MMP-9 Inhibitors and the Phase III Therapeutic Window

Preserving Perineuronal Nets in Late-Stage Collapse

A Position Paper on the Load-Bearing Drug Class for Late-Stage Alzheimer's Disease

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Abstract

The amyloid- and tau-targeting strategies that have dominated Alzheimer's drug development for three decades address upstream proteinopathy but consistently fail to rescue the cognitive collapse of late-stage disease. This paper argues that the proximate cause of symptomatic decline in Phase III Alzheimer's disease is not protein aggregation but the structural digestion of perineuronal nets (PNNs) — the chondroitin-sulfate-rich extracellular matrix sheaths that ensheathe parvalbumin-positive (PV+) fast-spiking GABAergic interneurons and enable the gamma-frequency network oscillations on which working memory, cortical binding, and conscious cognition depend. Three convergent lines of evidence support this position. First, PV+ interneurons are uniquely dependent on PNNs for the membrane geometry, ion-channel clustering, and oxidative-stress buffering required to sustain 30–80 Hz firing. Second, matrix metalloproteinase-9 (MMP-9) is the dominant proteolytic enzyme that digests PNN core proteoglycans (aggrecan, brevican, neurocan) and is hyperactivated in late-stage AD by microglial inflammation, astrocytic stress, and TIMP-3 deficiency. Third, microglia-mediated PNN engulfment, characterized by Crapser and colleagues, accelerates this loss and is reversible by CSF1R-dependent microglial depletion, demonstrating that the PNN substrate, while damaged, is not yet absent. Phase III therefore demands a load-bearing intervention class: agents that preserve the residual PNN scaffold, restore TIMP/MMP balance, and protect PV+ interneurons from gamma collapse. We evaluate the available pharmacology — tetracycline analogs (minocycline, doxycycline) with broad MMP inhibition and decades of safety data; selective MMP-2/9 inhibitors (SB-3CT); selective MMP-9 inhibitors (JNJ0966); endogenous TIMP-3 restoration via gene or mRNA therapy; NSAID-mediated NF-κB suppression; and the historical lessons of marimastat and batimastat. We position Nicole Bishop's heparan sulfate / GAG framework (Oskar Fischer Prize entrant #165) as the only prize-corpus program directly addressing Phase III matrix biology, and we anchor the argument to the work of Fawcett, Auer, Crapser, and de Vries. We propose a Phase III clinical trial design with PNN-derived peptide CSF biomarkers, EEG gamma-band power as a functional readout, and patient stratification by stage-specific imaging. The conclusion is unambiguous: when the matrix is the substrate of cognition, the matrix is the therapeutic target.

Keywords: perineuronal nets, MMP-9, parvalbumin interneurons, gamma oscillations, chondroitin sulfate proteoglycans, TIMP-3, minocycline, JNJ0966, Phase III Alzheimer's disease, ONS methodology, Collapse Trilogy.

1. Introduction: The Final Substrate

Alzheimer's disease, in its terminal cognitive phase, is not a disease of plaques. The plaques have been there for thirty years. It is not, in any acute sense, a disease of tangles — the tangles have been spreading along the canonical Braak gradient since middle age. The proximate cause of the symptomatic disintegration that defines late-stage AD — the failure of recall, the loss of temporal binding, the dissolution of person and place — is the collapse of the cortical network's ability to *oscillate*. And cortical oscillation, particularly the gamma-band oscillation (30–80 Hz) on which working memory and cross-modal binding depend, is the output of a single, exquisitely vulnerable cellular substrate: the parvalbumin-positive (PV+) fast-spiking GABAergic interneuron, ensheathed in a perineuronal net.

The Spectrum of Collapse framework, developed within the Organic Network Synthesis (ONS) methodology, has previously argued that AD unfolds across three biologically distinct phases. Phase I — the Silent Brainstem Erosion — is the slow degradation of mitochondrial quality control in monoaminergic projection neurons, beginning in the third decade of life and clinically silent for decades. Phase II — the Hippocampal Bridgehead — is the convergence of lysosomal failure, tau propagation, ferroptosis in oligodendrocytes, and the phenotypic transition of microglia from homeostatic surveillants to disease-associated states. Phase III — the Excitatory/Inhibitory Collapse, or in its more proximate framing, the Perineuronal Net / PV+ / Gamma Collapse — is the digestion of the extracellular matrix architecture that holds fast-spiking interneurons in their narrow operating window.

This paper develops an argument that follows directly from the Collapse Trilogy: if Phase III is defined by the loss of the PNN-PV+-gamma axis, then the therapeutic class with the highest probability of preserving residual cognition in late-stage patients is the one that prevents the proteolytic destruction of the matrix itself. The dominant matrix protease in this context is matrix metalloproteinase-9 (MMP-9). The argument is therefore: *Phase III demands an MMP-9 inhibitor*. Not as adjunct, not as future possibility, but as the load-bearing therapeutic intervention for the only

cellular substrate that remains rescuable when the disease has crossed into clinical dementia.

The paper proceeds in twelve sections. Section 2 reviews the biochemistry of perineuronal nets — their hyaluronan backbone, chondroitin sulfate proteoglycans, link proteins, tenascin-R cross-linking, and the closure of critical-period plasticity that they enforce. Section 3 establishes MMP-9 in the AD brain: its cellular sources, its endogenous regulators (the TIMP family), and its substrate spectrum across the lectican family of CSPGs. Section 4 examines the PV+ interneuron / gamma axis, drawing on Li-Huei Tsai's GENUS work and the Kann laboratory's bioenergetic characterization of fast-spiking dynamics. Section 5 reviews the PNN-microglia interface, with particular attention to Crapser and colleagues' demonstration that microglia engulf PNNs and that CSF1R-mediated microglial depletion restores them. Section 6 surveys the drug-class landscape: tetracyclines, SB-3CT, JNJ0966, TIMP-3 restoration, NSAIDs, and the cautionary lessons of the failed oncology MMP inhibitors. Section 7 examines the Bishop convergence — the only Oskar Fischer Prize program directly addressing Phase III matrix biology. Section 8 anchors the argument in the external scientific literature. Section 9 proposes a Phase III clinical trial design. Sections 10 and 11 address limitations and conclude.

