained. Each makes testable predictions. Each identifies therapeutic targets that its constituent frameworks, considered individually, could not have generated.

The four theses also share a set of conceptual commitments that suggest they may not be independent analyses at all. Each treats Alzheimer's disease as a disease of homeostatic failure rather than gain-of-function. Each identifies TGF-β signaling as an upstream constraint whose collapse permits downstream pathology, with the exception of the Propagation thesis, which identifies LRP1 as a parallel upstream gate operating through the lipid-availability axis. Each treats parvalbumin-positive inhibitory interneurons as the vulnerable substrate at which cognitive failure is ultimately decided. Each invokes either TREM2 (in H, M, S) or LRP1 (in P, and in the lipid gate) as a pivotal molecular gate whose loss-of-function risk allele status refuses to resolve within any purely activation-based framework. And each draws, at the decisive point in its argument, on the same piece of human tissue evidence — the de Vries and Carulli 2024 demonstration that cognitive resilience in the face of pathology is coextensive with preservation of perineuronal net integrity around PV+ interneurons. When four independent analyses of nominally distinct biological problems converge on the same signaling pathway, the same cell type, the same receptors, and the same resilience biomarker, the null hypothesis is that the four problems are not independent.

This chapter asks what the four theses, treated as inputs to a further layer of the ONS operation, together imply about the structure of Alzheimer's-disease pathogenesis. The question is not whether each thesis is correct — each stands on its own integration of primary literature, and the reader is referred to the respective documents for that work. The question is what the four theses jointly describe once their convergence structure is made explicit, and whether the joint description supports a model that is stronger than the disjunction of its components. We argue that it does, that the joint model is the Homeostatic–Matrix–Synaptic–Propagation (HMS+P) Collapse framework presented below, and that this framework carries therapeutic and biomarker implications that are specific to the integration and not available from any constituent thesis alone.

2. The Four Convergence Surfaces

Before the integration can be performed, the four theses must be presented in a form that exposes the surfaces at which they meet. We summarize each in the form of its convergence axes and its identification of the upstream variable it claims to have found.

2.1 Convergent Synaptic Collapse: The Synapse as Final Common Path

The CSC thesis organizes its eight constituent frameworks into four emergent convergence axes. The first, the Endosomal Nexus, unifies the Ramsden lipid peroxidation program, the Small retromer dysfunction program, and the Gouras inside-out amyloid pathology program around the shared claim that Alzheimer's pathogenesis begins in the synaptic endosomal compartment, that lipid peroxidation-driven disruption of ApoER2–Dab1–LRP1 signaling is the upstream initiator, and that extracellular amyloid plaque is a secondary consequence of endosomal rupture or exosomal

release rather than the primary event. The second, the Compensatory Homeostatic Paradigm, unifies the Moosmann chronic excitatory insufficiency framework, the Rappoport allostatic load framework, and the Huang monomer dose-response biphasic framework around the claim that early Alzheimer's disease is not dominated by pathology but by the metabolic and signaling cost of compensating for it, and that the transition from preclinical to symptomatic disease is the crossing of an allostatic threshold at which compensation itself becomes limiting. The third, the Cytoskeletal Collapse Mechanism, unifies the Huang monomer work with the Margolis synaptic confinement framework around the claim that dendritic spine restriction and proteostatic saturation jointly generate "proteostatic dead zones" in which recycling endosomes become congested and synapses become mechanically trapped. The fourth, the Neuroimmune Interface, unifies the Stevens complement cascade work with the Shatz C4d–LilrB2 cell-autonomous pruning pathway around the claim that developmental synaptic pruning programs are reactivated under chronic inflammation and that this reactivation is the executioner arm of the collapse.

The CSC thesis's four-phase progression — subclinical lipid peroxidation, preclinical inside-out amyloid accumulation, MCI-era compensatory saturation, and dementia-era synaptic proteostatic collapse — locates the synaptic endosome as the upstream site, the allostatic threshold as the decisive temporal event, and the reactivated developmental pruning pathway as the terminal effector. The framework treats the synapse as the final common path through which cognitive failure is produced, and its central contribution is to reveal that the apparent diversity of molecular mechanisms in sporadic AD is better understood as parallel feeds into a single convergence surface than as competing pathogenic accounts.

2.2 Homeostatic Microglial Collapse: The Microglial State as Upstream Variable

The Homeostatic Microglial Collapse thesis organizes its twelve constituent programs around the claim that the dominant theoretical impasse in microglial biology of Alzheimer's disease — between an "attack" framework in which microglia drive pathology through complement pruning, matrix degradation, and inflammatory cytokine release, and a "failure" framework in which dystrophic, senescent, phagocytically exhausted microglia withdraw neuroprotective support — dissolves when the TGF-β-maintained homeostatic microglial signature defined by Butovsky is recognized as the upstream variable whose loss is common to every pathological microglial state described in the downstream literature.

Three emergent convergences organize the model. First, homeostatic collapse is the single upstream event: DAM Stage 1 cells, DAM Stage 2 cells, LDAM cells, and dystrophic cells all share, as their most reproducible feature, the downregulation of the Butovsky P2ry12/Tmem119/Cx3cr1 signature, and they differ only in which downstream trajectory they adopt after collapse. Second, TREM2 is the collision point between the attack and failure frameworks: it gates a lipid-sensing and phagocytic salvage program whose successful execution produces protective clearance and whose failed execution produces collateral damage through effector enzyme release, and the

paradoxical status of TREM2 loss-of-function as a risk allele resolves only when both outcomes are recognized as products of the same receptor operating in post-homeostatic cells. Third, the perineuronal net represents the concrete mechanistic locus at which attack and failure become indistinguishable: the microglial digestion of aggrecan and tenascin-R around PV+ interneurons is simultaneously an act of matrix destruction (attack) and an act of protective withdrawal from the ensheathed cell (failure), produced in a single effector step.

The Homeostatic Collapse framework locates the upstream variable not at a synapse, a receptor, or a protein aggregate but at a cellular state: the TGF-β-maintained identity that distinguishes adult parenchymal microglia from the macrophage default, and whose age-dependent loss generates the post-homeostatic cells whose downstream behavior produces every pathological phenotype catalogued in the microglial literature.

2.3 Perineuronal Nets: The Matrix as Mechanical Substrate

The PNN thesis integrates the matrix biology literature around a self-reinforcing PNN Integrity–Microglial Activation Cycle: amyloid-β and tau aggregates trigger microglial activation via pattern recognition receptors (TLR4, CD14, TREM2); activated microglia release MMP-2, MMP-9, ADAMTS-4, and cathepsin-S into the perineuronal space; these enzymes digest the aggrecan, versican, hyaluronic acid, tenascin-R, and link protein architecture that constitutes the PNN; PNN degradation removes structural, ionic, and oxidative protection from the ensheathed parvalbumin-positive interneuron; and the resulting loss of PV+ circuit integrity destabilizes excitation–inhibition balance, amplifies glutamatergic excitotoxicity, and further activates microglia through the downstream inflammatory consequences of inhibitory circuit failure. Four convergence axes organize the PNN literature: the extracellular matrix–microglial nexus through which intact PNN CSPGs restrain microglial activation and PNN degradation unleashes it; the inhibitory circuit vulnerability through which PV+ interneurons depend on PNN-mediated structural and signaling support; the oxidative stress amplification through which PNN ECM proteins buffer reactive oxygen species and sequester redox-active metals, with PNN loss removing this buffering in the perisomatic zone where PV+ synapses concentrate; and the synaptic restriction axis through which PNNs normally restrain lateral diffusion of adhesion molecules and dendritic spine enlargement.

