SYNTHESIS · HMS+P

Templated Misfolding as the Fourth Substrate: HMS Becomes HMS+P

Butovsky · Fawcett · Stevens · Prusiner · Walker · Bu · Diamond · Lee–Trojanowski

Cross-Axis Synthesis Whitepaper — Unified Collapse, Revised

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Templated Misfolding as the Fourth Substrate: Why the Homeostatic–Matrix–Synaptic (HMS) Synthesis Must Be Revised to HMS+P

Abstract

The Homeostatic–Matrix–Synaptic (HMS) trilayered model has, since its consolidation in 2024, served as the load-bearing cross-axis synthesis of *Unified Collapse*. Its three substrates — H, the homeostatic microglial identity anchored in Butovsky's TGF-β/SMAD-dependent signature[1]; M, the perineuronal-net extracellular matrix anchored in Fawcett's architectural review of PNN function[2]; and S, the complement-mediated synaptic pruning axis anchored in Stevens's classical-cascade work and extended by Shatz and Brott[3,4] — were chosen because each, when ablated, produces downstream collapse across multiple cortical compartments. This whitepaper argues that the model, as currently drawn, is incomplete on its own terms. HMS omits the substrate by which neurodegenerative pathology actually advances across the cortical network: templated misfolding, the propagation axis whose conceptual scaffolding belongs to Prusiner[5,6], whose experimental architecture belongs to Walker and Jucker[7,8,9], whose receptor mechanism belongs to Bu[10,11], whose strain framework belongs to Diamond[12,13], and whose synucleinopathy program belongs to Lee, Trojanowski, and Luk[14,15].

The 2026 integration of these strands into a single mechanistic account — completed by the *Bu/Prusiner/Walker* monograph and its companion synucleinopathy literature — supplies the empirical foundation required to add Propagation as the fourth substrate of equal architectural weight to H, M, and S. The result is the HMS+P model. This paper makes four arguments. First, the three-substrate HMS model is insufficient because it cannot account for the Braak staging problem, the Diamond strain problem, or the lecanemab/donanemab progression-failure problem, each of which is structurally a propagation problem. Second, the Propagation substrate, as built from the Prusiner–Walker–Bu–Diamond–Lee–Trojanowski synthesis, is mechanistically distinct from H, M, and S and satisfies the substrate-inclusion criterion. Third, the four substrates form a fully connected 4-node interaction graph, gated at each node by LRP1-mediated lipid availability and modulated by APOE isoform. Fourth, the therapeutic and trial-design implications of HMS+P are immediate and load-bearing — they explain why every monotherapy targeting a single substrate has failed in late-onset disease, and they specify what combinatorial intervention architecture is required for disease modification. The next phase of work is to embed HMS+P into *Unified Collapse* Chapter 1 and to propagate the revision through the cross-axis whitepapers.

> **What remains uncertain:** *Whether the four-substrate HMS+P architecture is itself the terminal cross-axis synthesis, or whether subsequent axes — most plausibly Bioenergetic Collapse (ox-*

> *idative-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 is defensible at the current state of the literature; the question of architectural closure is not.*

Introduction

The *Unified Collapse* framework on AdultCognitiveDisease.com was built axis by axis. Each new mechanism — microglial homeostatic identity, perineuronal-net architecture, complement-mediated synapse elimination, retromer endosomal sorting, lipid-peroxidation cascades, and most recently templated propagation — entered the site through a dedicated monograph that examined its primary literature, mapped its mechanistic adjacencies, and integrated its findings with the established axes already in the corpus. The monographs were authored under the ONS methodology and were submitted to their respective senior investigators for review under the scientist-liaison protocol. The cross-axis synthesis chapters of *Unified Collapse* were updated as each new axis stabilized.

By early 2024, three of those axes had achieved sufficient empirical density and cross-domain reach to be elevated into the site's load-bearing synthesis: Homeostatic (microglial), Matrix (PNN/ECM), and Synaptic (PV+ interneuron, complement-pruning). The synthesis was named HMS. It served as the spine of *Unified Collapse* Chapter 1 and as the integrative scaffold against which subsequent axes were evaluated. New mechanisms entering the corpus were assessed on whether they fed into one of the three HMS substrates or whether they introduced novel substrate-level structure of their own. Most fed in. A small number — endo-lysosomal collapse, lipid-peroxidation cascades — modulated existing substrates without displacing them. None required architectural revision of HMS itself.

The propagation axis is structurally different. From the moment the Prusiner reconceptualization[6] entered the corpus through the dedicated monograph on prion-like proteinopathy, it became evident that propagation does not feed into a single HMS substrate. It traverses all three. Templated tau and α-synuclein spread destroys PV+ interneuron circuits directly (a Synaptic event), drives microglial uptake-induced DAM/LDAM transitions (a Homeostatic event), and is bidirectionally coupled to PNN degradation through the release of extracellular seeds previously sequestered by aggrecan-bearing matrix (a Matrix event)[16,17]. The propagation axis cannot be absorbed into any single HMS substrate. It must be added at the substrate level itself.

The integration was not architecturally possible until 2026. Two things changed in the interval. First, the Bu laboratory's identification of LRP1 as the master neuronal receptor for both tau[10] and α-synuclein[11] uptake supplied the molecular machinery for the propagation step that Prusiner and

Walker had described phenomenologically — closing a decade-long mechanistic gap. Second, Diamond's strain-faithful propagation work[12,13] and the Lee–Trojanowski–Luk demonstration of α-synuclein trans-synaptic transmission[14,15] established that propagation is not a uniform cellular event but a substrate with internal structure of its own, comprising templated misfolding, seeded transmission, receptor-mediated uptake, strain-faithful preservation, and trans-synaptic spread. By early 2026, the propagation substrate had the empirical density required to enter the cross-axis synthesis as a peer of H, M, and S.

This whitepaper makes the integration explicit. It revises HMS to HMS+P, supplies the architectural rationale, maps the four-node interaction graph, and specifies the therapeutic and trial-design implications. It is not a critical evaluation of any one scientist; it is the cross-axis synthesis paper required to lock the revised model into *Unified Collapse*. The central argument is unambiguous: HMS is incomplete without P, and the case for adding P is empirically irrefutable.

Literature Review and the Historiography of HMS

The HMS synthesis was not engineered top-down. It emerged from the cumulative weight of three distinct experimental programs, each of which initially appeared to be addressing a different problem, and which converged on a single trilayered architecture only after a decade of cross-citation and integrative review. Understanding why HMS was drawn the way it was — and, critically, why propagation was not included — requires a brief historiography of each of the three substrates.

