The Losing Axon

Amyloid-β as a signal of competition — Zhen Huang's theory that Alzheimer's disease is competitive synaptic plasticity gone awry, examined against the evidence of 2026

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Almost every theory of this disease begins by asking what amyloid-β does wrong. This one begins by asking what it is for — and answers that it is the molecule an axon secretes to protect itself and to mark its rivals for removal. What follows is an assessment of that idea, of the experiment built to test it, and of the four clinical read-outs that have since spoken to its one sharp practical claim.

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Abstract

Almost every theory of Alzheimer's disease begins by asking what amyloid-β does wrong. Zhen Huang's begins by asking what it is for. His answer is that amyloid-β is a competition signal — a molecule an axon secretes to protect itself and to mark its rivals for removal — and that Alzheimer's disease is what happens when that signalling system loses its balance.

The proposal rests on a structural analogy with bacterial competition. Bacteria that must compete with genetically identical neighbours secrete peptide antibiotics such as nisin, which do opposite things depending on their assembly state: near the producing cell the monomer binds an immunity protein and protects the secretor, while further out the peptide oligomerises and kills the neighbour. Amyloid-β has this profile. At picomolar concentrations it increases release probability, enhances long-term potentiation and improves memory; at high nanomolar concentrations, as an oligomer, it does the reverse. Amyloid-β is also a genuine antimicrobial peptide in its own right. Huang's claim is that a molecule with this grammar is built for competition, that nervous systems co-opted it to arbitrate which axons survive activity-dependent competition, and that Alzheimer's disease is the failure of the protective half of the system.

This paper evaluates that proposal as a body of work — a 2020 prize essay, its 2023 publication, a substantially different 2024 sequel, and one experimental paper from 2024 — against the independent evidence available in August 2026.

What holds. The loss-of-function genetics is the theory's strongest leg and it is not in dispute: removing the amyloid precursor protein, or removing the amyloid-oligomer receptor PirB, causes axons that should have been pruned to survive and expand. That is the signature of a punishment signal withdrawn, and it is a counterintuitive prediction that a pure toxicity model does not make. The concentration duality is real and independently replicated across several laboratories, including the finding that endogenous amyloid-β is *required* for normal plasticity and memory. The 2024 experiment supplies what the theory most needed — a molecular pathway by which monomeric amyloid-β restrains a glial cell, running through the precursor protein itself, a heterotrimeric G-protein chaperone, and the matrix protease MMP9 — and in doing so revives a receptor claim about the precursor protein that has been dormant since 1993. And the theory's central pathological inference, that losing the soluble monomer matters more than gaining the aggregate, has since been reached independently from human biomarker data by a separate research programme with no connection to it.

What does not. The concentration axis on which the analogy rests turns out not to be one axis. The neuronal effects Huang calls low-concentration occur at 100–200 picomolar; the microglial effects his own laboratory reports begin at 50 nanomolar — several hundred-fold higher, and precisely the concentration at which his own summary table has amyloid-β starting to suppress synaptic transmission. The variable that separates the two faces is conformation, not amount — which weakens the bacteriocin analogy at its hinge, because in bacteria concentration *drives*

conformation and thereby generates the spatial structure that makes the signal a competition signal at all. The 2024 experiment demonstrates the pathway in culture and the phenotype in the animal but never shows amyloid-β activating the pathway in a living brain, a gap the reviewers pressed and the author conceded on the record. A 2025 result from an independent laboratory finds that the highest-affinity ligand for the receptor Huang uses as his punishment-signal exemplar is not amyloid-β but a complement fragment. And the 2024 extension of the framework to apolipoprotein E has grown to the point where the same gene is protective in one cell type and destructive in another, with the risk allele performing the protective function best — an accommodation that costs the theory its constraint.

What the last three years adjudicated. Four sets of clinical results now bear on the model's central therapeutic prediction, and read together they favour it: two antibodies that bind the monomer produced nothing in the two populations where they should have worked best; two that spare the monomer and clear aggregates produced small but real effects; and an antibody designed to *activate* microglia failed with confirmed target engagement. Meanwhile the fly genetics that supplies the theory's mechanism has produced a result pointing the other way — culling unfit neurons in an amyloid model is protective, not harmful — and the human tissue work that has established glial synapse engulfment in Alzheimer's disease identifies the tags on the engulfed synapses as tau oligomers and exposed phosphatidylserine rather than amyloid-β.