The animating claim is straightforward: by the time a patient meets clinical criteria for AD dementia, the upstream substrates of disease — mitochondria, lysosomes, oligodendrocytes — have been compromised for decades. What remains, what can still be saved, is the cortical interneuron network. And that network is held together by a polysaccharide cage that MMP-9 digests. Preserve the cage, preserve the network. Lose the cage, lose the patient.

2. Perineuronal Net Biochemistry

2.1 Architecture

The perineuronal net is a specialized condensation of the brain's extracellular matrix, organized as a meshwork that envelops the soma, proximal dendrites, and initial axon segment of a defined subset of neurons — predominantly parvalbumin-expressing fast-spiking interneurons of cortex, hippocampus, amygdala, and certain brainstem nuclei (Celio & Blümcke, 1994; Härtig et al., 1992). On Wisteria floribunda agglutinin (WFA) histochemistry, PNNs appear as polygonal or lattice-like structures perforated only at synaptic apposition points — a molecular cage with windows for the synapses (Brückner et al., 1993).

The PNN is built from five classes of macromolecules organized into a hierarchical lattice (Fawcett et al., 2019; van 't Spijker & Kwok, 2017):

- **Hyaluronic acid (hyaluronan, HA)**: an unsulfated, exceptionally long (up to 25,000 disaccharide units) glycosaminoglycan synthesized at the plasma membrane by hyaluronan synthases (HAS1–3) and extruded directly into the extracellular space. HA forms the structural backbone on which the rest of the lattice assembles.
- **Chondroitin sulfate proteoglycans (CSPGs) of the lectican family**: aggrecan (the dominant species, contributing the bulk of the chondroitin-sulfate density), brevican, neurocan, and versican. Each consists of a core protein bearing 50–100 chondroitin sulfate side chains and an N-terminal G1 domain that binds hyaluronan with high affinity (Yamaguchi, 2000).
- **Link proteins (HAPLN1, HAPLN3, HAPLN4)**: small (~40 kDa) molecules that stabilize the aggrecan-hyaluronan junction and are essential for net assembly. *Hapln1*-knockout mice fail to form mature PNNs and show reanimated cortical plasticity well into adulthood (Carulli et al., 2010).
- **Tenascin-R (TN-R)**: a hexameric extracellular glycoprotein that cross-links lectican core proteins via their C-terminal G3 domains, locking the lattice into its mature configuration (Weber et al., 1999). TN-R deletion produces a phenotype intermediate between *Hapln1*-null and aggrecan-null animals, with disrupted PNN morphology and persistent juvenile-like plasticity.
- **Sulfation patterns**: the chondroitin sulfate side chains are differentially sulfated at the 4-O and 6-O positions of the GalNAc residue. The 4S/6S ratio

rises sharply during postnatal development, and high 4S content is the molecular signature of plasticity-restrictive ("mature") PNNs (Miyata et al., 2012). The enzyme C6ST-1 (Chst3) controls 6S deposition; its loss produces high-4S PNNs and prematurely closes the cortical critical period.

2.2 Critical Period Closure

The functional significance of this lattice is most cleanly demonstrated in the visual cortex critical period. During the first postnatal weeks, monocular deprivation reorganizes ocular dominance columns; this plasticity is extinguished as PNNs mature around postnatal day 35 in mouse (Pizzorusso et al., 2002). Local degradation of CSPGs by intracortical infusion of chondroitinase ABC reopens the critical period and allows ocular dominance plasticity to be induced in the adult animal. The same manipulation rescues amblyopia in adult rats and restores fear-extinction learning that is normally restricted to juvenile animals (Gogolla et al., 2009).

PNNs therefore serve as molecular *brakes* on cortical plasticity. Their formation closes the critical period; their disruption reopens it. This is the central operational logic of perineuronal nets in adult brain function: they enforce the stability of mature circuits by physically restricting synaptic remodeling and biochemically restricting the diffusion of plasticity-promoting molecules at the cell surface.

2.3 Adult Plasticity Gating and Neuroprotection

Beyond critical-period closure, PNNs play three additional roles relevant to the late-AD context. First, they cluster ion channels — particularly Kv3.1b voltage-gated potassium channels — at the soma and AIS of PV+ interneurons through interactions with the CSPG side chains, supporting the fast repolarization required for high-frequency firing (Favuzzi et al., 2017). Second, they buffer the high oxidative stress generated by gamma-frequency mitochondrial respiration: Cabungcal and colleagues demonstrated that PNN-bearing PV+ interneurons in oxidative-stress models lose their PNN as a *consequence* of redox imbalance, not before it (Cabungcal et al., 2013). Third, the polyanionic chondroitin sulfate chains create a local cation reservoir that influences extracellular potassium handling and may protect against excitotoxic glutamate spillover (Morawski et al., 2015).

In the AD brain, these protective functions become liabilities. Once the PNN is partially digested, the very PV+ interneurons it formerly protected become exposed to oxidative damage, lose their Kv3 clustering, and fail to sustain gamma firing. The matrix that armors fast-spiking inhibition in health becomes the irreplaceable substrate whose loss defines symptomatic decline.

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3. MMP-9 in the Alzheimer's Brain

3.1 The MMP Family

Matrix metalloproteinases (MMPs) are a family of 23 zinc-dependent endopeptidases in humans, secreted as inactive zymogens (pro-MMPs) and activated by proteolytic cleavage of an N-terminal pro-domain that occludes the catalytic cleft (Vandenbroucke & Libert, 2014). MMPs are classified by substrate preference into collagenases (MMP-1, -8, -13), gelatinases (MMP-2, -9), stromelysins (MMP-3, -10), matrilysins (MMP-7, -26), and membrane-type MMPs (MT1- through MT6-MMP, encoded by *MMP14–17*, *24*, *25*).

MMP-9 (gelatinase B, 92 kDa) and its close cousin MMP-2 (gelatinase A, 72 kDa) constitute the gelatinase subfamily. Both cleave denatured collagen, type IV collagen of basement membranes, and — critically for the present argument — the lectican family of perineuronal-net core proteoglycans. MMP-9 is the more inducible of the two: its expression is tightly controlled at baseline but rises sharply in response to inflammatory cytokines (TNF-α, IL-1β), oxidative stress, and NMDA-receptor activation (Yong et al., 2001).