The Homeostatic substrate was crystallized by the 2014 Butovsky *Nature Neuroscience* paper identifying the TGF-β-dependent molecular and functional signature of brain microglia.[1] Prior to Butovsky's work, microglia had been conceptualized largely through the M1/M2 polarization heuristic borrowed from peripheral macrophage biology, a framework that proved inadequate for explaining the cell-state transitions actually observed in the aging and degenerating brain. Butovsky's identification of a canonical homeostatic signature — P2RY12, TMEM119, TGFBR1, SALL1, and approximately a hundred additional transcripts whose expression required continuous TGF-β/SMAD signaling — supplied the baseline against which loss-of-homeostasis states (DAM, LDAM, dystrophic microglia) could be defined.[18,19] By 2020, the homeostatic-collapse axis had been independently consolidated by Keren-Shaul's DAM characterization[20], Marschallinger's LDAM phenotype[21], and the Streit dystrophic-microglia literature, all of which mapped trajectories away from the Butovsky baseline.

The Matrix substrate was crystallized by Fawcett's 2019 *Nature Reviews Neuroscience* review of perineuronal-net and perinodal ECM function in neuronal physiology.[2] The review consolidated two decades of work — Pizzorusso's chondroitinase ABC critical-period reopening experiments[22], Oohashi's molecular dissection of the link-protein–lectican complex, and the broader literature on aggrecan, brevican, neurocan, versican, HAPLN1, and tenascin-R — into a coherent architectural

account of how PNNs stabilize the parvalbumin-positive (PV+) interneuron compartment and gate cortical plasticity. By 2020, the PNN-collapse axis had been extended to neurodegeneration through the Crapser *EBioMedicine* paper demonstrating that microglia facilitate PNN loss in the Alzheimer's-disease brain[23], and through the Tsai laboratory's broader work linking matrix dysfunction to PV+ interneuron failure and gamma-rhythm collapse.[24]

The Synaptic substrate was crystallized by the 2007 Stevens *Cell* paper demonstrating that the classical complement cascade mediates CNS synapse elimination[3], and was extended by Schafer's 2012 *Neuron* work establishing that microglial CR3-mediated phagocytosis is the effector mechanism[25], by Hong's 2016 *Science* paper demonstrating that the same machinery is reactivated in Alzheimer's-disease models[26], and by the Shatz–Brott C4d–LilrB2 axis that links the complement substrate to MHC class I-dependent synaptic signaling.[4] The PV+ interneuron compartment, by virtue of its perisomatic complement load and its dependence on PNN stabilization, sits at the intersection of the Matrix and Synaptic substrates and was identified as the convergent failure point of both axes.

By 2024, the three programs had been read together as a single architecture. Homeostatic microglial collapse degrades the very cells that, in their dysregulated state, drive complement-mediated synaptic pruning; the synaptic pruning preferentially targets the PV+ compartment exposed by PNN degradation; the PNN degradation is itself facilitated by the dysregulated microglia whose homeostatic identity has collapsed. The three substrates form a tight triangular interaction graph in which each substrate's failure both causes and is caused by the failure of the other two. The triangular structure is what made HMS a credible synthesis rather than a list. It also explained why interventions targeting any single substrate (CSF1R inhibitors for microglia; chondroitinase ABC for PNN; complement-pathway blockade for synaptic pruning) showed transient benefit followed by failure: the two remaining substrates regenerated the failure of the targeted one.

Propagation was deliberately left out. The reason was methodological, not theoretical. As of 2024, the receptor mechanism for trans-synaptic spread of tau and α-synuclein was not known with sufficient resolution to permit substrate-level integration. Walker and Jucker had established *that* spread occurred[7,8]; Prusiner had established *why* it mattered[5,6]; but the molecular machinery by which extracellular misfolded protein gained cytoplasmic access in recipient neurons remained contested. Multiple receptor candidates — HSPGs[27], LDL-receptor family members, scavenger receptors — were partially implicated; none unified the data across cell types and protein species. Without a defined molecular substrate, propagation could not be added to HMS without compromising the substrate-inclusion criterion. The Bu LRP1 work in 2020–2022[10,11], the Diamond strain-faithful propagation work[12,13], and the Lee–Trojanowski–Luk synucleinopathy synthesis[14,15] collectively closed the gap. By 2026, propagation had the molecular substrate it had lacked.

Analytical Framework and Methodology

The argument of this whitepaper rests on a single substrate-inclusion criterion, which has governed the HMS synthesis from its inception and which is here applied to evaluate Propagation as a candidate fourth substrate. The criterion: *a mechanism qualifies as a substrate if and only if its dysfunction causes downstream collapse across multiple existing monographs in the corpus, and if its mechanistic structure cannot be reduced to the existing substrates already in the synthesis.* The first clause distinguishes substrates from local mechanisms; the second distinguishes substrates from substrate-modulators. H, M, and S each satisfy both clauses. The question of this paper is whether Propagation does as well.

The methodological approach is comparative-architectural. The paper synthesizes across two literature bodies. The first is the propagation literature: Prusiner's 1982 and 2012 syntheses[5,6]; the Walker–Jucker experimental seeding program[7,8,9]; the Bu LRP1 receptor work[10,11]; the Diamond strain-faithful propagation framework[12,13]; and the Lee–Trojanowski–Luk synucleinopathy program[14,15], with the Holmes HSPG-mediated uptake work[27] and the Sanders tau-strain dissection[13] providing additional molecular detail. The second is the HMS literature: Butovsky and the homeostatic-signature literature[1,18,19,20,21]; Fawcett and the PNN/ECM literature[2,22]; Stevens, Schafer, Hong, and the complement-synaptic literature[3,25,26]; the Shatz–Brott C4d–LilrB2 extension[4]; the Crapser microglia–PNN coupling literature[23]; and the Tsai cross-axis work on PV+ interneuron failure.[24]

The integration is performed by mapping each substrate's primary failure mode onto each other substrate's susceptibility profile, identifying the mechanistic intersections at which one substrate's collapse drives another's. The result, presented in Chapter 4, is a 4-node interaction graph in which every node both feeds and is fed by every other. The graph is what justifies elevating Propagation from an axis to a substrate: the depth of cross-coupling is at the same order of magnitude as the H–M, H–S, and M–S couplings that originally justified the trilayered HMS synthesis. The methodology does not rest on novel experimental claims. It rests on the cumulative empirical density of the cited literature, evaluated against the substrate-inclusion criterion.

The paper proceeds as follows. Chapter 1 recapitulates the canonical HMS trilayer in sufficient detail to ground the subsequent argument. Chapter 2 identifies three specific empirical problems the HMS model cannot solve on its own terms and argues that each is structurally a propagation problem. Chapter 3 builds the propagation substrate from the Prusiner–Walker–Bu–Diamond–Lee–Trojanowski synthesis, demonstrating that propagation has internal mechanistic structure of substrate-level density. Chapter 4 presents the HMS+P interaction graph. Chapter 5 derives the therapeutic and trial-design implications. The conclusion specifies how the revision propagates through the rest of *Unified Collapse*.