Critically, the PNN framework identifies latent TGF-β sequestered within the perineuronal matrix as a tonic anti-inflammatory signal released during matrix turnover, establishing the PNN itself as a reservoir of the signaling molecule whose collapse the microglial thesis identifies as the upstream variable of homeostatic collapse. The PNN thesis's central empirical anchor is the de Vries 2024 demonstration that cognitive resilience in humans correlates with PNN preservation around PV+ interneurons despite high amyloid and tau burdens, establishing PNN integrity as both mechanistic hub and resilience substrate. The framework locates the critical variable neither at the synapse nor at the microglia but at the extracellular matrix whose integrity mediates between them.

2.4 Convergent Propagation Collapse: The Templating Substrate

The Propagation thesis, articulated in the Bu–Prusiner–Walker monograph and its synucleinopathy companion, organizes five literature programs into a substrate-level account of how pathology advances across the cortical network. The conceptual foundation belongs to Prusiner's prion theory and its 2012 *Science* extension to Aβ, tau, α-synuclein, TDP-43, SOD1, huntingtin, and the polyglutamine repeat proteins. The experimental architecture belongs to the Walker–Jucker collaboration, whose intracerebral and peripheral inoculation experiments established that misfolded aggregates from one brain can nucleate identical pathology in another, that the pathology spreads along neuroanatomical projections, and that different strains produce reproducibly different signatures. The molecular machinery belongs to Bu's 2020–2022 program, which identified LRP1 as the master neuronal receptor for both tau and α-synuclein uptake, with targeted LRP1 knockdown in iPSC-derived neurons and in murine in-vivo models effectively halting cellular uptake and trans-synaptic propagation; the binding interaction depends on specific lysine residues in the microtubule-binding region of tau and on the N-terminal lysine cluster of α-synuclein. The strain framework belongs to Diamond's laboratory, which established that distinct tau prion strains propagate in cells and mice and define different tauopathies. The trans-synaptic spread component belongs to the Luk and Lee–Trojanowski synucleinopathy program, whose 2012 *Science* demonstration that pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in wild-type mice supplied the cellular and circuit-level evidence that propagation occurs in vivo along anatomically defined projections.

The Propagation substrate has five internal mechanistic components — templated misfolding, seeded transmission, receptor-mediated uptake, strain-faithful propagation, and trans-synaptic spread — which together possess the architectural density required for substrate-level integration into the cross-axis synthesis. The substrate explains three empirical phenomena that the trilayered HMS framework could not generate within its own terms: the Braak staging sequence, the strain-faithful propagation of tauopathies, and the lecanemab/donanemab progression gap (the observation that amyloid-clearance antibodies produce only modest slowing of clinical decline despite robust amyloid removal, because they engage no HMS substrate and do not block the propagation cascade that continues unabated). The Propagation framework locates the upstream variable not at a cell state, a receptor, a matrix structure, or a synapse but at the conformational templating event whose downstream consequences depend on LRP1-mediated receptor access at the recipient cell membrane.

3. The Quadruple Convergence: Where the Four Models Meet

The four convergence surfaces presented in Section 2 each identify a different upstream variable — the synaptic endosome (CSC), the homeostatic microglial state (HCC), the perineuronal net (PNN), and the templated propagation step (Propagation) — and each traces cognitive failure

through a different mechanistic corridor. Taken individually, they look like four independent analyses that happen to share some molecular vocabulary. Taken jointly, they describe a structure in which the four upstream variables are not independent: each is upstream of the others through a small set of shared nodes, the four frameworks are better understood as four views of a single tetralayered collapse than as four distinct convergence analyses, and a fifth upstream variable — brain lipid availability, set by APOE isoform — operates as a cross-cutting gate on all four. We identify five emergent convergences at which this joint structure becomes visible.

3.1 Convergence I: The PV+ Perisomatic Zone as Shared Anatomical Substrate

The most striking shared feature of the four theses is that each, when traced to its mechanistic terminus, arrives at the same anatomical structure: the perisomatic zone of the fast-spiking parvalbumin-positive interneuron, encased in its perineuronal net, receiving GABAergic input that gates cortical and hippocampal excitation. The CSC framework arrives at this zone through its cytoskeletal collapse and neuroimmune arms: Margolis-style synaptic confinement applies most severely to the high-firing PV+ interneuron whose metabolic demands are the greatest in cortex, and the complement-mediated pruning of inhibitory perisomatic synapses is, in the Shatz and Stevens accounts, one of the earliest detectable synaptic phenotypes in Alzheimer's-disease models. The Homeostatic Collapse framework arrives at this zone through its identification of the PNN as the substrate at which attack and failure become indistinguishable, and at which post-homeostatic microglial effector activity produces its most consequential cognitive output. The PNN framework arrives at this zone definitionally, because the PNN is the perisomatic ECM ensheathing the PV+ interneuron, and the entire framework is organized around the consequences of its degradation. The Propagation framework arrives at this zone through its receptor-access argument: the PV+ perisomatic surface, once denuded of its protective matrix, presents an unusually concentrated array of LRP1 and HSPG receptors at exactly the membrane region where extracellular tau and α-synuclein seeds accumulate after release from synaptic vesicles in the engulfment step.

The joint implication is that the PV+ perisomatic zone is not one of many possible substrates through which Alzheimer's disease might produce cognitive failure but the single anatomical structure at which the four upstream variables identified by the four theses meet and at which their consequences become inextricable. This is not a coincidence of vocabulary. The PV+ interneuron is metabolically the most expensive neuron in the neocortex; it is the neuron whose firing rates generate the greatest oxidative load and therefore the greatest demand for the PNN's iron-chelation and ROS-buffering functions; it is the neuron whose perisomatic synapses are preferentially tagged by C4d and C1q in the mouse models on which the Stevens and Shatz programs depend; it is the neuron whose loss drives the excitation–inhibition imbalance that generates the Moosmann chronic excitatory insufficiency phenotype; it is the neuron whose receptor-rich perisomatic membrane provides the highest-density uptake target for templated seeds in the propagation substrate; and it is the neuron whose preservation or loss de Vries and Carulli identified in

2024 as the single morphological correlate of cognitive resilience in amyloid- and tau-positive human brains. The four theses are not converging on the PV+ perisomatic zone by accident. They are converging on it because it is the single structure at which synaptic, microglial, matrix, and propagation pathology meet and in which the distinction between them dissolves.

3.2 Convergence II: TGF-β/SMAD as Shared Upstream Signaling for the Three HMS Substrates

The second convergence is that TGF-β/SMAD signaling occupies a position upstream of three of the four frameworks in a way that none of the three, considered individually, can fully articulate. Within the Homeostatic Microglial Collapse framework, TGF-β is the niche signal that maintains the Butovsky homeostatic signature: its collapse, mediated by the age-dependent dysregulation of SMAD2/3 transcription and the accumulation of SMAD7 inhibitory feedback described by von Bernhardi, is the specific signaling event through which homeostatic microglia enter the post-homeostatic state. Within the PNN framework, TGF-β is sequestered in latent form within the perineuronal matrix itself via LTBP-containing complexes, and its tonic release during physiological matrix turnover supplies a continuous anti-inflammatory signal to the microglia patrolling the perisomatic zone. Within the CSC framework, TGF-β restrains the reactivation of the developmental complement cascade that drives the Stevens pruning pathway and the C4d-mediated Shatz pathway, and its loss is a permissive condition for the developmental pruning reactivation that the CSC framework identifies as the terminal effector of synaptic collapse.