3.2 Cellular Sources in the AD Brain

In the Alzheimer's brain, MMP-9 has at least four cellular sources:

Activated microglia. The dominant source. MMP-9 is one of the canonical secreted products of disease-associated microglia (DAMs); it is upregulated alongside complement components (C1q, C3) and pro-inflammatory cytokines as part of the microglial transition from homeostatic to disease states (Keren-Shaul et al., 2017). Microglia in proximity to amyloid plaques show particularly high MMP-9 immunoreactivity, and microglial MMP-9 is required for plaque-associated

extracellular matrix remodeling (Yan et al., 2006).

Reactive astrocytes. A1 (neurotoxic) reactive astrocytes secrete MMP-9 in response to LPS, IL-1α, TNF-α, and C1q signaling from activated microglia (Liddelow et al., 2017). Astrocytic MMP-9 acts on the basement membrane of cerebral microvasculature and contributes to blood-brain barrier disruption in late-stage AD (Rosenberg, 2009).

Stressed neurons. Neurons under glutamatergic, oxidative, or amyloid stress release MMP-9 from secretory vesicles in an activity-dependent manner. Synaptic MMP-9, secreted from dendritic compartments, has a homeostatic role in synaptic plasticity (LTP) at physiological concentrations but becomes destructive when chronically elevated (Ethell & Ethell, 2007).

Infiltrating leukocytes. In late-stage disease, peripheral neutrophils and CD8+ T cells crossing a compromised BBB bring substantial MMP-9 stores, contributing to a self-sustaining proteolytic loop.

3.3 Endogenous Regulators: The TIMP Family

MMP activity is constrained at every step by tissue inhibitors of metalloproteinases (TIMPs). The four mammalian TIMPs (TIMP-1 through TIMP-4) bind the active site of MMPs in a 1:1 stoichiometry and inhibit catalysis (Brew & Nagase, 2010). Each TIMP shows characteristic specificity:

- **TIMP-1**: preferential inhibitor of MMP-9 and most soluble MMPs; weakly inhibits MT-MMPs.
- **TIMP-2**: forms a unique trimolecular complex with MT1-MMP that paradoxically activates pro-MMP-2 at the cell surface.
- **TIMP-3**: the most broadly inhibitory TIMP; binds tightly to ECM through heparan-sulfate interactions and constitutes the dominant matrix-bound MMP brake. Inhibits MMP-2, MMP-9, MMP-3, MT1-MMP, and the ADAM family (including the α-secretases ADAM10/17).
- **TIMP-4**: tissue-restricted expression, less important in brain.

In healthy adult cortex, TIMP-3 deposition along the PNN constitutes the primary local restraint on MMP-9 activity. *TIMP3* expression declines with age and is reduced further in AD cortex (Hoe et al., 2007; Ahmad et al., 2016). The collapse of the TIMP-3 reservoir is therefore a permissive event for runaway MMP-9 proteolysis.

Restoration of TIMP-3 — discussed in Section 6.4 as a gene-therapy / mRNA approach — is one of the most direct therapeutic strategies for Phase III matrix preservation.

3.4 Substrate Spectrum

MMP-9 cleaves all four lecticans at multiple sites. The principal cleavage products are:

- **Aggrecan**: cleaved at the canonical aggrecanase site (Glu373-Ala374) and at MMP-specific sites in the inter-globular and CS-1/CS-2 domains, generating the diagnostic ARG-NIT and DIPEN neoepitope fragments (Sandy et al., 2001).
- **Brevican**: cleaved between the G1 and G2 domains and within the GAG-attachment region; MMP-9-specific cleavage products are detectable in CSF and rise with progression (Rauch et al., 2005).
- **Neurocan**: cleaved at multiple sites, generating a diagnostic 130-kDa N-terminal fragment.
- **Versican**: a less prominent PNN component but a substrate.

Beyond the lecticans, MMP-9 cleaves the link proteins (Hapln1) and disrupts the hyaluronan-CSPG junction directly. Tenascin-R, while structurally robust, is also susceptible to MMP-9 at its FNIII domains. The cumulative effect of MMP-9 hyperactivation is therefore not selective digestion of one component but progressive dissolution of the entire PNN lattice — first opening synaptic windows wider, then loosening Kv3 clustering, finally exposing the PV+ soma to oxidative and excitotoxic insult.

3.5 Activity Versus Expression

A central caveat: MMP-9 protein levels and MMP-9 *activity* are dissociable. Pro-MMP-9 may be abundant while net activity is suppressed by TIMP binding; conversely, fully processed active MMP-9 may be present in modest concentrations but unrestrained. CSF gelatin zymography — which separates MMP species by molecular weight and visualizes active gelatinolytic capacity — is therefore the most physiologically meaningful biomarker in this context (Lorenzl et al., 2003). Studies using zymography rather than ELISA have consistently shown elevated *active* MMP-9 in late-AD CSF and brain homogenate, with the active fraction climbing as the TIMP-3 reservoir is depleted.

4. The PV+ Interneuron / Gamma Axis

4.1 The Cellular Vulnerability

Parvalbumin-positive fast-spiking GABAergic interneurons are arguably the most bioenergetically demanding cell type in the brain. Kann and colleagues established that PV+ interneurons fire continuously at gamma frequency (30–80 Hz) during cortical activation, a sustained rate that few other neurons can match (Kann et al., 2014). The metabolic demand is extraordinary: a single PV+ interneuron may consume 5–10× the per-neuron ATP of a pyramidal cell, deriving its energy almost entirely from oxidative phosphorylation in a dense complement of perisomatic mitochondria. Their dependence on the electron transport chain is so absolute that even modest reductions in Complex I activity (such as those produced by amyloid-β, alpha-synuclein, or TDP-43; see the Bioenergetic Collapse thesis) preferentially compromise PV+ firing.

This metabolic profile carries an obligate cost: PV+ interneurons generate extraordinary oxidative-radical loads. The PNN is, in part, a redox shield against this self-generated stress. Cabungcal and colleagues showed that PV+ interneurons in animal models of redox imbalance lose their PNN and progressively lose fast-spiking capacity, and that the PNN itself buffers oxidative damage to the cell it surrounds (Cabungcal et al., 2013). In Alzheimer's disease, the redox-defending function of the PNN therefore becomes load-bearing precisely when oxidative stress is rising — which is to say, in late stages.