Chapter 1: Recapitulating the HMS Trilayer

The HMS model occupies the spine of *Unified Collapse* Chapter 1 because each of its three substrates, when ablated, produces downstream collapse across the cortical microenvironment, and because the three substrates physically interact in the same tissue compartment — the PV+ interneuron-rich perisomatic surface of layer-II/III and layer-V pyramidal cells, surrounded by aggrecan-bearing perineuronal nets, surveyed by P2RY12-positive homeostatic microglia, and gated by C1q-tagged perisomatic synapses. The trilayer is not a list of three independent failures. It is a triangular architecture in which each substrate's collapse drives and is driven by the failure of the other two.

1.1 H — Homeostatic Microglial Collapse

The homeostatic substrate is built on the Butovsky signature: the TGF-β/SMAD-dependent transcriptional program that defines parenchymal microglial identity and that distinguishes microglia from peripheral macrophages and CNS-border-associated macrophages.[1] The canonical markers — P2RY12, TMEM119, TGFBR1, SALL1, CX3CR1, MERTK, GAS6, FCRLS — are continuously maintained by paracrine TGF-β signaling from neighboring astrocytes and neurons. The signature collapses along three trajectories. The disease-associated microglia (DAM) trajectory, first characterized by Keren-Shaul[20], involves coordinated downregulation of homeostatic markers and upregulation of TREM2-dependent activation transcripts (APOE, CST7, LPL, SPP1). The lipid-droplet-accumulating microglia (LDAM) trajectory, characterized by Marschallinger[21], is age-dependent and marked by ferritin accumulation, lysosomal dysfunction, and impaired phagocytic capacity. The dystrophic-microglia trajectory, characterized by the Streit laboratory, is morphologically defined by cytoplasmic beading, fragmentation, and loss of process complexity, and is the terminal state of the homeostatic-collapse cascade.

Homeostatic collapse is not cell-autonomous failure. The Butovsky signature is maintained by external TGF-β; its collapse follows from disruption of the signaling environment as well as from intrinsic cellular damage. The collapse is bidirectionally coupled to both M and S. Loss of homeostatic identity degrades the surveillance function on which extracellular-matrix maintenance depends, accelerating PNN turnover. The DAM transition concomitantly enhances complement-mediated synaptic engulfment, accelerating the synaptic substrate's collapse.

The homeostatic-collapse trajectories share a downstream failure that is not visible in the Butovsky-signature framing alone: declining microglial phagocytic capacity. Bu and colleagues showed that microglia-specific *Lrp1* deletion reduces $A\beta_{42}$ cellular uptake and broadly suppresses phagocytic output.[37,39] The DAM transcriptional program upregulates APOE, CST7, LPL, and SPP1, all of which intersect the lipid-handling machinery on which LRP1-mediated phagocytosis depends. LRP1 is therefore not just the propagation receptor (§3.3); it is also a homeostatic-sub-

strate component whose loss accelerates the same surveillance failure that drives DAM transition. The H–S coupling articulated in §1.4 is, on this reading, partly an LRP1-coupling, and the implications of this for the four-node graph are developed in §4.8.

1.2 M — Matrix (PNN/ECM) Collapse

The matrix substrate is built on Fawcett's architectural account of perineuronal nets.[2] PNNs are condensed extracellular-matrix structures that surround the cell body and proximal dendrites of fast-spiking PV+ interneurons (and, to a lesser extent, a subset of other neurons) throughout cortex, hippocampus, and amygdala. Their molecular composition — chondroitin-sulfate proteoglycans of the lectican family (aggrecan, brevican, neurocan, versican), tenascin-R, link proteins (HAPLN1, HAPLN4), and hyaluronan synthesized by membrane-bound HAS enzymes — is highly characteristic. PNNs serve multiple functions: they stabilize mature synaptic configurations, they buffer the extracellular ionic environment of the high-firing-rate PV+ compartment, they sequester growth factors and morphogens, and they restrict the diffusion of extracellular molecules.[22]

Matrix collapse is driven by the regulated activity of matrix metalloproteinases (predominantly MMP-9) and the ADAMTS family (ADAMTS-4 and ADAMTS-5), which cleave the lectican core proteins at canonical sites. Crapser's 2020 *EBioMedicine* work demonstrated that activated microglia are the principal agents of PNN degradation in Alzheimer's-disease models, mechanistically linking the H and M substrates.[23] The collapse of PNNs exposes the perisomatic surface of PV+ interneurons to extracellular insults — including, critically, extracellular tau and α-synuclein seeds — and to complement-mediated synapse elimination by demasking previously matrix-shielded synaptic contacts.

1.3 S — Synaptic Collapse

The synaptic substrate is built on Stevens's 2007 demonstration that the classical complement cascade mediates developmental synapse elimination in the lateral geniculate nucleus, and on the subsequent work establishing that the same machinery is pathologically reactivated in the adult and aging brain.[3] The mechanism is now well characterized: C1q binds to synapses tagged for elimination (the recognition step), the classical cascade proceeds to C3 cleavage and C3b deposition (the opsonization step), and microglia bearing complement receptor 3 (CR3, the CD11b/CD18 integrin) recognize C3b-opsonized synapses and engulf them through phagocytic cup formation (the effector step).[25] Hong's 2016 *Science* paper demonstrated that this exact mechanism is reactivated in APP/PS1 and J20 Alzheimer's-disease models, with C1q deposition preceding overt amyloid pathology and complement-deficient mice exhibiting protection from synaptic loss.[26]

Shatz and Brott extended the synaptic substrate to MHC class I-dependent signaling, demonstrating that the C4d cleavage fragment, classically considered an inert byproduct of complement activation, signals through the PirB/LilrB2 receptor on the neuronal surface to suppress synaptic

strength.[4] This axis links the complement-engulfment story to a parallel, non-engulfment mechanism by which the same substrate impairs synaptic function. The PV+ compartment is, again, the most vulnerable: its perisomatic synapses bear the highest complement load, and PNN degradation accelerates the synaptic substrate's collapse by exposing these synapses to the engulfment machinery.

The complement-engulfment mechanism does not exhaust the synaptic substrate's failure modes. Bu and colleagues (2010, *J Neurosci*) showed that adult-onset neuronal *Lrp1* knockout in mice produces, in the absence of any amyloid or complement insult, a catastrophic depletion of brain cholesterol, sulfatide, and galactosylceramide; progressive dendritic-spine loss; reduced membrane localization of NMDA receptor 1 and GluR1; and overt memory deficits.[37] The mechanism is the loss of astrocyte-to-neuron lipid delivery: cholesterol does not cross the blood-brain barrier,[38] the CNS depends on de novo astrocyte synthesis, and neurons receive their membrane-lipid supply through APOE-packaged lipoprotein particles internalized predominantly via neuronal LRP1.[39] A cell-autonomous, non-complement, lipid-availability failure mode of the synaptic substrate therefore sits alongside the Stevens–Schafer engulfment mechanism. The two routes converge on the same outcome — synapse loss — but they are not mechanistically reducible to each other. Section 4.8 examines the implications of this for the HMS+P interaction graph.