The joint implication is that TGF-β/SMAD is not one of many signaling pathways involved in Alzheimer's disease but the single pathway whose collapse is sufficient to unleash pathology in all three HMS layers simultaneously. Jointly, the frameworks describe a feed-forward loop: collapse of TGF-β/SMAD signaling in microglia produces post-homeostatic cells that release matrix metalloproteinases into the perineuronal space; digestion of the perineuronal matrix depletes the reservoir of latent TGF-β that was sequestered there; depletion of latent TGF-β further reduces the tonic signal restraining microglial activation and complement reactivation; reduced TGF-β restraint permits the developmental pruning programs to reactivate and execute their terminal effector pathway; and the resulting loss of PV+ inhibitory coverage generates the excitatory overload that amplifies oxidative stress and further dysregulates the SMAD pathway. The loop closes. There is no privileged upstream entry point, because the three upstream variables identified by the three HMS theses are, in this feed-forward structure, co-extensive. The HMS Collapse Model describes this co-extension explicitly.

The Propagation substrate sits outside this TGF-β feed-forward loop in its proximal causation — propagation depends on conformational templating and on LRP1-mediated uptake, neither of which is directly TGF-β-regulated — but inside it in its substrate dependencies: PNN degradation (driven by the TGF-β loop) exposes the receptor-rich PV+ membrane required for propagation receptor access, and homeostatic-collapsed microglia (driven by the TGF-β loop) are the principal

failed clearance machinery for extracellular seeds that the propagation cascade depends on accumulating. The TGF-β loop is therefore a proximal upstream constraint on H, M, and S, and an indirect constraint on P. A second upstream variable — the lipid/APOE gate of §3.5 — operates as a parallel constraint on all four substrates including P.

3.3 Convergence III: TREM2 as Shared Molecular Pivot

The third convergence is TREM2. Each of the three HMS theses identifies TREM2 as a critical molecular pivot in its own right, and each derives from it a different but compatible interpretation. In the Homeostatic Microglial Collapse framework, TREM2 is the receptor that gates the DAM Stage 1 to Stage 2 transition, whose loss-of-function variants confer risk by impairing the salvage program that post-homeostatic microglia attempt, and at which the attack and failure frameworks collide. In the PNN framework, TREM2 is engaged by CSPG fragments released during matrix degradation, amplifying microglial lipid-sensing and phagocytic programs in response to the very substrate whose destruction they mediate, producing a positive feedback loop in which PNN degradation drives further microglial activation. In the CSC framework, TREM2-dependent oversampling of synapses is identified as the complement-independent arm of the synaptic pruning mechanism, coupling microglial lipid metabolism and endosomal trafficking to the elimination of synaptic elements, and linking the Ramsden–Small–Gouras endosomal nexus to the Shatz–Stevens neuroimmune interface through a single receptor expressed on microglia that have already undergone homeostatic collapse.

The joint implication is that TREM2 is the single molecular node at which the endosomal, microglial, matrix, and synaptic pathologies of the three HMS frameworks converge mechanistically, and that its paradoxical status as a loss-of-function risk allele is resolved only when all three interpretations are held simultaneously. TREM2 loss-of-function variants confer risk because they (i) impair the Stage 2 DAM transition that would have allowed productive lipid clearance, (ii) impair the CSPG fragment sensing that would have allowed matrix-restorative phagocytic programs, and (iii) impair the endosomal lipid coupling that would have allowed post-homeostatic cells to execute productive salvage rather than dysregulated synaptic oversampling. The three effects are not additive; they are three descriptions of the same event, because TREM2 is a single receptor operating in a single cell whose downstream program is gated by the same adapter (DAP12/TYROBP), the same kinase (SYK), and the same metabolic state (mTOR-coupled oxidative phosphorylation). The repeated clinical failures of TREM2 agonist programs in advanced disease populations are explained by the HMS+P Collapse Model in a way that none of the three HMS theses alone can fully articulate: agonism of a receptor whose downstream execution depends on a metabolically competent, homeostatically preserved cell cannot rescue outcomes in a population whose microglia have already undergone homeostatic collapse, whose perineuronal matrices have already been degraded, and whose synaptic endosomes have already entered proteostatic gridlock. TREM2 agonism is the right receptor at the wrong layer.

3.4 Convergence IV: LRP1 as the Shared Receptor for Matrix Access, Propagation, and Lipid Delivery

The fourth convergence — visible only after the propagation substrate is added to the synthesis — is that LRP1 occupies a position structurally analogous to TREM2 but for a different set of substrates. Within the Propagation framework, LRP1 is the master neuronal receptor for tau and α-synuclein uptake, and the molecular gateway through which the propagation cascade advances. Within the lipid-availability gate developed in §3.5, LRP1 is the receptor at which APOE-packaged lipoprotein particles are internalized in neurons, microglia, and the cerebrovasculature, and the molecular bottleneck through which brain lipid homeostasis is maintained. Within the matrix framework, LRP1's exposure on the receptor-rich PV+ perisomatic membrane — exposure conditional on PNN integrity — couples matrix collapse to propagation cascade kinetics. Within the homeostatic microglial framework, microglial LRP1 supports phagocytic uptake of both amyloid and apoptotic-cell debris and supports the metabolic state on which the Butovsky signature depends.

The joint implication is that LRP1 is the single transmembrane protein at which four substrate-level mechanisms — propagation, lipid delivery, matrix-conditioned receptor access, and homeostatic phagocytic competence — converge on a single membrane-localized event. The structural promiscuity of LRP1, which the receptor literature has historically treated as a curiosity, is on the HMS+P account the structural basis for the cross-substrate coupling that distinguishes the four-substrate architecture from the trilayer it supersedes. The translational implication is sharp: any pharmacological intervention on LRP1 must be selective with respect to which of these four functions it modulates. The APOE3-Christchurch (R136S) resilience case — in which a single mutation that reduces APOE binding to LRP1 produces dramatic protection against autosomal-dominant Alzheimer's disease — is, on this reading, the in-vivo experiment of nature that confirms the principle: *selective dampening* of an LRP1 interaction (here, APOE binding) yields benefit because it dampens the lipid-availability gate without compromising LRP1's other functions. The principle generalizes: a successful LRP1-targeted therapy will not be an LRP1 agonist or antagonist; it will be a selective modulator of a specific LRP1–ligand interaction.

3.5 Convergence V: Lipid Availability and the APOE Modifier

The fifth convergence — the most consequential for understanding why APOE4 is the strongest genetic risk factor for late-onset AD — is that brain lipid availability operates as a cross-cutting upstream gate on all four substrates, in parallel with but mechanistically distinct from the TGF-β/SMAD loop. The CNS holds roughly 20% of total body cholesterol despite representing 2% of body mass, and cholesterol does not cross the blood-brain barrier. Astrocyte de novo synthesis followed by APOE-packaged delivery to neurons, microglia, and the cerebrovasculature is the entire supply chain. LRP1, the receptor at the recipient end of that chain, is therefore a node on which every substrate's mechanism partially depends.

The dependence is asymmetric across the substrates but absent from none. In S, neuronal LRP1 supplies the cholesterol and sphingolipid pool that supports synaptic-membrane turnover and AMPA/NMDA receptor surface expression; Bu's 2010 demonstration that adult-onset neuronal Lrp1 knockout produces catastrophic depletion of brain cholesterol, sulfatide, and galactosylceramide, with progressive dendritic-spine loss, reduced membrane localization of NMDA receptor 1 and GluR1, and overt memory deficits, establishes a cell-autonomous, non-complement failure mode of the synaptic substrate that the trilayered HMS framework had no place for. In H, microglial LRP1 supports phagocytic uptake of both amyloid and apoptotic-cell debris; its loss accelerates the DAM trajectory through impaired clearance and lipid-droplet accumulation. In M, the perinodal interface where PNN core proteins attach to the neuronal membrane is itself lipid-organized, and lipid composition affects MMP-9-driven proteolysis kinetics. In P, endocytic uptake of misfolded protein assemblies depends on membrane fluidity and on the surface availability of LRP1 itself, which is regulated by intracellular cholesterol via SREBP-mediated transcriptional feedback.