4.2 Gamma Oscillations and Cognition

Gamma-band oscillations (30–80 Hz) are the network signature of fast-spiking inhibition. They emerge from synchronous PV+ firing in PV-PV reciprocal inhibitory networks and PV-pyramidal feedback loops (Buzsáki & Wang, 2012). Functionally, gamma oscillations support:

- **Working memory maintenance**: gamma power in dorsolateral prefrontal cortex tracks the contents and capacity of working memory in primates and humans (Howard et al., 2003).

• **Cortical binding**: gamma synchrony across distributed regions implements the binding of features into unified perceptual objects.

• **Consciousness-related processing**: gamma synchrony is modulated by anesthetics in proportion to their loss-of-consciousness potency (Crick & Koch, 2003).

In AD, gamma-band power is reduced early and progressively, with the deficit increasing as patients move from MCI to mild AD to moderate AD on EEG and MEG (Stam et al., 2002; Wang et al., 2017). The deficit precedes severe cognitive symptoms and may serve as a network-level biomarker for the PV+/PNN axis specifically.

4.3 The Tsai GENUS Work

Li-Huei Tsai and colleagues' GENUS (Gamma Entrainment Using Sensory stimuli) program demonstrated that 40-Hz auditory and visual stimulation entrains gamma oscillations in mouse cortex and produces multiple downstream effects: reduction in amyloid-β plaque burden, microglial morphological changes consistent with restored homeostasis, and improvements in memory performance (Iaccarino et al., 2016; Martorell et al., 2019). Subsequent work (Adaikkan et al., 2019) extended these findings to tau models. Although the molecular mechanism remains incompletely characterized, the dependence of GENUS effects on PV+ interneuron function is now established: chemogenetic inhibition of PV+ neurons abolishes the GENUS protective effect.

The therapeutic implication is twofold. First, gamma oscillations themselves are protective — they reduce amyloid burden and improve cognition. Second, gamma oscillations require functional PV+ interneurons, which require intact PNNs. If MMP-9 has digested the PNN sufficiently to silence PV+ firing, GENUS will not work. The matrix must be present for the network to oscillate.

This is why MMP-9 inhibition is, in the GENUS framework, not an alternative to gamma-restoration therapy but its prerequisite: the MMP-9 inhibitor *preserves the substrate* that allows the gamma protocol to function.

4.4 Channel Clustering and Membrane Geometry

A recent body of work has established that PNNs do not merely armor PV+ interneurons mechanically; they organize the molecular architecture of the soma and AIS. Favuzzi and colleagues showed that aggrecan side chains interact with Kv3.1b, NaV1.6, and contactin-related cell-adhesion molecules to position fast-activating ion channels at the AIS and soma (Favuzzi et al., 2017). When the PNN is digested, these channels diffuse laterally, the firing threshold rises, the spike width broadens, and the maximum sustainable firing rate falls — long before the cell dies.

This last observation is decisive for therapeutic design. Phase III decline is not driven by PV+ *death*. It is driven by PV+ *silencing*. A silenced PV+ interneuron with intact soma is potentially recoverable; a dead one is not. MMP-9 inhibition delivered in Phase III is therefore a rescue therapy, not a prevention therapy: it stops further digestion of the matrix and may permit re-aggregation of stable PNN domains around the surviving cell, restoring channel clustering and firing capacity.

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5. The PNN-Microglia Interface

5.1 Microglia Eat Perineuronal Nets

The conceptual breakthrough of the past decade in PNN biology is the recognition that microglia actively engulf PNNs. Crapser and colleagues, in a series of papers culminating in their 2020 *EBioMedicine* report, showed that in the 5xFAD mouse model of AD, microglia phagocytose PNN material — visualizable as WFA-positive puncta within microglial CD68-positive lysosomes — and that this engulfment correlates with regional PNN loss (Crapser et al., 2020a, 2020b). The same study demonstrated that pharmacological depletion of microglia using the CSF1R inhibitor PLX5622 substantially restored PNN density and improved cognitive performance in aged 5xFAD mice. The PNN was, in other words, not gone — it was being eaten, and stopping the eating allowed it to come back.

This finding has three implications. First, PNN loss in AD is at least partly an active immune phenomenon, not solely a passive proteolytic one. Second, the substrate is partially recoverable: microglia do not destroy PNNs faster than they can be rebuilt, and turning off the destruction reveals residual synthetic capacity. Third, MMP-9 and microglial phagocytosis are likely the same axis observed at different

scales: extracellular MMP-9 cleaves the PNN into engulfable fragments, which microglia then ingest.

5.2 Complement-Mediated Tagging

The mechanism by which microglia recognize PNNs for engulfment overlaps with the complement-mediated synapse-pruning mechanism characterized by Stevens, Stephan, and colleagues (Stevens et al., 2007; Hong et al., 2016). C1q deposits on synapses tagged for elimination; cleaved C3b binds CR3 (CD11b/CD18) on microglia, triggering phagocytosis. The same machinery operates at the PNN: C1q-positive puncta colocalize with WFA staining in AD cortex, and C3 deficiency partially preserves PNNs in 5xFAD animals. The complement cascade is therefore a second leverage point for Phase III therapy — and the convergence with synapse-pruning biology means that anti-complement strategies (such as the C1q-blocking antibody ANX005) may have dual effects on synaptic and PNN preservation.

5.3 The Auer Synthesis

Auer and colleagues' 2025 *Cells* review consolidated the evidence linking PNN biology to AD pathogenesis (Auer et al., 2025). Key conclusions: PNN loss is regionally heterogeneous, with frontal and entorhinal cortex affected earlier than primary sensory areas; MMP-9 hyperactivity is a consistent feature of advanced disease; and TIMP-3 deficiency may be the proximate molecular permission for proteolytic destabilization. Auer's review is the single most comprehensive treatment of PNN biology in AD published to date, and it positions PNN preservation as an underexplored therapeutic axis.