1.4 The Trilayer as an Architecture

HMS is a triangular architecture because each substrate is bidirectionally coupled to the other two. Microglial homeostatic collapse drives PNN degradation through MMP-9/ADAMTS upregulation[23]; PNN degradation exposes PV+ synapses to complement-mediated engulfment; complement engulfment proceeds through microglial CR3, returning the cycle to the H substrate. The architecture explains both the convergence of multiple etiologies on a single failure pattern (the PV+ interneuron compartment) and the failure of single-substrate interventions to halt disease (the two un-targeted substrates regenerate the failure of the targeted one). It is, at the substrate level, an elegant and empirically dense synthesis. What it does not contain is any account of how pathology advances across the cortical network. That is the gap Chapter 2 examines.

Chapter 2: Why the HMS Model Is Incomplete

The HMS model is internally consistent and empirically dense, but it is not architecturally complete. Three empirical phenomena have, for the last decade, sat outside any account the HMS framework can supply. Each is structurally a propagation problem, and each — taken individually — would not necessarily mandate substrate-level revision of HMS. Taken together, they do.

2.1 The Braak Staging Problem

The first problem is the most empirically dense and the least controversial. Neurofibrillary tau pathology in Alzheimer's disease does not appear stochastically across the cortex; it appears in a stereotyped sequence — the Braak stages — that begins in the transentorhinal cortex (Stage I/II), advances into the limbic system (Stage III/IV), and culminates in association cortices (Stage V/VI).[28] The sequence is not merely descriptive. It is reproducible across patients, recapitulated in vivo by tau-PET imaging, and respected by the disease's clinical phenomenology: amnestic onset, then dysexecutive and visuospatial deficits, then global cognitive collapse.

The HMS model cannot generate the Braak sequence. The three substrates are present everywhere in cortex; their failure modes are not regionally specific in any way that would predict the entorhinal-first, association-cortex-last trajectory. Regional vulnerability of PV+ interneurons does not match the Braak sequence. Regional variation in microglial homeostatic identity does not match it either. Regional PNN density (highest in primary sensory cortices and motor cortex) is, if anything, inversely correlated with Braak severity. The Braak sequence is a network phenomenon — it follows the topology of cortico-cortical projections from the entorhinal cortex outward — and is structurally a propagation problem, not an HMS problem.

2.2 The Diamond Strain Problem

The second problem belongs to Diamond's tau-strain framework. Sanders et al. demonstrated in 2014 that distinct tau prion strains propagate in cells and mice and define different tauopathies — that the same tau protein, depending on the conformational template that initiated its aggregation, produces reproducibly different pathological signatures, including different cellular vulnerabilities, different histopathological appearances, and different rates of spread.[13] Strain-faithful propagation has now been demonstrated for tau across multiple tauopathies (AD, PSP, CBD, CTE, FTD) and for α-synuclein across multiple synucleinopathies (PD, DLB, MSA).[29] The strain framework is fundamental to the prion-like paradigm: it is the molecular mechanism by which pathology, once initiated, preserves its identity across rounds of templated misfolding.

The HMS model has no account of strain-faithful propagation. The three substrates have no mechanism by which a particular conformational signature could be transmitted with fidelity across a chain of templating events. The strain phenomenon is intrinsically a propagation phenomenon — it requires the cell-to-cell transfer of a specific misfolded conformation — and it cannot be generated within the HMS framework.

2.3 The Lecanemab/Donanemab Problem

The third problem belongs to the recent clinical record. Lecanemab and donanemab, the first anti-amyloid antibodies to achieve robust amyloid-clearance endpoints in late-onset Alzheimer's disease, produce modest but statistically reliable slowing of clinical progression — approximately

27% reduction in CDR-SB decline at 18 months for lecanemab, approximately 35% for donanemab in tau-low/intermediate populations.[30,31] These benefits, while real, fall dramatically short of what the amyloid-clearance magnitude would predict if amyloid burden were the principal driver of clinical progression. Patients with substantially cleared amyloid plaques continue to progress; tau pathology continues to advance; clinical decline continues, albeit more slowly.

The progression gap cannot be explained by the HMS model. The HMS framework predicts that synaptic loss, driven by complement-mediated engulfment in the PNN-degraded PV+ compartment, should be the proximal driver of clinical progression. Anti-amyloid therapy does not directly engage any HMS substrate; it should not, on the HMS account, slow progression at all unless amyloid clearance secondarily reduces complement-pathway activation. The fact that progression is slowed but not stopped — and that tau pathology continues to advance — points to a substrate of progression that is neither amyloid-driven nor HMS-driven. That substrate is propagation: templated tau spread along cortico-cortical projections, which lecanemab and donanemab do not engage.

2.4 The Convergence of the Three Problems

Each of the three problems, taken in isolation, might be absorbed into HMS by some auxiliary hypothesis. The Braak sequence might be assigned to a regional-vulnerability gradient. The strain problem might be assigned to a downstream consequence of regional cellular environment. The lecanemab/donanemab gap might be assigned to insufficient amyloid clearance. None of these auxiliary moves is empirically credible, and the cumulative weight of the three problems is decisive: all three are structurally propagation problems, all three demand an account of how pathology advances across the cortical network, and none of the three can be solved within the trilayered HMS framework. The framework, on its own terms, requires a propagation substrate. That is what Chapter 3 supplies. A fourth empirical problem — the APOE4 dose–risk gradient, in which a single APOE4 allele approximately quadruples late-onset AD risk and homozygosity approximately twelvefold — is also unsolvable within the bare HMS framework, since none of the H, M, or S substrates exhibits a mechanism by which APOE isoform directly controls its collapse threshold. The APOE4 problem is structurally a *gate* problem rather than a propagation problem; it is addressed in §4.8.

Chapter 3: The Propagation Substrate

The propagation substrate is built from the integration of five literature programs that, until 2026, had progressed in parallel: Prusiner's prion-theoretical synthesis; Walker and Jucker's experimental seeding program; Bu's LRP1 receptor identification; Diamond's strain framework; and the Lee–Trojanowski–Luk α-synucleinopathy program. The substrate has five internal mechanistic compo-

nents — 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.