The APOE genotype is the upstream variable that sets how this gate functions. APOE2, APOE3, and APOE4 differ in their binding kinetics to LRP1 and VLDLR; APOE4 saturates LRP1, reducing Aβ-clearance capacity and the lipid-delivery throughput simultaneously. The APOE4–Aβ complex is preferentially routed to VLDLR with slower internalization kinetics, whereas APOE2/3–Aβ complexes use both LRP1 and VLDLR efficiently. The Ramsden ApoE–ApoER2 peroxidation cascade hypothesis (evaluated as a companion document in the synaptic-collapse corpus) supplies the molecular instantiation of this gate: APOE4-specific failure of disulfide-bridge protection → PUFA peroxidation → ApoE–ApoER2 pyrrole crosslinking → Dab1/PI3K/GSK3β starvation → tau hyperphosphorylation and PSD95 disassembly. The APOE3-Christchurch (R136S) variant, identified in a remarkably resilient autosomal-dominant AD case, reduces APOE binding to LRP1 and LDLR and is paradoxically protective — dampening lipoprotein-particle uptake enough to reduce intracellular lipid peroxidation and lipofuscin accumulation without crossing the threshold into lipid starvation.

Lipid availability is therefore not a fifth substrate in the substrate-inclusion sense (its dysfunction does not produce a substrate-irreducible collapse pattern of its own; it potentiates the collapse of the four existing substrates). It is an upstream gate, and APOE genotype is the variable that sets it. The HMS+P interaction graph should be read as four nodes connected pairwise *and* gated, at each node, by a fifth upstream variable that determines the threshold at which collapse becomes self-sustaining. The therapeutic corollary — that no monotherapy against H, M, S, or P will be effective at population scale unless the lipid/APOE gate is also addressed — is exactly what the Christchurch case predicts.

3.6 Convergence VI: Resilience as Quadruple Preservation

The sixth convergence is that the de Vries and Carulli 2024 neuropathology — the single empirical anchor that all four theses cite — is most naturally read not as evidence for preserved PNN in-

tegrity alone, nor as evidence for preserved microglial homeostasis alone, nor as evidence for preserved PV+ synaptic coverage alone, nor as evidence for restrained propagation alone, but as evidence that all four are preserved jointly in the resilient brain and that their joint preservation, gated by a non-saturated APOE/LRP1 axis, is the biological substrate of cognitive resilience. The de Vries cohort exhibited AD-threshold amyloid and tau burdens without clinical dementia; they exhibited preserved aggrecan and tenascin-R immunostaining around PV+ interneurons; they exhibited microglial transcriptional signatures lacking the MMP-2/MMP-9/cathepsin-S upregulation of symptomatic disease; they exhibited intact synaptic contacts onto the ensheathed PV+ neurons; and — although the original analysis did not measure it directly — the integrated framework predicts they should also exhibit absence of strain-faithful tau propagation signatures along corticocortical projections from the entorhinal cortex outward. Each of the four theses reads this result as support for its own upstream variable, and each is individually correct. But the joint reading is stronger: resilience is not the preservation of any one layer but the preservation of the co-extensive TGF-β-maintained system that keeps three layers intact simultaneously, combined with an APOE/LRP1 axis that has not been driven into receptor saturation.

This reading has a sharp implication. Any therapeutic intervention that preserves only one of the four layers — say, anti-amyloid antibodies that reduce pathological substrate without restoring homeostatic microglial identity, or complement inhibitors that block downstream pruning without restoring the upstream TGF-β tone, or chondroitinase-resistant matrix stabilization that preserves CSPGs without addressing the microglia that digest them, or LRP1 propagation antagonists that block tau/α-synuclein uptake without restoring the microglial clearance and lipid-delivery functions on which the homeostatic substrate depends — will produce partial and unsustainable benefit because the other three layers will continue to collapse and will feed back on the preserved layer through the loop described in §3.2 and the gate described in §3.5. Resilience, in the de Vries sense, is coherent. Partial restoration, in the therapeutic sense, is not. This is the central therapeutic lesson of the HMS+P Collapse Model.

4. The Homeostatic–Matrix–Synaptic–Propagation (HMS+P) Collapse Model

The integrated model may now be stated. Alzheimer's disease is the clinical expression of the age-dependent, cumulative collapse of two upstream regulatory systems and their four co-extensive downstream substrates: (i) a TGF-β/SMAD-maintained homeostatic signaling loop whose three co-extensive substrates — the homeostatic microglial state, the perineuronal matrix, and the synaptic proteostatic and excitatory-inhibitory balance — jointly sustain cognitive function in the adult brain and whose failure generates the pathological phenotypes catalogued in the CSC, HCC, and PNN theses; and (ii) an APOE/LRP1-mediated lipid-availability gate whose substrate dependencies link APOE-packaged cholesterol and sphingolipid delivery, microglial phagocytic capacity,

perinodal membrane organization, and the receptor-mediated propagation step into a single, isoform-dependent threshold whose crossing licenses the fourth substrate — templated propagation of tau and α-synuclein — to advance the pathology across the cortical network. The four substrates and two upstream gates are not independent targets of a shared pathogenic mechanism; they are aspects of a single tetralayered, dual-gated homeostatic architecture that fails as a unit.

The HMS+P Collapse Model decomposes the collapse into a structure with four substrate layers, two upstream gating systems, and six bidirectional couplings. The substrate layers are (i) the microglial homeostatic state, defined by the Butovsky signature and maintained by TGF-β/SMAD signaling from the parenchymal niche; (ii) the perineuronal matrix, defined by aggrecan, tenascin-R, hyaluronic acid, link protein, and CSPG sulfation architecture, serving as both mechanical scaffold and reservoir of latent TGF-β; (iii) the PV+ perisomatic synaptic zone, defined by the competent inhibitory coverage of fast-spiking interneurons whose firing gates cortical and hippocampal excitation–inhibition balance; and (iv) the templated propagation substrate, defined by the conformational templating event itself, the receptor-mediated uptake step (LRP1, with HSPG co-receptor handoff), the strain-faithful preservation of conformational identity across cycles of templating, and the trans-synaptic spread that advances the cascade along anatomically defined cortico-cortical projections. The upstream gating systems are (i) the TGF-β/SMAD signaling loop that maintains the homeostatic state of H, the latent reservoir in M, and the complement restraint in S; and (ii) the APOE/LRP1-mediated lipid-availability gate that sets the threshold at which each substrate's collapse becomes self-sustaining and that licenses LRP1-mediated uptake in P.

The six bidirectional couplings, summarized from the HMSP whitepaper, are H–M (microglial homeostatic collapse drives PNN degradation through MMP-9/ADAMTS upregulation), H–S (microglial CR3-mediated complement-engulfment activity is gated by homeostatic state), M–S (PNN degradation exposes PV+ synapses to complement-mediated engulfment and to direct extracellular insults), H–P (homeostatic-collapsed microglia fail to clear extracellular seeds and themselves accumulate seed-induced lysosomal burden that drives the DAM transition), M–P (PNN degradation exposes the LRP1- and HSPG-rich PV+ perisomatic membrane that is the propagation cascade's principal uptake target), and S–P (complement-mediated synaptic engulfment is a controlled release of synaptic content that constitutes the next round of propagation seeds). Each coupling is bidirectional. The graph is fully connected. The substrates feed each other through the loop, the gates set the threshold at which the loop becomes self-sustaining, and no privileged upstream entry point exists.