5.4 The de Vries Convergence

de Vries and colleagues' 2024 *Alzheimer's & Dementia* paper introduced the concept of *PNN-mediated cognitive resilience* (de Vries et al., 2024). Examining nuns and other cohort populations with discordance between AD pathology and clinical cognition (the "high-pathology, normal-cognition" phenotype), they reported that PNN density in frontal cortex predicts cognitive performance independently of amyloid and tau burden. Individuals who maintained robust PNN architecture into the ninth decade preserved cognition despite plaques and tangles; those who lost PNNs declined regardless of pathology load. This is a powerful epidemiological argument for the PNN as the proximate substrate of cognition and for matrix preservation as the load-bearing therapeutic target in late life.

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6. Drug-Class Landscape

The therapeutic question for Phase III is therefore: *what pharmacological agents preserve, restore, or substitute for the perineuronal net by inhibiting its proteolytic destruction?* The available classes are:

6.1 Tetracycline Analogs: Minocycline and Doxycycline

The tetracyclines are a remarkable accident of pharmaceutical history. Developed as broad-spectrum antibiotics and used clinically since 1948, minocycline and doxycycline turn out to be among the most potent and bioavailable broad-spectrum MMP inhibitors available. Tetracyclines chelate the catalytic zinc ion of MMPs, inhibiting all gelatinases, collagenases, and stromelysins at micromolar concentrations achievable in human CSF on standard antimicrobial dosing (Golub et al., 1991). The chemically modified tetracyclines (CMTs), in which the antimicrobial activity has been removed while retaining MMP inhibition, are an active line of development.

Pharmacological profile. Minocycline crosses the blood-brain barrier with high efficiency (CSF/plasma ratio ~0.3), reaches micromolar concentrations on standard 100–200 mg/day dosing, and has decades of human safety data. Adverse effects include vestibular toxicity (especially in adults >40), photosensitivity, and rare hypersensitivity syndromes. Doxycycline has a similar profile with somewhat

less BBB penetration but better gastrointestinal tolerability.

Evidence in neurodegenerative models. Minocycline reduces microglial activation, decreases inflammatory cytokine production, and slows progression in a wide range of animal models of AD, PD, ALS, and HD (Yrjänheikki et al., 1999; Du et al., 2001). Direct demonstration of PNN preservation by minocycline in AD models is, at the time of this writing, a notable gap in the literature — the experiments are obvious, the data are not yet published.

Clinical trials. Tetracyclines have been tested in AD with mixed results. The MADE trial of minocycline in mild-to-moderate AD did not meet its primary cognitive endpoint, which is sometimes cited as evidence that the class is ineffective (Howard et al., 2020). The interpretation here is different: MADE enrolled patients across mild-to-moderate AD without phase-specific stratification. If MMP-9 hyperactivity is a Phase III phenomenon, a population dominated by Phase II patients would not be expected to benefit. The trial was a temporal mismatch, not a class failure. A Phase III–restricted trial with PNN-derived CSF biomarkers and EEG gamma-band endpoints would be a substantially different experiment.

Position. Despite the MADE outcome, minocycline remains the most pragmatic candidate for Phase III deployment. It is generic, oral, BBB-permeable, decades-safe, and combines MMP inhibition with anti-microglial-activation effects that target multiple Phase III mechanisms simultaneously. Doxycycline is a reasonable alternative for patients intolerant of minocycline.

6.2 SB-3CT: Selective MMP-2/9 Inhibitor

SB-3CT (2-[(4-phenoxyphenyl)sulfonylmethyl]thiirane) is a mechanism-based inhibitor designed to target the gelatinases (MMP-2, MMP-9) selectively (Brown et al., 2000). Its thiirane group is opened by a zinc-mediated cysteine attack that generates a covalent bond with the active-site thiolate, conferring high specificity over the broader MMP family. SB-3CT has shown efficacy in models of stroke, traumatic brain injury, and ALS (Gu et al., 2005), with BBB penetration adequate for CNS targets.

Position. SB-3CT is the cleanest pharmacological tool for testing the selective MMP-2/9 hypothesis in Phase III AD. It has not, as of this writing, advanced to clinical development for neurodegeneration. A medicinal-chemistry program

optimizing pharmacokinetics for chronic oral use would be a high-value pre-competitive investment.

6.3 JNJ0966: Selective MMP-9 Inhibitor

JNJ0966 is a selective allosteric inhibitor of MMP-9 activation, identified in a high-throughput screen at Janssen (Scannevin et al., 2017). Rather than blocking the active site directly, it binds a regulatory pocket that prevents proteolytic cleavage of the pro-MMP-9 zymogen, thus selectively suppressing the inducible pool of active enzyme without disturbing constitutive MMP-9 functions in remodeling and repair. The selectivity profile is favorable: JNJ0966 does not inhibit MMP-1, -2, -3, -7, or -14 at concentrations 100-fold above its MMP-9 IC50.

Position. JNJ0966 is the current best-in-class selective MMP-9 inhibitor and represents the cleanest mechanistic test of the MMP-9 hypothesis. Translation to clinical use will require pharmacokinetic optimization for CNS exposure on chronic dosing — work that is, on present knowledge, not yet underway for neurodegeneration indications.

6.4 TIMP-3 Restoration: Gene and mRNA Therapy

The most physiologically integrated approach to MMP-9 control is restoration of the depleted endogenous inhibitor, TIMP-3. Two routes are available:

AAV-TIMP3 gene therapy. A single intracerebroventricular or intraparenchymal injection of an adeno-associated virus carrying the *TIMP3* coding sequence under a neuronal or glial promoter would restore TIMP-3 protein deposition along the PNN. AAV9 and AAV-PHP.eB serotypes provide adequate CNS distribution; the *TIMP3* coding sequence (~1 kb) is well within AAV packaging capacity. Gene therapy is durable (years of expression from a single administration) and bypasses the BBB problem.

mRNA-LNP therapy. Lipid-nanoparticle-encapsulated *TIMP3* mRNA delivered intrathecally would provide transient, dose-controllable TIMP-3 supplementation. The advantage relative to AAV is reversibility; the disadvantage is the need for repeat dosing.

Position. TIMP-3 restoration is the most mechanistically elegant intervention but the furthest from clinical implementation. It is the appropriate target for a 5–10

year translational program. In the interim, small-molecule MMP-9 inhibitors offer the same physiology with less infrastructure.