3.1 Templated Misfolding (Prusiner)

The conceptual foundation of the propagation substrate is Prusiner's prion theory: the demonstration that a misfolded protein can act as a conformational template, inducing a native counterpart to adopt the same misfolded conformation, and that this templating event propagates indefinitely without nucleic-acid intermediates.[5] The 1982 demonstration of templated misfolding for PrP^Sc was, for two decades, considered to apply narrowly to the transmissible spongiform encephalopathies. Prusiner's 2012 *Science* synthesis[6] extended the framework to encompass Aβ, tau, α-synuclein, TDP-43, SOD1, huntingtin, and the polyglutamine repeat proteins, arguing that all major neurodegenerative diseases share a common prion-like templating mechanism. The synthesis was contested, but the contestation was rhetorical rather than empirical, and by 2020 the field had largely accepted that templated misfolding was the principal mechanism by which neurodegenerative proteinopathies propagated their pathological signature.

Two scope notes for cross-axis coherence. "Templated misfolding" here names the conformational step — seed-induced conversion of native protein — not the release-and-uptake machinery, which is supplied by the cellular trafficking systems detailed in §§3.3 and 3.6 (LRP1, HSPGs, exosomal secretion, endosomal escape). The upstream trigger for seed release in donor neurons is not autonomous templating but endosomal-trafficking and autophagy-lysosomal failure: retromer dysfunction and proteostatic exhaustion force pathological tau into the exosomal pathway, as developed in the Convergent Synaptic Collapse thesis. Templated propagation and proteostatic collapse are therefore the conformational and trafficking halves of a single mechanism, not competing accounts of how pathology advances.

3.2 Seeded Transmission (Walker–Jucker)

The experimental architecture of the propagation substrate belongs to the Walker–Jucker collaboration. The central experimental design — intracerebral inoculation of dilute brain extracts from diseased animals or postmortem human tissue into the brains of young, asymptomatic transgenic hosts — has been adapted and replicated across dozens of laboratories worldwide.[7] The Eisele *Science* paper of 2010 demonstrated that intracerebral and even peripheral inoculation of Aβ-containing brain homogenate could nucleate cortical amyloidosis in transgenic mice; the seeds recapitulated the morphology and distribution of the donor pathology.[9] The 2013 *Nature* review[8] and the 2018 *Nature Neuroscience* review[32] synthesized the seeded-transmission evidence across the major proteinopathies into a unified empirical foundation. The Walker–Jucker program established four empirical pillars: misfolded aggregates from one brain can nucleate identical pathology in an-

other; the pathology spreads along neuroanatomical projections; different strains produce different signatures; and the spread is, in principle, blockable.

3.3 Receptor-Mediated Uptake (Bu and Diamond)

The molecular machinery of the propagation step belongs to two parallel programs. Bu's laboratory identified LRP1 as the master neuronal receptor for both tau[10] and α-synuclein[11] uptake, demonstrating that targeted knockdown of LRP1 in iPSC-derived neurons and in murine in-vivo models effectively halts 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; chemical capping of these residues abrogates uptake. In parallel, Diamond and Holmes demonstrated that heparan sulfate proteoglycans (HSPGs) mediate cellular uptake of tau and α-synuclein seeds through a clathrin-independent endocytic mechanism that can be blocked by heparin or by genetic ablation of HSPG biosynthesis.[27] The two receptor systems are not mutually exclusive: they likely operate in parallel, with LRP1 dominating neuronal uptake and HSPGs serving as universal capture co-receptors that hand seeds off to LRP1 or to other endocytic machinery. LRP1's role here is narrower than its broader function as the central node of brain lipid homeostasis and APOE-mediated cholesterol delivery (§4.8); the propagation mechanism described in this section exploits a receptor whose primary physiological function is lipid-particle endocytosis.

3.4 Strain-Faithful Propagation (Diamond and Lee)

The strain framework belongs principally to Diamond's laboratory. The Sanders et al. 2014 *Neuron* paper[13] established that distinct tau prion strains propagate in cells and mice and define different tauopathies, recapitulating the strain-faithfulness that Prusiner's PrP work had originally established for the TSEs. Subsequent work by Diamond and by Lee and Trojanowski extended the strain framework to α-synuclein, demonstrating that PD, DLB, and MSA represent distinct α-synuclein strains with reproducibly different cellular vulnerabilities and rates of propagation.[29] The strain framework is what makes propagation a true substrate rather than a transport phenomenon: it preserves pathological identity across rounds of templating, and it implies that any therapeutic strategy must engage strain-specific molecular features rather than generic protein-aggregate features.

3.5 Trans-Synaptic Spread (Luk and Lee–Trojanowski)

The trans-synaptic spread component belongs to the Luk and Lee–Trojanowski synucleinopathy program. The Luk et al. 2012 *Science* paper[15] demonstrated that pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in wild-type mice — a single intrastriatal injection of pre-formed fibrils nucleates progressive α-synuclein pathology that spreads along anatomically defined projections to the substantia nigra, neocortex, and beyond, recapitulating the Braak

staging of PD. Volpicelli-Daley's 2011 *Neuron* paper[33] demonstrated the cellular equivalent: exogenous α-synuclein fibrils added to cultured neurons template endogenous monomer into insoluble, hyperphosphorylated aggregates that propagate cell-to-cell. The trans-synaptic component is also well established for tau through the work of Frost, de Calignon, and Hyman, and through Bu's in-vivo AAV-mediated spread experiments.

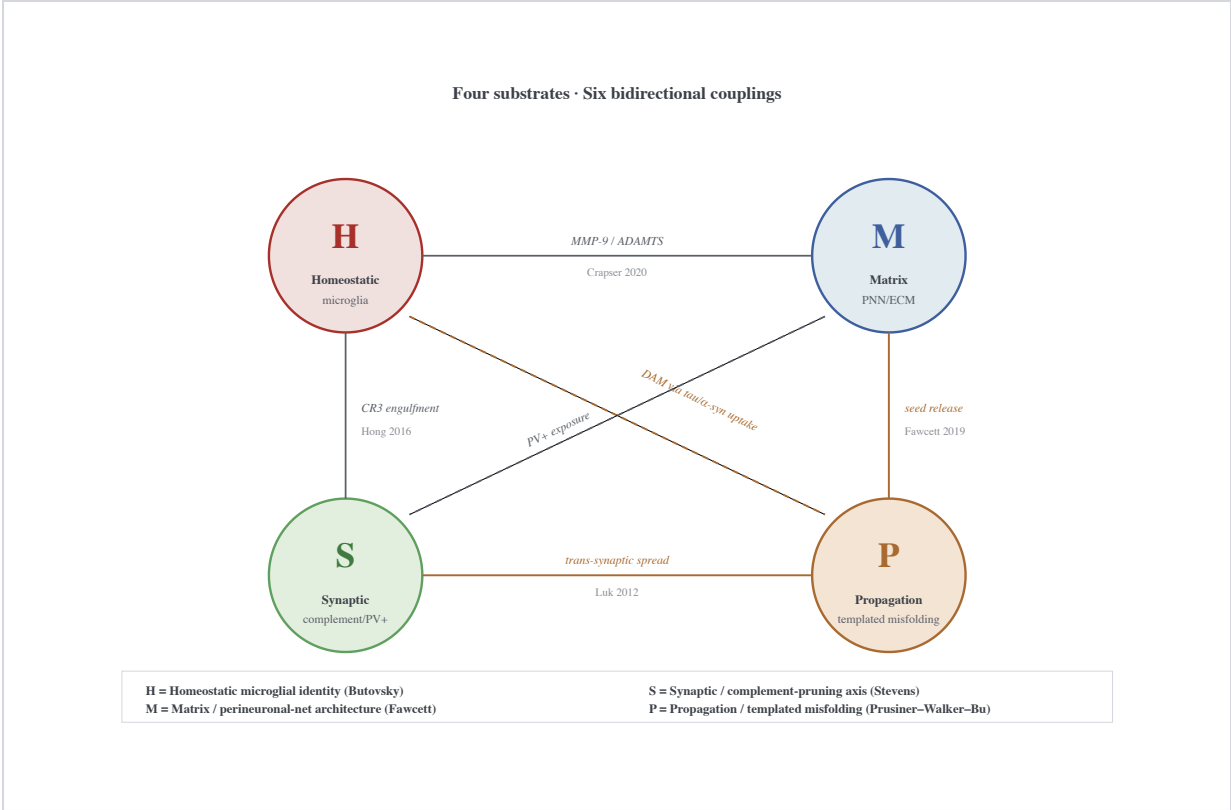
3.6 The Propagation Substrate as an Integrated Mechanism