In the preserved state, the four layers sustain each other, and the two gating systems hold them in the homeostatic attractor. Homeostatic microglia maintain non-destructive surveillance of the perineuronal matrix and do not release matrix metalloproteinases. The intact matrix sequesters latent TGF-β and releases it at physiological rates, reinforcing microglial homeostasis and restraining complement reactivation. The preserved matrix buffers reactive oxygen species and chelates iron in the perisomatic zone, allowing the PV+ interneuron to sustain high firing rates without oxidative

damage. The preserved PV+ interneuron sustains inhibitory tone, preventing the glutamatergic overload that would otherwise generate excitotoxic calcium influx and further oxidative stress. LRP1-mediated lipid delivery, set by an APOE genotype that has not driven the receptor into saturation, supplies the cholesterol and sphingolipid pool that maintains synaptic-membrane function, microglial phagocytic capacity, perinodal membrane organization, and the propagation-receptor turnover required to keep uptake kinetics below the threshold at which templated spread becomes self-sustaining. The system is stable because each layer reinforces the others and each gate holds them at the threshold below which collapse becomes self-sustaining.

In the collapsing state, the four layers destabilize each other, and the two gating systems progressively lose their hold. Age-dependent oxidative stress dysregulates SMAD2/3 signaling in microglia, as described by von Bernhardi; microglia begin to lose the Butovsky signature and enter the post-homeostatic state. Post-homeostatic cells release matrix metalloproteinases and cathepsin-S into the perineuronal space; the matrix begins to degrade. Latent TGF-β release falls below the level required to restrain further microglial collapse and to block complement reactivation. CSPG fragments released from the degrading matrix engage TREM2, amplifying further phagocytic engagement and further matrix degradation. Oxidative buffering in the perisomatic zone fails. PV+ firing-driven oxidative damage accumulates. Inhibitory coverage of principal neurons fails. Excitation–inhibition balance tilts toward excitotoxicity. Glutamatergic overload further amplifies oxidative stress and feeds back into microglial dysregulation. Developmental synaptic pruning programs reactivate under the permissive conditions of reduced TGF-β tone and elevated complement deposition; synapses are eliminated. The Ramsden–Small–Gouras endosomal pathology accelerates under the metabolic burden. Simultaneously, the APOE/LRP1 axis is progressively saturated by accumulating misfolded protein and APOE-particle traffic; the lipid-delivery throughput falls, dendritic-spine lipid composition deteriorates, and propagation-receptor access on the now-exposed PV+ perisomatic membrane reaches the threshold at which templated tau and α-synuclein spread becomes self-sustaining along cortico-cortical projections from the entorhinal cortex outward. The system enters the four-phase trajectory described in §5, with each phase corresponding to a specific degree of collapse in the joint tetralayered architecture rather than to a specific accumulation of any individual pathological substrate. The allostatic threshold identified by the Rappoport framework, at which compensation becomes limiting and MCI transitions to dementia, is in the HMS+P reading the threshold at which the feed-forward loop between the four layers becomes self-sustaining and the system can no longer return to the homeostatic attractor even if the upstream stressors are removed.

5. The Four-Phase Trajectory Reinterpreted

The CSC thesis organized Alzheimer's disease pathogenesis into four progressive phases — subclinical lipid peroxidation, preclinical amyloid accumulation, MCI-era compensatory saturation,

and dementia-era synaptic collapse. The HMS+P Collapse Model preserves this temporal structure but reinterprets each phase in terms of the joint state of the four substrate layers and the two upstream gates.

Phase 1 is characterized by the first detectable failures of the microglial homeostatic signature and the first detectable saturation of the APOE/LRP1 lipid gate in APOE4 carriers. At this stage, the perineuronal matrix remains structurally intact; PV+ synaptic coverage is preserved; the Butovsky signature is only marginally reduced; and propagation is undetectable. The CSC-era lipid peroxidation is occurring, driven preferentially by APOE4 carriers whose disulfide-bridge protection is absent (per the Ramsden mechanism), but the microglial layer has not yet entered post-homeostatic territory at the population level, the matrix-sequestered TGF-β reservoir is still adequate to restrain the subthreshold dysregulation of SMAD signaling, and the LRP1 receptor pool has not yet saturated to the point of permitting trans-synaptic propagation. Individuals in this phase are clinically silent and would be identifiable only by high-resolution microglial transcriptomic readouts of early Butovsky signature decay or by APOE-dependent stratification of lipid-peroxidation biomarkers.

Phase 2 is characterized by the onset of localized post-homeostatic microglial populations in regions of highest amyloid exposure, the first detectable reductions in perineuronal matrix integrity around the PV+ interneurons of those regions, and the first detectable seeding events at the propagation level. The CSC-era inside-out endosomal amyloid accumulation is accelerating, in part because TREM2-dependent lipid clearance is now operating in cells whose homeostatic baseline has already been lost and whose salvage programs are generating more collateral than clearance. The compensatory NMDA upregulation of the Moosmann framework has begun and is sustaining cognitive performance, but the matrix-buffered oxidative environment of the PV+ perisomatic zone is beginning to fail. The propagation substrate has initiated locally — in the entorhinal cortex layer II for tau, in the locus coeruleus and dorsal raphe for early monoaminergic-system tauopathy, and in the dorsal motor nucleus of the vagus and olfactory bulb for α-synuclein in those individuals destined for synucleinopathy — but trans-synaptic spread has not yet propagated through the cortico-cortical network. Clinically, the individual is still within the preclinical envelope, but the HMS substrate of resilience is no longer fully intact, and the lipid gate is approaching saturation in APOE4 carriers.

Phase 3 corresponds to MCI and is characterized by the crossing of the allostatic threshold and the entry of the propagation cascade into the cortico-cortical spreading regime. At this point, a critical proportion of the parenchymal microglial population has entered the post-homeostatic state; matrix-sequestered TGF-β release has fallen below the level required to restrain further collapse; complement reactivation has commenced; developmental pruning programs are tagging PV+ perisomatic synapses; inhibitory coverage is beginning to fail; the compensatory excitatory programs are saturating under the dual load of pathological substrate and impaired inhibitory restraint; and the LRP1 receptor pool on the now-exposed PV+ perisomatic membrane is saturated

to the point of permitting Braak-pattern trans-synaptic tau spread. The Rappoport allostatic threshold, the HMS self-sustaining feed-forward threshold, and the HMS+P propagation-self-sustaining threshold are, in this reading, the same threshold viewed from different angles. Clinical symptoms emerge.

Phase 4 corresponds to dementia and is characterized by irreversible collapse of all four substrate layers. Microglia are predominantly in DAM Stage 2, LDAM, or dystrophic states, with only a minority preserving the Butovsky signature. The perineuronal matrix is extensively degraded in the regions where cognitive function was most recently generated. PV+ perisomatic synaptic coverage has collapsed; excitation–inhibition balance is destroyed; complement- and TREM2-driven synaptic elimination is generalized; the CSC-era endosomal pathology has reached the "proteostatic dead zone" state in which recycling endosomes are mechanically trapped within shrinking dendritic spines; templated tau and α-synuclein propagation has saturated the cortico-cortical network from the entorhinal cortex outward; and the APOE/LRP1 lipid gate is fully saturated, leaving the residual healthy neurons starved of lipid-delivery throughput. The feed-forward loop between the four layers, gated through the saturated APOE/LRP1 axis, is fully self-sustaining and cannot be reversed by removing any single upstream stressor.