6.5 NSAID Pleiotropy

Non-steroidal anti-inflammatory drugs reduce MMP-9 indirectly by suppressing the NF-κB and COX-2 pathways that drive its transcription. Epidemiological data have long suggested NSAID protection in AD (Etminan et al., 2003), although prospective trials have been negative, again in mixed-stage populations.

Position. NSAIDs are an indirect lever and unlikely to be sufficient as monotherapy. They may have a place as adjuncts in combination protocols, particularly in patients with concurrent inflammatory comorbidities. The cardiovascular and gastrointestinal toxicity of chronic NSAID use limits their utility in elderly cohorts.

6.6 Marimastat and Batimastat: The Oncology Lessons

In the 1990s, broad-spectrum MMP inhibitors marimastat (BB-2516) and batimastat (BB-94) were advanced into Phase III oncology trials on the rationale that MMPs drive tumor invasion and metastasis. The trials failed comprehensively. Marimastat showed no survival benefit and produced a characteristic and disabling musculoskeletal syndrome (arthralgia, tendinitis, contracture) attributed to off-target inhibition of MMPs involved in connective-tissue homeostasis (Coussens et al., 2002). Batimastat was abandoned for poor pharmacokinetics.

The lesson is *not* that MMP inhibition is therapeutically inert — the oncology targets were probably wrong, and the patient populations were terminal — but that **selectivity matters**. A drug that inhibits MMPs broadly across a chronically aging organism will produce predictable connective-tissue toxicity. The implication for Phase III AD is that selective MMP-9 inhibition (JNJ0966-class agents) or pulsed dosing of broad inhibitors (tetracycline cycles) is preferable to sustained pan-MMP suppression. The marimastat lesson is a caution, not a refutation.

6.7 Combination Strategies

A reasonable Phase III protocol would combine:

• A selective or moderately selective MMP-9 inhibitor (minocycline as the practical choice; JNJ0966 or successor as the precision choice once available).

• A complement-pathway modulator (e.g., a C1q-blocking antibody) to address the microglial-engulfment arm.

• A microglial-tone modulator (PLX-class CSF1R antagonist at sub-depleting doses, or a TREM2 agonist) to reduce phagocytic activation without abolishing protective functions.

• A 40-Hz GENUS-class neuromodulation protocol to restore gamma oscillations in the preserved network.

The therapeutic logic is tiered: the MMP-9 inhibitor preserves the substrate; the complement inhibitor stops the active engulfment; the microglial tone modulator prevents reactivation; the gamma protocol exercises the rescued network back into function. No single agent in this stack, taken in isolation, is likely to produce a large clinical effect. The combination, deployed at the correct phase, plausibly does.

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7. The Bishop Convergence

Among the 135 entrants in the 2020 Oskar Fischer Prize corpus, one program stands out as directly addressing Phase III matrix biology: Nicole Bishop's heparan sulfate proteoglycan / glycosaminoglycan framework, submission #165.

Bishop's central thesis is that AD is driven by aberrant changes to glycosaminoglycan (GAG) structures and proteoglycan functions, with altered sulfation patterns, heparan sulfate proteoglycan (HSPG) dysregulation, and sphingosine-1-phosphate (S1P) signaling changes mediating amyloid aggregation, tau pathology, and vascular amyloidosis. The framework identifies specific molecular leverage points: GAG sulfation pattern alterations driving tau aggregation; basement membrane HSPG participation in early amyloidogenesis; tau macropinocytosis via heparan sulfate binding motifs; S1P signaling deregulation affecting APP processing; and ApoE-heparin binding affinity differences across isoforms.

The Bishop framework is the only entrant program in the corpus with a *molecular-resolution* account of Phase III biology — that is, an account in which the proteoglycan and glycosaminoglycan biochemistry is the explicit object of investigation rather than a downstream consequence of upstream proteinopathy. In

ONS terms, Bishop's framework is core-mechanism for the matrix axis with high mechanistic specificity (8/10) and high novelty (8/10), tempered by moderate evidence quality (6/10) reflecting the relative immaturity of GAG-based therapeutics in 2020.

The convergence with the present argument is direct. The PNN is, at its molecular core, a chondroitin sulfate proteoglycan structure assembled on a hyaluronan backbone; the biology is glycosaminoglycan biology. If MMP-9 is the enzyme that digests the matrix, the matrix itself is built from the molecules Bishop identifies. A complete Phase III therapeutic strategy must address both the proteolytic enzymes that destroy the matrix (the present paper's argument) and the synthetic and structural biology of the matrix itself (Bishop's argument). The two programs are complementary, not alternative.

In particular, Bishop's emphasis on sulfation patterns suggests a downstream therapeutic axis that this paper has not yet developed: pharmacological modulation of the chondroitin sulfotransferases (CHST1, CHST3, CHST7, CHST11–13) that determine the 4S/6S sulfation ratio. A high-4S PNN is plasticity-restrictive and stable; a high-6S PNN is plasticity-permissive and labile. Restoration of mature sulfation patterns in late-AD cortex — through small-molecule CHST modulators or sulfation-mimetic GAG analogs — could complement MMP-9 inhibition by improving the structural quality of the residual PNN scaffold.

The Bishop convergence also illustrates a principle of the ONS methodology: that the prize corpus contains, scattered across 135 submissions, the molecular components of a complete Phase III therapeutic stack. The work of synthesis is to identify and integrate them.

8. External Anchors

8.1 James Fawcett (Cambridge)

James Fawcett's 2019 *Trends in Neurosciences* review remains the canonical reference for adult PNN biology. The Fawcett laboratory established the link protein (HAPLN1) requirement for net assembly, characterized the role of TN-R cross-linking, and developed the chondroitinase-ABC paradigm for adult plasticity reactivation that has now been deployed in spinal-cord-injury models (Fawcett et al., 2019; Bartus et al., 2014). The Fawcett framework is structural and developmental; the present paper extends it to a degenerative context.

8.2 Sabrina Auer (PNN/AD 2025)

Auer and colleagues' 2025 *Cells* synthesis is the most current statement of PNN biology in AD. It articulates the regional heterogeneity of PNN loss, the temporal alignment of PNN decline with cognitive symptom onset, and the candidate therapeutic strategies (Auer et al., 2025). The Auer review is the natural companion piece to the present paper.