The five components form a single integrated substrate. Pathology initiated at a seed site (most plausibly the entorhinal cortex or locus coeruleus for tau, and the dorsal motor nucleus of the vagus or olfactory bulb for α-synuclein) advances by extracellular release of misfolded protein (which the trans-synaptic spread literature has localized to vesicular secretion and to exosome-mediated release), capture of released seeds by HSPGs at the recipient cell surface, internalization by LRP1-mediated endocytosis[10,11], endosomal escape into the cytoplasm of the recipient neuron, templated misfolding of native cytoplasmic protein in the recipient[5,6], preservation of the strain-specific conformational signature[13], and re-release of seeds to advance the cascade to the next neuron along the projection.[15] The substrate has the mechanistic density, the molecular specificity, and the empirical reproducibility that the substrate-inclusion criterion requires. It satisfies the criterion as completely as H, M, and S do.

Chapter 4: The Architecture of HMS+P

The argument of Chapters 2 and 3 establishes that Propagation must be added to the cross-axis synthesis. The architectural question is how. The answer, presented in this chapter, is that the four substrates form a fully connected interaction graph in which each node both feeds and is fed by every other. The triangular HMS architecture becomes a tetrahedral HMS+P architecture, with six bidirectional couplings rather than three. The six couplings are mechanistically specified below.

The HMS+P Architecture: A Fully Connected Four-Node Interaction Graph



The HMS+P architecture as a fully connected four-node interaction graph. The triangular HMS architecture (H–M, H–S, M–S edges) is preserved unchanged from the canonical synthesis; three new edges (H–P, M–P, S–P) connect Propagation to each existing substrate. The six bidirectional couplings are specified mechanistically in Sections 4.1–4.6. Solid edges denote the canonical HMS couplings; the H–P and M–S diagonals are drawn dashed for visual clarity. Edge labels indicate the principal mechanistic linkage and the primary citation.

4.1 P → S: Propagation Feeds Synaptic Collapse

Trans-synaptic spread of α-synuclein and tau destroys PV+ interneuron circuits directly. The Luk demonstration of α-synuclein-mediated propagation along the nigrostriatal projection[15] and the de Calignon demonstration of tau propagation from entorhinal cortex into the hippocampal trisynaptic loop establish that propagation reaches PV+ targets before complement-mediated pruning would otherwise complete the job. The synaptic substrate, on the HMS account, attributes PV+ failure to complement engulfment in the matrix-degraded compartment; the propagation substrate adds that PV+ failure is additionally driven by direct templated misfolding within the PV+ compartment, which is itself a propagation target.

4.2 P → H: Propagation Feeds Homeostatic Collapse

Microglial uptake of extracellular tau and α-synuclein drives the DAM transition. Microglia phagocytose extracellular seeds as part of their canonical clearance function; the phagocytosed material accumulates in lysosomes whose acidification and proteolytic machinery is inadequate to degrade the seeded conformations, producing lysosomal-burden-driven activation that maps onto the LDAM and DAM transcriptional signatures.[34] Microglial endocytic uptake of α-synuclein has been demonstrated to drive NLRP3 inflammasome activation and IL-1β release, both of which are downstream components of the homeostatic-collapse signature. The propagation substrate is therefore not orthogonal to the homeostatic substrate; it accelerates it.

4.3 P → M: Propagation Feeds Matrix Collapse

The matrix substrate is upstream and downstream of the propagation substrate. Upstream: PNNs sequester extracellular tau and α-synuclein within the PV+ compartment, restricting their diffusion to neighboring cells; PNN degradation releases these previously sequestered seeds into the extracellular space, accelerating the propagation cascade. Downstream: pathological tau released by spread acts as a substrate for MMP-9 activation and as a driver of further PNN turnover. The bidirectional coupling between M and P is mechanistically tight and is one of the principal arguments for treating P as a substrate rather than an axis.

4.4 H → P: Homeostatic Collapse Feeds Propagation

Microglia in their homeostatic state are the principal extracellular clearance machinery for diffuse Aβ, extracellular tau, and α-synuclein. The collapse of the Butovsky signature degrades this clearance function: P2RY12-low DAM and LDAM microglia have measurably reduced extracellular-seed clearance capacity, and dystrophic microglia have essentially none.[21,35] The accumulation of extracellular seeds that the failing homeostatic substrate fails to clear becomes the substrate on which the propagation cascade advances. Homeostatic collapse, on the HMS+P account, is not merely a downstream consequence of disease — it is an upstream driver of the propagation step itself.

4.5 M → P: Matrix Collapse Feeds Propagation

PNN degradation exposes PV+ interneuron surfaces that bear high levels of LRP1 and HSPGs — the two principal receptors for tau and α-synuclein uptake.[10,11,27] In the intact matrix, the dense lectican-tenascin-hyaluronan mesh restricts access of extracellular seeds to the perisomatic membrane; matrix degradation opens this access. The matrix-degraded PV+ compartment is therefore an exceptionally efficient propagation target, simultaneously concentrating the uptake receptors and removing the diffusion barrier. Matrix collapse accelerates the propagation cascade at precisely the substrate (PV+ interneurons) that is most vulnerable to it.