6. Resilience as Joint Preservation

The HMS+P Collapse Model predicts that cognitive resilience, as observed in the de Vries cohort, reflects joint preservation of the four layers against the pathological substrate of amyloid and tau deposition, gated through an APOE/LRP1 axis that has not been driven into saturation. This is a specific and testable prediction, and it is distinct from the prediction made by each constituent thesis alone. The PNN thesis alone predicts that resilience correlates with PNN preservation; it does, but the PNN thesis cannot predict whether PNN preservation is sufficient without accompanying microglial, synaptic, and propagation preservation. The Homeostatic Microglial Collapse thesis alone predicts that resilience correlates with homeostatic microglial preservation; it does, but it cannot predict whether homeostatic preservation is sufficient without accompanying matrix, synaptic, and propagation preservation. The CSC thesis alone predicts that resilience correlates with sustained compensatory capacity below the allostatic threshold; it does, but it cannot predict whether the compensatory capacity is sustained by matrix and microglial preservation or by some other mechanism. The Propagation thesis alone predicts that resilience correlates with restrained trans-synaptic spread; it does, but it cannot predict why such restraint occurs in some individuals at high amyloid burden and not in others. Jointly, the four theses predict that resilience is the phenotype in which all four preservations are observed simultaneously, and that the joint preservation regime is achievable only in individuals whose APOE genotype does not drive the LRP1 axis to early saturation. No single layer of preservation is sufficient alone.

The de Vries 2024 data support this joint prediction at least qualitatively for three of the four substrates: the resilient cohort exhibits all three HMS preservations, not one or two. A stronger test would be to identify human cohorts in which one of the four is preserved while the others collapse, and to determine whether those individuals are clinically resilient or not. The HMS+P Collapse Model predicts that they are not, that isolated preservation of any single layer is insufficient, and that the feed-forward loop between layers — modulated by the lipid/APOE gate — will propagate collapse from whichever layer begins first. The fourth substrate (propagation) has been measured in only a small number of resilience cohorts to date; a direct test of whether transsynaptic tau spread is restrained in de Vries-style resilient individuals at AD-threshold pathology burden would constitute a decisive test of the four-substrate prediction. The model further predicts that APOE3-Christchurch-like resilience cases — where a partial dampening of the LRP1 axis confers protection at very high genetic-pathology burden — should also exhibit joint preservation of the four substrates as the downstream consequence of the dampened gate, rather than independent preservation of any single layer.

7. Therapeutic Implications

The therapeutic implications of the HMS+P Collapse Model are distinct from those of any of the four constituent theses considered alone and from those of the mainstream Alzheimer's-disease therapeutic literature more broadly. They can be stated as five principles.

First, monotherapies targeting any single layer will produce only partial and unsustainable benefit. This prediction is supported retrospectively by the clinical history of the field: anti-amyloid antibodies, which target the pathological substrate rather than any of the four homeostatic layers, produce modest and inconsistent cognitive benefit disproportionate to their effect on amyloid burden; complement inhibitors, which target the downstream pruning arm of the CSC and HCC frameworks without addressing upstream TGF-β collapse, have not produced durable benefit in trials to date; NSAIDs and broad anti-inflammatory agents, which silence downstream cytokine output without addressing the homeostatic collapse that generates it, have failed repeatedly across decades of trials; TREM2 agonists, which boost a receptor whose downstream execution requires a homeostatically preserved cell, have produced disappointing results in advanced disease populations; and the propagation-substrate monotherapies now entering clinical development (anti-tau antibodies, anti-α-synuclein antibodies, LRP1-binding-domain antagonists, HSPG-mimetic seed sequestrants, strain-specific conformational therapeutics) are predicted by the HMS+P architecture to reduce propagation transiently and to fail to halt progression because the three HMS substrates continue to regenerate the conditions under which propagation can resume. Each of these failures is coherent with the HMS+P Collapse Model's prediction that single-layer interventions cannot break the self-sustaining feed-forward loop between layers once the allostatic and propagation-self-sustaining thresholds have been crossed. The repeated clinical disap-

pointments of the field are not evidence that the individual targets were wrong; they are evidence that the interventions were applied at the wrong layer of the collapse architecture.

Second, the therapeutic class most likely to produce durable benefit is homeostatic restoration combined with lipid-gate stabilization. The HMS+P Collapse Model identifies TGF-β/SMAD signaling as the single pathway whose collapse is upstream of pathology in three of the four substrate layers, and the APOE/LRP1 axis as the upstream gate whose saturation is upstream of pathology in all four. Pharmacological interventions aimed at the homeostatic-restoration class include SMAD7 inhibitors, enhanced TGF-β receptor signaling in microglial compartments, oxidative stress reduction targeted to the microglial cytoplasm, and restoration of niche signaling inputs that sustain the Butovsky signature. Pharmacological interventions aimed at the lipid-gate-stabilization class include isoform-selective APOE modulation (mimetic peptides of APOE2 or APOE3-Christchurch), selective blockade of the propagation-relevant LRP1 interactions while preserving the clearance and lipid-delivery interactions, and upstream restoration of astrocyte-derived lipid supply (ABCA1 agonists, LXR-mediated lipidation enhancers). Neither class has been systematically developed as an Alzheimer's-disease therapeutic, and the HMS+P Collapse Model predicts that the combination of the two classes should be a development priority. The model further predicts that homeostatic restoration applied early in the trajectory — Phase 1 or Phase 2 — should produce greater benefit than the same intervention applied in Phase 3 or Phase 4, because the feed-forward loop is easier to break before it becomes self-sustaining and the matrix and synaptic layers are still close enough to the homeostatic attractor to be pulled back into it.

Third, perineuronal net integrity around PV+ interneurons is the single most compact biomarker of therapeutic success. Because the PV+ perisomatic zone is the anatomical substrate at which all four layers meet, and because its preservation is the joint de Vries signature of human resilience, any intervention that preserves or restores PNN integrity around PV+ interneurons is, by that fact, acting on the joint homeostatic system rather than on a single layer. The HMS+P Collapse Model predicts that PNN imaging — whether by Wisteria floribunda agglutinin staining in preclinical models or by emerging in-vivo techniques for matrix visualization in humans — is the single most informative readout of whether a given therapeutic intervention is operating at the HMS+P level or only at the level of a single layer. Interventions that reduce amyloid burden without preserving PNN integrity are operating on the wrong layer. Interventions that preserve PNN integrity regardless of their effect on amyloid burden are operating on the right layer. This is a falsifiable biomarker claim, and it is distinct from the amyloid- and tau-centric biomarker paradigms that currently dominate the field.

Fourth, combination therapy across layers and gates should produce superadditive benefit relative to any monotherapy. Because the four substrate layers feed back on each other through the loop described in §3.2 and the gate described in §3.5, interventions that simultaneously address two or more layers plus one or both gates should produce benefit that exceeds the sum of their individual layer-specific effects. The HMS+P Collapse Model suggests that the combination most likely to

produce clinical benefit couples (i) substrate reduction, via anti-amyloid antibodies or related agents, to lower the load driving homeostatic collapse; (ii) homeostatic restoration, via TGF-β/SMAD enhancement or oxidative stress reduction, to reinforce the upstream signaling that sustains the three TGF-dependent layers; (iii) matrix stabilization, via chondroitinase-resistant CSPG sulfation enhancement or MMP-selective inhibition, to preserve the mechanical and signaling substrate of PV+ protection while homeostatic restoration takes effect; (iv) propagation blockade, via selective blockade of the propagation-relevant LRP1 interactions or strain-specific conformational antibodies, to prevent the spread that the homeostatic and matrix interventions cannot directly halt; and (v) lipid-gate stabilization, via APOE isoform modulation or astrocyte lipidation enhancement, to keep the upstream gate below saturation. The prediction is that this five-arm combination should produce benefit in populations for whom any single component has failed in prior trials, and that the benefit should be measurable at the PNN biomarker readout before it is measurable at the cognitive endpoint.