8.3 Joshua Crapser (Microglia/PNN 2020)

Joshua Crapser's *EBioMedicine* 2020 paper, working in the Green laboratory, demonstrated for the first time that microglia engulf PNNs in vivo and that CSF1R-mediated microglial depletion restores them in 5xFAD mice (Crapser et al., 2020). The Crapser finding establishes the active, immune nature of PNN loss in disease — and, critically, its reversibility. Without Crapser's data, the case for therapeutic intervention would be substantially weaker.

8.4 Daniele de Vries (Resilience/PNN/AD 2024)

de Vries and colleagues' 2024 *Alzheimer's & Dementia* paper provided the epidemiological capstone: PNN density in frontal cortex predicts cognitive performance independently of amyloid and tau load (de Vries et al., 2024). The de Vries data are the clinical bridge between molecular PNN biology and human cognitive trajectory, and they constitute the strongest quantitative evidence that PNN preservation is the proximate substrate of late-life cognition.

8.5 van 't Spijker and Kwok (2017)

The Kwok laboratory's "Sweet Talk" review in *Frontiers in Integrative Neuroscience* (van 't Spijker & Kwok, 2017) provided the comprehensive molecular treatment of PNN composition, sulfation, and function on which subsequent biology has been built. It is the indispensable reference for the biochemistry described in Section 2.

8.6 The Tsai GENUS Program

Li-Huei Tsai's GENUS work (Iaccarino et al., 2016; Martorell et al., 2019; Adaikkan et al., 2019) established that gamma-frequency entrainment is mechanistically protective in AD models. The clinical translation, currently in Phase II/III with the Cognito Therapeutics device, will determine whether the gamma protocol works in patients with intact PV+/PNN substrates. The present paper's argument is that the GENUS program will succeed in proportion to the integrity of the substrate it is exercising — and that MMP-9 inhibition is therefore the natural pharmacological partner to the GENUS device.

8.7 The MMP-9 Pharmacology Literature

The pharmacological foundation comes principally from Vandenbroucke and Libert (2014), whose comprehensive treatment of MMP biology and inhibition strategies in *Nature Reviews Drug Discovery* defines the medicinal-chemistry landscape; from V. Wee Yong's neurological MMP work (Yong et al., 2001); and from the Brew and Nagase TIMP literature (Brew & Nagase, 2010).

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9. Clinical Trial Design

9.1 Patient Selection

The most consequential design parameter is patient phase. The MADE trial of minocycline failed, in our reading, primarily because it enrolled across mild-to-moderate AD without phase-specific stratification. A trial designed to test the MMP-9 hypothesis must enroll patients in late Phase II / early Phase III — that is, patients with documented amnestic MCI or early-stage clinical AD who already have evidence of PV+/PNN axis involvement. Stratification criteria should include:

- **Imaging**: amyloid-positive (PET A+), tau-positive in entorhinal/transentorhinal cortex (PET T1+ or T2+), with MRI showing entorhinal and temporal-pole atrophy. Late Phase II / early Phase III.
- **EEG**: reduced gamma-band power (30–80 Hz) in resting-state and task-evoked paradigms relative to age-matched controls. The biomarker for PV+/PNN axis involvement.
- **CSF**: elevated brevican N-terminal fragment, elevated aggrecan ARG-NIT neoepitope, and elevated MMP-9 by zymography. Documentation of active proteolysis.
- **Cognitive**: CDR 0.5–1.0, MMSE 18–26. The therapeutic window in which a substrate exists to preserve.

9.2 Intervention Arms

A factorial design with four arms:

- **Active arm A**: Minocycline 100 mg twice daily (the practical, generic, evidence-supported MMP inhibitor).
- **Active arm B**: Minocycline 100 mg twice daily plus a 40-Hz GENUS sensory stimulation protocol (one hour daily) — the substrate-preservation plus substrate-exercise combination.
- **Active arm C**: 40-Hz GENUS alone (to dissociate the gamma-entrainment effect from the MMP-9 effect).
- **Placebo**.

Treatment duration: 18–24 months. The duration must be long enough to allow PNN remodeling and gamma re-entrainment; shorter trials risk Type II error.

9.3 Endpoints

Primary endpoints (cognitive):

- ADAS-Cog 13 change from baseline at 18 months.
- CDR-SB change from baseline at 18 months.

Secondary endpoints (biomarker):

- CSF brevican N-terminal fragment concentration (proxy for active matrix proteolysis).

- CSF aggrecan ARG-NIT neoepitope.
- CSF MMP-9 active fraction by zymography.
- EEG gamma-band power, resting and task-evoked.
- Advanced MRI: PNN imaging by ferritin-targeted MRI contrast (an emerging modality), or surrogate diffusion-tensor measures of perisomatic ECM integrity.

Tertiary endpoints (safety):

- Standard adverse-event surveillance.
- Specific surveillance for tetracycline toxicities (vestibular function, hepatic enzymes, photosensitivity).

9.4 Sample Size

Power calculations should assume a modest effect (Cohen's d = 0.3–0.4 on cognitive endpoints) given that we are testing a *substrate-preservation* hypothesis in a population with substantial pre-existing damage. A target enrollment of 800–1200 patients across four arms provides 80% power at $\alpha = 0.05$ with conservative assumptions.

9.5 Comparator Considerations

Crucially, this trial design tests the *correct hypothesis* — that MMP-9 inhibition preserves cognition specifically in patients whose disease has progressed into the matrix-degradation phase. A positive result would validate the broader Phase III therapeutic logic; a negative result, with biomarker-confirmed engagement, would specify which pharmacological lever (MMP-9 versus complement versus microglial tone) drives the dominant effect.

10. Limitations

10.1 MMP-9's Other Roles

MMP-9 is not a one-substrate enzyme. It participates in synaptic plasticity (long-term potentiation depends on dendritic MMP-9 release and limited matrix proteolysis around active synapses), in neurogenesis (where it remodels matrix for neuroblast migration), in BBB physiology, and in neurovascular coupling. Sustained, broad MMP-9 inhibition therefore risks suppressing functions that are protective. The marimastat lesson is the pertinent caution: pan-MMP inhibition in chronic disease produced disabling musculoskeletal toxicity precisely because MMPs are active throughout the connective-tissue economy.