4.6 S → P: Synaptic Collapse Feeds Propagation

Complement-mediated synaptic engulfment is, at the cellular level, a controlled release of synaptic content. The engulfed synaptic boutons contain vesicular tau and α-synuclein; the engulfment process — whether complete and lysosomal or partial and abortive — releases a fraction of this material into the extracellular space, where it constitutes the next round of propagation seeds. The synaptic substrate is therefore not merely a target of propagation; it is one of the principal seed sources by which propagation advances. The S → P coupling closes the architecture: every substrate both feeds and is fed by Propagation, just as every HMS substrate is bidirectionally coupled to the other two within the original trilayer.

4.7 The Substrate-Inclusion Criterion Is Satisfied

The four-node interaction graph satisfies the substrate-inclusion criterion in full. Propagation cannot be reduced to H (microglial uptake-driven DAM is a P → H coupling, not a P-in-H reduction), to M (the M ↔ P coupling is bidirectional, ruling out subordination either way), or to S (trans-synaptic spread depends on synaptic infrastructure but is mechanistically distinct from complement-mediated engulfment). And Propagation's failure produces downstream collapse across all three other substrates, satisfying the cross-monograph clause of the criterion. HMS+P is, on its own terms, the minimum architecturally complete account of the cross-axis pathology.

4.8 Lipid Availability and the APOE Modifier

The four-substrate architecture is gated by a cross-cutting variable that the H, M, S, and P substrates each depend on but none individually contains: brain lipid availability. The CNS holds roughly 20% of total body cholesterol despite representing 2% of body mass,[38] 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.[37,39] In H, microglial LRP1 supports phagocytic uptake of both amyloid and apoptotic-cell debris; its loss accelerates the DAM trajectory.[39] 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 — the connection is weaker than for H or S but not absent. 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.[39] The APOE4–Aβ complex is preferentially routed to VLDLR with slower internalization kinetics, whereas APOE2/3–Aβ complexes use both LRP1 and VLDLR efficiently.[40] 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 — likely because it dampens lipoprotein-particle uptake enough to reduce intracellular lipid peroxidation and lipofuscin accumulation without crossing the threshold into lipid starvation.[41] The Christchurch finding is the cleanest existing demonstration that *therapeutic dampening* of an LRP1 interaction can yield benefit, anticipating the central translational puzzle of the propagation substrate: which LRP1 interactions to amplify, and which to selectively block.

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 interaction graph above should therefore 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, and is taken up in Chapter 5.

> **What remains uncertain:** *Whether the six bidirectional couplings of the HMS+P graph are independently weighted equally, or whether one or two of the couplings (most plausibly H → P, given the centrality of microglial clearance failure, and M → P, given the receptor-exposure mechanism) dominate the others quantitatively, and whether the lipid/APOE gate operates symmetrically across the four substrates or weights one of them (most plausibly S, given Bu's 2010 neuronal-Lrp1 KO findings) more heavily than the others. The architecture is correct at the level of mechanism; the relative edge weights and gate weights remain to be empirically determined, most plausibly through systems-level perturbation experiments in iPSC-derived cortical organoids or in chronic two-photon in-vivo imaging models. The clinical implication — that monotherapy will fail regardless of the substrate targeted, and that gate-aware combinatorial regimens are required — is unaffected by the open question of relative weights.*

Chapter 5: Therapeutic and Trial-Design Implications

The architectural revision from HMS to HMS+P is not a cosmetic adjustment to the cross-axis synthesis. It has immediate and load-bearing implications for therapeutic strategy and for clinical trial design. The implications are derivable directly from the four-node interaction graph: if every

substrate both feeds and is fed by every other, then monotherapy targeting any single substrate cannot succeed in late-onset disease, because the three remaining substrates regenerate the failure of the targeted one. The combinatorial requirement is not a contingent fact about current therapeutic technology; it is a structural consequence of the architecture.

5.1 Why Monotherapy Fails

The failure pattern of late-onset Alzheimer's-disease therapeutics is well documented and theoretically informative. CSF1R inhibitors (microglial depletion) reset the homeostatic substrate but rebound rapidly upon withdrawal, with the matrix and synaptic substrates regenerating the inflammatory environment that drives renewed homeostatic collapse.[36] Chondroitinase ABC (matrix degradation reversal) restores PV+ plasticity transiently, but homeostatic-collapsed microglia and complement-driven synaptic loss continue to advance the disease. Complement-pathway blockade (C1q antibodies, C3 small-molecule inhibitors) reduces synapse loss transiently, but matrix degradation continues to expose new synaptic targets and the propagation substrate continues to seed new pathology in regions the antibody cannot protect. Anti-amyloid antibodies reduce amyloid burden dramatically but slow clinical progression only modestly, because the propagation substrate (tau spread along cortico-cortical projections) continues unabated.[30,31]

A second reason the anti-amyloid antibodies under-deliver is that they engage neither the P substrate (templated propagation, Chapter 3) nor the upstream lipid/APOE gate (§4.8). Anti-amyloid clearance does not restore LRP1-mediated cholesterol delivery, does not rescue APOE4-driven receptor saturation, and does not reverse synaptic-membrane lipid depletion. The APOE3-Christchurch case provides the cleanest existing precedent for an intervention that operates on the gate rather than on its downstream consequences: dampening, not amplifying, an LRP1 interaction yielded resilience against autosomal-dominant disease.[41] A substrate-aware combinatorial strategy for late-onset AD must therefore include at least one arm that operates on the LRP1/APOE axis — either by isoform-selective APOE modulation, by selective blockade of the propagation-relevant LRP1 interactions while preserving the clearance- and lipid-delivery interactions, or by upstream restoration of astrocyte-derived lipid supply.

The HMS+P architecture predicts each of these failure modes. It also predicts the failure of the analogous propagation-substrate monotherapies that will emerge over the next decade: anti-tau antibodies, anti-α-synuclein antibodies, LRP1-binding-domain antagonists, HSPG-mimetic seed sequestrants, and strain-specific conformational therapeutics. Each of these will reduce propagation transiently; each will fail to halt progression because the three HMS substrates continue to regenerate the conditions under which propagation can resume.

5.2 Combinatorial Architecture

The HMS+P framework specifies the combinatorial architecture required for disease modification. An effective regimen must engage all four substrates: (1) clearance restoration aimed at the homeostatic substrate, plausibly through TGF-β pathway support, TREM2 agonism, or microglial-replacement therapies; (2) matrix stabilization aimed at preventing PNN degradation, plausibly through MMP-9/ADAMTS inhibition or through direct HAPLN1 supplementation; (3) synaptic preservation aimed at the complement-pruning substrate, plausibly through C1q or C3 blockade in the perisomatic compartment; and (4) propagation blockade aimed at the templated-misfolding substrate, plausibly through LRP1-specific blockade of the lysine-mediated binding site for tau and α-synuclein, through HSPG-targeted seed sequestration, or through strain-specific conformational antibodies.