Fifth, APOE genotype should stratify both trial inclusion and combination composition. The HMS+P Collapse Model predicts that APOE4 carriers cross the lipid-gate saturation threshold earlier than non-carriers and therefore enter the four-phase trajectory earlier, so trial inclusion windows must be APOE-stratified to capture the appropriate phase. It further predicts that the lipid-gate-stabilization arm of the combination regimen has its largest expected effect in APOE4 carriers and a smaller expected effect in APOE2/3 individuals whose gate has not yet saturated. Stratification by APOE genotype is therefore not a covariate-adjustment requirement but a structural feature of the trial design that the architecture mandates.

8. Testable Predictions

The HMS+P Collapse Model is distinct from its four constituent theses only insofar as it generates predictions that none of them alone can generate. We enumerate the most consequential of these.

Prediction 1. Single-cell and spatial transcriptomic analyses of resilience cohorts will reveal joint preservation of (i) the Butovsky microglial signature in parenchymal microglia adjacent to the PV+ perisomatic zone, (ii) intact aggrecan/tenascin-R/hyaluronic acid matrix architecture around PV+ interneurons in the regions where cognitive function was most recently generated, (iii) competent PV+ inhibitory coverage of principal neurons in the same regions, and (iv) absence of strain-faithful tau propagation signatures along cortico-cortical projections from the entorhinal cortex outward. The four preservations will be observed together, not separately, and no individual preservation will be sufficient to produce the resilience phenotype.

Prediction 2. Human cohorts with isolated preservation of any single layer — for example, individuals with intact PNNs but post-homeostatic microglia, or individuals with preserved microglial homeostasis but degraded matrix, or individuals with restrained propagation but failed inhibitory

coverage — will not be clinically resilient at AD-threshold amyloid and tau burdens. The feed-forward loop between layers, modulated by the lipid/APOE gate, will propagate collapse from whichever layer is unprotected.

Prediction 3. Pharmacological interventions that restore TGF-β/SMAD signaling in microglial compartments will produce joint preservation of all four layers in animal models, whereas interventions that target downstream effectors (complement inhibitors, MMP inhibitors, TREM2 agonists, LRP1-binding-domain antagonists) will preserve at most one or two layers and will not produce durable cognitive benefit.

Prediction 4. The allostatic threshold at which MCI transitions to dementia is the threshold at which the feed-forward loop between the four substrate layers becomes self-sustaining, and its crossing is reversible by combined homeostatic restoration + lipid-gate stabilization applied before but not after the crossing. This predicts a sharp temporal window for intervention that is earlier than the window currently targeted by most trials, and that is shifted earlier in APOE4 carriers.

Prediction 5. The clinical benefit of anti-amyloid antibodies is mediated primarily by the reduction in substrate load on the microglial compartment rather than by the removal of amyloid per se, and the benefit should be enhanced by co-administration of homeostatic restoration agents and lipid-gate stabilizers, attenuated in populations with advanced microglial collapse, and minimal in APOE4 carriers whose lipid gate has already saturated. Retrospective re-analysis of completed anti-amyloid trials, stratifying patients by microglial transcriptomic state, PNN imaging, and APOE genotype, should reveal substantial subgroup heterogeneity consistent with this prediction.

Prediction 6. Shingrix vaccination, which the HMSP whitepaper §4.3 predicts engages a TLR4-driven innate axis on top of its adaptive VZV suppression, should produce measurable serum cathelicidin elevation within 48–96 hours of vaccination, and the incremental neuroprotective benefit of Shingrix over Zostavax should be larger in vitamin-D-sufficient individuals than in vitamin-D-deficient individuals. This prediction sits outside the four-substrate architecture proper but extends from the lipid/APOE gate via the broader trained-immunity literature that the HMSP whitepaper references.

Prediction 7. TREM2 agonism should produce benefit in early-phase populations with preserved microglial metabolism but should produce no benefit or harm in late-phase populations with collapsed homeostasis. The failures of advanced-disease TREM2 agonist trials are thus predictable, and the redesign of TREM2 agonist programs around early-phase populations stratified by Butovsky signature and APOE genotype should produce different results.

Prediction 8. Cognitive resilience can be induced pharmacologically in animal models by combined homeostatic restoration + matrix stabilization + lipid-gate stabilization + selective LRP1 propagation blockade, and the induced resilient state will recapitulate the de Vries 2024 human phenotype in its joint preservation of the four layers rather than in any single layer alone. The in-

duction of resilience by rational five-arm combination therapy, guided by the HMS+P Collapse Model, is the strongest available test of the framework.

9. Conclusion

Four prior ONS analyses — of the synaptic collapse literature, the microglial homeostasis literature, the perineuronal net literature, and the templated propagation literature — each identified a distinct upstream variable whose collapse the analysis claimed was sufficient to generate the pathology catalogued in its constituent literature. Taken individually, the four analyses describe four different pathogenic hubs. Taken jointly, subjected to the same convergence operation that each performed on its own inputs, they describe a single tetralayered, dual-gated homeostatic architecture whose four components — homeostatic microglia, perineuronal matrix, PV+ perisomatic synaptic coverage, and the templated propagation step — are not independent targets of a shared pathogenic mechanism but four aspects of a single TGF-β-maintained system whose collapse is modulated, in turn, by an APOE/LRP1-mediated lipid-availability gate. The Homeostatic–Matrix–Synaptic–Propagation (HMS+P) Collapse Model is the framework in which this joint description becomes explicit.

The model is stronger than the disjunction of its four inputs because it explains observations that none of them alone can explain. The paradoxical status of TREM2 loss-of-function as a risk allele, the paradoxical status of LRP1 as both a clearance and a propagation receptor, the convergence of four analytically independent theses on the same resilience biomarker, the systematic failure of single-target monotherapies across decades of clinical trials, the sharp temporal threshold at which MCI transitions to dementia, the disproportion between amyloid clearance and cognitive benefit in anti-amyloid programs, the Braak staging sequence of tau propagation, the strain-faithful preservation of conformational identity across rounds of templating, and the dramatic protection conferred by the APOE3-Christchurch mutation — each of these observations is either unexplained or only partially explained within any single constituent thesis, and each is explained within the HMS+P Collapse Model as a consequence of the joint four-layer architecture and the lipid/APOE gate that modulates it. The model is also more parsimonious than the disjunction of its inputs, because it replaces four upstream variables with one upstream signaling pathway and one upstream gate whose collapse propagates through a specified set of molecular interfaces to produce the four downstream phenotypes that the constituent theses each identified.

The therapeutic implications of the integration are not incremental. They suggest that the decades-long history of single-target failures in Alzheimer's-disease trials is not evidence that the individual targets were wrong but evidence that the interventions were applied at the wrong layer of an architecture whose integrity cannot be restored by acting on any single layer alone. They suggest that the therapeutic class with the highest prior probability of producing durable benefit is

homeostatic restoration via TGF-β/SMAD signaling combined with lipid-gate stabilization via APOE/LRP1-axis intervention, a combination that has not been systematically developed for Alzheimer's disease. They suggest that the most informative biomarker of therapeutic success is PNN integrity around PV+ interneurons, not amyloid or tau burden, because PNN integrity is the single readout at which all four layers meet. They suggest that rational combination therapy across layers should produce superadditive benefit and that the combinations most likely to succeed couple substrate reduction with homeostatic restoration, matrix stabilization, propagation blockade, and lipid-gate stabilization. And they suggest that the induction of resilience — the recapitulation of the de Vries phenotype by pharmacological means — is the most rigorous available test of the framework and, if successful, the most durable available mode of clinical benefit.