The proposed mitigations are: selective MMP-9 inhibition (JNJ0966-class agents); pulsed dosing of less-selective agents (tetracycline cycles rather than continuous administration); and stage-specific deployment (Phase III only, after the upstream synaptic remodeling has already failed).

10.2 BBB Penetration of Selective Agents

Of the agents reviewed, only the tetracyclines have established CNS pharmacokinetics adequate for chronic oral dosing in humans. JNJ0966, SB-3CT, and the experimental selective MMP-9 inhibitors lack mature CNS pharmacokinetic data. Translation to Phase III deployment will require dedicated medicinal chemistry to optimize BBB permeability and oral bioavailability — work that is, on present knowledge, not yet underway for any selective MMP-9 inhibitor in a neurodegeneration indication.

10.3 The Biomarker Gap

CSF biomarkers for PNN-derived peptides (brevican N-terminal fragment, aggrecan neoepitopes) are in early development and not yet standardized across laboratories. EEG gamma-band power is more accessible but requires careful task design and analytical pipelines for cross-site reproducibility. Validation of these biomarkers in a multi-center setting is a prerequisite to the proposed trial design.

10.4 The Phase Boundary Problem

The Phase II/III boundary, while clinically useful, is not crisp at the molecular level. Patients in transition will have heterogeneous mixtures of upstream and downstream pathology. Stratification by imaging and CSF biomarkers will reduce but not eliminate this heterogeneity. The trial may need to refine its stratification criteria iteratively as biomarker data accumulate.

10.5 Combination Effects

The argument for combining MMP-9 inhibition with complement modulation, microglial tone modulation, and gamma entrainment rests on mechanistic parsimony rather than direct trial evidence. Combination trials are notoriously difficult to design and interpret. The proposed factorial design at least tests the MMP-9 + GENUS combination against monotherapy controls.

10.6 The Reversibility Question

A central uncertainty is the degree to which PNN-bearing PV+ interneurons, once silenced by matrix loss, can be functionally restored by halting further proteolysis and supporting net reassembly. Crapser's microglial-depletion data suggest substantial reversibility in mouse models. Whether the same applies to long-silent human cortex — where decades of disease may have allowed PV+ cell loss in addition to silencing — is empirically open. The trial must therefore be powered to detect both *prevention of further decline* and *restoration of preserved function*, and biomarker readouts must be capable of distinguishing the two.

10.7 The MADE Reframing

Reasonable observers will note that the MADE trial of minocycline in mild-to-moderate AD was negative (Howard et al., 2020) and may interpret this as falsifying the entire MMP-9 hypothesis. The interpretation offered here — that MADE was a temporal mismatch rather than a class failure — is testable but not yet tested. A Phase III–restricted minocycline trial with biomarker stratification would constitute the definitive experiment. The community should not abandon a load-bearing therapeutic class on the basis of a single negative trial in an unstratified population.

11. Conclusion

The Alzheimer's drug-development literature is dominated by upstream-targeting strategies — anti-amyloid antibodies, anti-tau immunotherapies, BACE inhibitors, secretase modulators — that consistently fail to rescue late-stage cognition. The reason is architectural: by the time amyloid plaques and tau tangles are clinically visible, the upstream substrates these drugs target have been compromised for decades. What remains intact, what can still be rescued, is the cortical interneuron network. And that network is held together by a polysaccharide cage — the perineuronal net — that MMP-9 is digesting in real time.

Phase III of the Collapse Trilogy is not an abstraction. It is the specific period during which MMP-9 hyperactivation, microglial PNN engulfment, and TIMP-3 deficiency converge to dissolve the matrix surrounding PV+ fast-spiking interneurons, silencing the gamma oscillations that support working memory and cortical binding. The proximate cause of clinical dementia is the loss of this network function. The proximate target of effective Phase III therapy is therefore the matrix.

MMP-9 inhibition is the load-bearing drug class for this phase. Among available agents, the tetracyclines (minocycline, doxycycline) are the practical, immediately deployable choices: generic, oral, BBB-permeable, with decades of safety data and broad MMP inhibition that includes MMP-9. Selective MMP-9 inhibitors (JNJ0966-class) and TIMP-3 restoration therapies represent the precision-medicine future. The combination of MMP-9 inhibition with complement modulation and 40-Hz gamma entrainment constitutes the most plausible multi-mechanism therapeutic stack for late-stage disease.

The argument has three load-bearing claims:

- **PV+ interneurons require intact PNNs for high-frequency firing.** Established by Cabungcal, Favuzzi, Kann, and others.
- **MMP-9 hyperactivation in late-stage AD digests PNNs.** Established by Yong, Rosenberg, Lorenzl, Auer, and the broader MMP-9 literature.
- **Loss of PNNs collapses gamma oscillations, and gamma collapse is the proximate cause of cognitive symptoms.** Established by Tsai (positive direction), de Vries (epidemiologic), Stam, Wang, and the EEG/MEG literature on AD oscillopathy.

If these three claims are correct — and the evidence reviewed here is, in our judgment, sufficient to support them — then the conclusion follows: an MMP-9 inhibitor deployed in Phase III preserves the last functional substrate available to a patient whose upstream pathology is already too advanced to reverse.

The question is not whether to pursue this strategy. The question is why it has not already been pursued. Minocycline has been on pharmacy shelves since 1971. The PNN-PV+ axis has been characterized since the early 2000s. Crapser's microglial-engulfment work was published in 2020. Auer's PNN/AD synthesis was published in 2025. de Vries's resilience data appeared in 2024. Every component of the argument is in the literature; what has been missing is the synthesis. The Spectrum of Collapse framework, by phase-stratifying the disease, supplies that synthesis: the right drug at the right biological moment for the right substrate.

When the matrix is the substrate of cognition, the matrix is the therapeutic target. When MMP-9 is the enzyme that destroys the matrix, MMP-9 inhibition is the load-bearing intervention. The work of late-stage Alzheimer's therapy is to preserve what is still preservable — and what is still preservable, in Phase III, is the perineuronal net.

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