The combinatorial architecture has obvious implementation challenges. The current pharmaceutical industry is organized around single-target trials and single-target IP. Combinatorial regimens face regulatory, commercial, and trial-design barriers that single-agent monotherapies do not face. The HMS+P architecture does not solve these barriers; it specifies that they must be solved, because the architecture rules out monotherapy success on first principles.

5.3 Trial-Design Implications

Three trial-design implications follow directly. First, patient stratification must be performed by substrate-failure profile rather than by single-biomarker thresholds. A patient with substantial homeostatic collapse and minimal matrix collapse should not be enrolled into the same trial arm as a patient with the reverse profile; the substrate-failure pattern determines which combinatorial regimen is appropriate. The development of substrate-failure biomarker panels — plasma sTREM2 and GFAP for homeostatic state; CSF or plasma aggrecan fragments for matrix state; CSF C4d and C3b for synaptic state; CSF or blood tau-spread biomarkers and α-synuclein seed-amplification assays (RT-QuIC) for propagation state — is a prerequisite for trial stratification under the HMS+P framework.

Second, trial endpoints must be substrate-specific. Composite cognitive endpoints such as CDR-SB and ADAS-Cog are downstream consequences of substrate collapse, integrated across all four substrates; they have inadequate resolution to detect substrate-specific therapeutic effects. Substrate-specific endpoints — homeostatic-signature recovery measured by plasma proteomic panels, PNN integrity measured by Wisteria floribunda agglutinin (WFA) tau-PET or plasma aggrecan fragments, synapse density measured by SV2A-PET, and propagation halt measured by serial tau-PET trajectory — are required to evaluate combinatorial regimens whose mechanism of action engages multiple substrates.

Third, dosing architecture must be considered combinatorial rather than sequential. The standard pharmaceutical-industry strategy of demonstrating single-agent efficacy first and considering

combination later is, on the HMS+P account, structurally inadequate. The substrates are coupled in real time; intervening on one without simultaneously intervening on the others will produce the monotherapy failure pattern detailed in Section 5.1. Combinatorial trials must therefore be designed and run as combinatorial from the outset, with appropriate factorial designs to identify which combinations of substrate-targeting agents produce supra-additive effects.

5.4 The Temporal Window

The HMS+P architecture also clarifies the temporal window for intervention. Pathology that has already propagated through the cortex cannot be reversed by propagation-blockade interventions; it can only be prevented from advancing further. Synaptic loss that has already occurred cannot be restored by complement-pathway blockade; it can only be prevented going forward. Matrix that has been degraded can in principle be reconstituted but only over weeks to months. Homeostatic identity can be reset by microglial-replacement strategies but the reset is partial and slow. The HMS+P framework therefore predicts that the therapeutic window is necessarily early — at the prodromal stage in which the four substrates are collapsing but cortical infrastructure remains largely intact — and that interventions deployed at the dementia stage will produce only marginal benefit regardless of the substrate-coverage breadth of the regimen. The implication for trial design is that prodromal cohorts, identified by plasma p-tau217 elevation and minimal Aβ-PET burden, must be the principal target population for HMS+P-architected trials.

5.5 The Open Therapeutic Frontier

The most consequential open frontier is the substrate-selective LRP1 antagonist that would block tau and α-synuclein uptake without disturbing LRP1's Aβ-clearance or APOE-transport functions. The structural prerequisite — atomic-resolution mapping of the LRP1 binding-domain architecture sufficient to permit cluster-specific antagonist design — is being pursued in multiple structural-biology laboratories. The clinical prerequisite — biomarkers that detect propagation in vivo, since the proposed therapy halts progression rather than removing existing burden — depends on the maturation of serial tau-PET and α-synuclein seed-amplification assays. The HMS+P architecture identifies this as the highest-leverage single therapeutic target in the propagation substrate; whether it is also the highest-leverage single target across all four substrates is an open question that combinatorial trial data over the next decade will resolve.

Conclusion

The HMS+P model is the architectural payoff of the 2026 integration of the propagation literature into *Unified Collapse*. It is not a speculative extension; it is the minimum revision of the cross-axis synthesis required to accommodate the empirical density of the propagation substrate as that

substrate has been constituted by the cumulative work of Prusiner, Walker, Jucker, Bu, Diamond, Lee, Trojanowski, Luk, Volpicelli-Daley, Holmes, Sanders, and the broader proteopathic-propagation community. The case for the revision is empirically irrefutable on the substrate-inclusion criterion that HMS itself was built to satisfy.

The HMS+P architecture is also predictively rich. It generates testable hypotheses about combination therapeutics (every successful regimen must engage all four substrates), about biomarker panels (substrate-specific panels are required for trial stratification), about trial endpoints (substrate-specific endpoints are required for mechanism-of-action discrimination), and about the temporal window for intervention (the prodromal stage is the principal target). It explains, on first principles, the failure pattern of the past two decades of single-substrate monotherapy trials in late-onset disease. It identifies the propagation substrate as the principal driver of clinical progression — the substrate whose halt is the single most consequential available intervention — while making clear that propagation-blockade monotherapy will itself fail unless the three HMS substrates are simultaneously engaged.

The next phase of work for the *Unified Collapse* framework is to embed HMS+P into Chapter 1, replacing the trilayered HMS synthesis with the four-substrate HMS+P synthesis, and to propagate the revision through the cross-axis whitepapers that depend on Chapter 1's architecture. Specifically: the *Convergent Synaptic Collapse* monograph must be updated to reflect that synaptic collapse is partially driven by direct propagation as well as by complement-mediated engulfment; the *Homeostatic Microglial Collapse* monograph must be updated to reflect that homeostatic collapse is partially driven by microglial uptake of propagating seeds; the *Matrix Collapse* monograph must be updated to reflect the bidirectional M ↔ P coupling and the consequences for PV+ interneuron vulnerability; and the new *Convergent Propagation Collapse* monograph must be cross-referenced as the fourth pillar of the synthesis rather than as a free-standing axis.

The integration carries one further implication that has gone unstated in the body of the paper and deserves brief mention here. The substrate-inclusion criterion that justified the move from HMS to HMS+P does not, in principle, exclude further substrates. Two candidate substrates — Bioenergetic Collapse (oxidative-phosphorylation failure, NAD^+ depletion, mitochondrial-quality-control collapse) and Network-Oscillatory Collapse (gamma/theta dysrhythmia, theta-gamma coupling failure) — have been advancing in the corpus and may, within the next eighteen months, achieve the empirical density required for substrate-level inclusion. If both achieve that threshold, HMS+P will become HMS+P+B+O, and the four-node tetrahedron will become a five- or six-node graph with correspondingly more bidirectional couplings. The HMS+P revision presented in this paper should therefore be understood as architecturally final at the current state of the literature, but as in principle extensible if the empirical density of the bioenergetic and oscillatory axes continues to grow at its current rate. The cross-axis synthesis of *Unified Collapse* is, by design, a living architecture; HMS+P is the present state of that architecture, not its terminus.

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