The work ahead is to develop the pharmacology of homeostatic restoration, to engineer APOE-isoform-selective modulators and LRP1-arm-selective antagonists, to establish PNN integrity imaging as a clinical biomarker, to reinterpret the existing clinical literature through the HMS+P lens with APOE stratification, and to design the combination trials that the model predicts will succeed. The epistemological lesson of the integration is one that the ONS methodology was designed to deliver: the Alzheimer's-disease field has repeatedly mistaken the visible surfaces of a deep homeostatic collapse for the distinct pathogenic mechanisms it has been searching for. Synapses, microglia, matrix, and propagating seeds are surfaces. The TGF-β/SMAD-maintained homeostatic architecture together with the APOE/LRP1-mediated lipid gate is the process. The therapeutic task is neither to clear the substrate, nor to silence the microglia, nor to rebuild the matrix, nor to block the seed in isolation, but to reinstate the homeostatic systems whose joint collapse generates all four surface pathologies in concert.

References

A complete reference list compiled across the four constituent theses and the supporting primary literature accompanies the cross-axis whitepaper *Templated Misfolding as the Fourth Substrate: HMS Becomes HMS+P*. Foundational references include, in addition to those listed in the four constituent theses:

1. Butovsky O, Jedrychowski MP, Moore CS, et al. (2014). Identification of a unique TGF-β-dependent molecular and functional signature in microglia. *Nature Neuroscience*, 17(1), 131–143.

2. Keren-Shaul H, Spinrad A, Weiner A, et al. (2017). A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*, 169(7), 1276–1290.e17.

3. Crapser JD, Spangenberg EE, Barahona RA, et al. (2020). Microglia facilitate loss of perineuronal nets in the Alzheimer's disease brain. *EBioMedicine*, 58, 102919.

4. de Vries LE, et al. (2024). Perineuronal nets and cognitive resilience in Alzheimer's disease. *Alzheimer's & Dementia*, 20.

5. Fawcett JW, Oohashi T, Pizzorusso T (2019). The roles of perineuronal nets and the perinodal extracellular matrix in neuronal function. *Nature Reviews Neuroscience*, 20, 451–465.

6. Stevens B, et al. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell*, 131(6), 1164–1178.

7. Werneburg S, et al. (2025). C4d, a high-affinity LilrB2 ligand, is elevated in Alzheimer's disease and mediates synapse pruning. *Proceedings of the National Academy of Sciences*, 122.

8. von Bernhardi R, Eugenín-von Bernhardi L, Eugenín J (2015). Microglial cell dysregulation in brain aging and neurodegeneration. *Frontiers in Aging Neuroscience*, 7, 124.

9. Marschallinger J, et al. (2020). Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nature Neuroscience*, 23(2), 194–208.

10. Huang Y, et al. (2021). Microglia use TAM receptors to detect and engulf amyloid β plaques. *Nature Immunology*, 22(5), 586–594.

11. Small SA, Petsko GA (2015). Retromer in Alzheimer's disease, Parkinson's disease and other neurological disorders. *Nature Reviews Neuroscience*, 16, 126–132.

12. Gouras GK, et al. (2000). Intraneuronal Aβ42 accumulation in human brain. *American Journal of Pathology*, 156(1), 15–20.

13. Prusiner SB (2012). A unifying role for prions in neurodegenerative diseases. *Science*, 336(6088), 1511–1513.

14. Jucker M, Walker LC (2013). Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature*, 501(7465), 45–51.

15. Rauch JN, Luna G, Guzman E, et al. (2020). LRP1 is a master regulator of tau uptake and spread. *Nature*, 580(7803), 381–385.

16. Chen K, Martens YA, Meneses A, et al. (2022). LRP1 is a neuronal receptor for α-synuclein uptake and spread. *Molecular Neurodegeneration*, 17, 57.

17. Sanders DW, Kaufman SK, DeVos SL, et al. (2014). Distinct tau prion strains propagate in cells and mice and define different tauopathies. *Neuron*, 82(6), 1271–1288.

18. Luk KC, Kehm V, Carroll J, et al. (2012). Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science*, 338(6109), 949–953.

19. Holmes BB, DeVos SL, Kfoury N, et al. (2013). Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. *PNAS*, 110(33), E3138–E3147.

20. Liu Q, Trotter J, Zhang J, et al. (2010). Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration. *Journal of Neuroscience*, 30(50), 17068–17078.

21. Dietschy JM, Turley SD (2004). Cholesterol metabolism in the central nervous system during early development and in the mature animal. *Journal of Lipid Research*, 45(8), 1375–1397.

22. Bu G (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nature Reviews Neuroscience*, 10(5), 333–344.

23. Tachibana M, Holm M-L, Liu C-C, et al. (2019). APOE4-mediated amyloid-β pathology depends on its neuronal receptor LRP1. *Journal of Clinical Investigation*, 129(3), 1272–1277.

24. Arboleda-Velasquez JF, Lopera F, O'Hare M, et al. (2019). Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nature Medicine*, 25(11), 1680–1683.

25. Ramsden CE, et al. — lipid peroxidation and ApoE–ApoER2–Dab1 disruption in sporadic Alzheimer's disease. (Companion document: *Evaluating the Lipid Peroxidation and ApoER2–Dab1 Disruption Hypothesis in Sporadic Alzheimer's Disease*, March 2026, revised May 2026.)

26. Moosmann B, Behl C — chronic excitatory insufficiency and compensatory homeostatic signaling. (Primary references to be consolidated in final version.)

27. *Templated Misfolding as the Fourth Substrate: HMS Becomes HMS+P* — cross-axis synthesis whitepaper, AdultCognitiveDisease.com, May 2026. §4.8 (Lipid Availability and the APOE Modifier) provides the formal substrate-level framing of the gate concept used throughout this chapter.

Appendix: Relationship to the Four Constituent Theses

This synthesis is a fifth-layer ONS analysis and depends directly on four prior documents:

- *Convergent Synaptic Collapse Thesis* (Convergent Synaptic Collapse/ONS_SynapticCollapse_Thesis.pdf), which integrates eight frameworks (Ramsden, Small, Gouras, Moosmann, Rappoport, Huang, Margolis, Shatz–Stevens) into the four-phase CSC model.
- *Homeostatic Microglial Collapse Thesis* (Homeostatic Microglial Collapse/ONS_HomeostaticCollapse_Thesis.md), which integrates twelve programs (Butovsky, Keren-Shaul/Amit, Colonna, Stevens, Shatz, Crapser, Lemke, Marschallinger, Prinz/Kierdorf, Streit, von Bernhardi, de Vries) into the Homeostatic Collapse model.
- *Perineuronal Net Integrity Thesis* (PNN/PNN_Alzheimers_Thesis.pdf), which integrates the Crapser, de Vries, Fawcett, Auer, and van 't Spijker programs into the PNN Integrity–Microglial Activation Cycle.
- *Convergent Propagation Collapse Thesis* (Bu·Prusiner·Walker monograph, *propagation_bu_lr-p1-receptor-hijack.pdf*, May 2026), which integrates the Prusiner, Walker–Jucker, Bu, Diamond, and Lee–Trojanowski programs into the five-component Propagation substrate, and the companion *Templated Misfolding as the Fourth Substrate* whitepaper that establishes the HMS+P architecture and the §4.8 lipid/APOE gate.

The HMS+P Collapse Model presented here does not supersede any of these analyses. It integrates them. The reader is referred to the four constituent theses and to the HMSP whitepaper for the primary-literature substantiation of the claims that the HMS+P framework treats as inputs.

Prepared under the Organic Network Synthesis methodology as an integrating synthesis across four prior ONS theses and one cross-axis synthesis whitepaper. This work is part of the ongoing effort at AdultCognitiveDisease.com to apply systematic integrative methods to the Alzheimer's-disease framework literature.