The verdict offered here is that the theory is best read not as a rival account of what starts the disease but as the most complete available account of *what amyloid-β is for*, from which a disease model follows as a corollary. On that reading its most valuable output is a single therapeutic principle, stated years before the trial data that now support it: do not remove the monomer.

1. Introduction: A Theory About What the Peptide Is For

1.1 The question that is rarely asked

The amyloid precursor protein is old. Homologues are present in nematodes and flies, and the gene family predates the nervous system that its best-known cleavage product is now blamed for destroying. A molecule of that antiquity, expressed at high level in every neuron, cleaved by a dedicated and tightly regulated enzymatic apparatus, and released in an activity-dependent manner, is unlikely to exist in order to cause a disease of late life. It does something. The question of what has been asked far less often, and far less systematically, than the question of what goes wrong with it.

Zhen Huang, of the Departments of Neuroscience and Neurology at the University of Wisconsin–Madison, has spent the past several years answering the first question and deriving the second from it. His proposal, in one sentence: amyloid-β is a signal that mediates competition between axons and synapses, and Alzheimer's disease is that signalling system losing its balance.

This is not the familiar concessive move of granting that amyloid-β "has a physiological function" and then returning to the cascade. It is a claim about a *specific* function, with a specific molecular grammar borrowed from a specific place — bacterial competition — and it makes the disease a disorder of a normal process rather than the intrusion of an abnormal one. That shift has consequences all the way down to what a drug should be designed to do.

1.2 Two kinds of theory

It is worth being explicit at the outset about what kind of object is being assessed, because the field routinely conflates two.

A **theory of onset** answers the question *what starts it*. The amyloid cascade hypothesis is precisely an answer of this kind, and was restated as such at its twenty-fifth anniversary [1]. Theories of onset are adjudicated by temporal priority in human tissue, and human tissue offers one frozen frame of a process that runs for two decades. Very few can be settled, which is why so many coexist.

A **theory of function** answers the question *what is this molecule for*. It is adjudicated by intervention: remove the molecule and see what breaks; add it back and see what recovers; identify the receptor and interrupt the coupling. These are ordinary experimental questions with ordinary answers.

Huang's work is mostly the second kind with a disease model attached. That is a considerable advantage, and it is worth insisting on it, because the framework is usually filed alongside the cascade and the tau hypothesis as one more candidate origin story — and read that way it looks weaker than it is, because origin claims cannot be tested and function claims can.

1.3 The documents

Four pieces of work state and test the proposal.

The **2020 essay**, submitted to the Oskar Fischer Prize, is the fullest statement: the bacteriocin analogy, the concentration duality, the cell-competition machinery, the neural loss-of-function genetics, the adult homeostatic module, a unifying disease model built on chronic microglial hyperactivity, a treatment of how genetic and non-genetic risk factors converge on microglial state through cholesterol metabolism and innate immune memory, and an explanation of why precursor-protein-overexpressing mice do not develop neurofibrillary tangles. It cites 258 sources.

The **2023 review** in the *Journal of Alzheimer's Disease* is that essay published, largely intact [2].

The **2024 review**, in the same journal, is not a restatement [3]. It is a substantially different document, and the difference matters for how the programme should be assessed. Where the earlier argument put microglial hyperactivity at the centre, the 2024 argument puts apolipoprotein E, phosphatidylserine, the classes of dendritic spine, DNA damage repair and sleep at the centre. Cholesterol metabolism, trained immunity and the animal-modelling argument are absent. The phrase "microglial hyperactivity" scarcely appears.

The **2024 experimental paper**, in *eLife*, is the laboratory work: an attempt to find a receptor mechanism for monomeric amyloid-β acting on microglia, using mouse genetics and a developmental phenotype [4].

There are no further primary publications from the laboratory bearing on this question as of August 2026.

1.4 What this evaluation asks

Three questions organise what follows.

Is the analogy load-bearing, or decorative? The bacteriocin comparison is the theory's engine. If amyloid-β really has the concentration-and-conformation grammar of a peptide antibiotic, much follows — including a principled account of how a diffusible molecule can produce a spatially selective outcome. If the resemblance is a family resemblance among peptides that happen to aggregate and happen to be toxic, then the theory is a metaphor with a bibliography.

Does the disease model follow from the physiology, or is it bolted on? A theory of what a molecule is for and a theory of how a disease begins are different objects with different evidential requirements. The framework's authority comes from the first; its ambition lies in the second.

What have the last three years done to it? The 2020 essay was written before the anti-amyloid antibodies read out, before the first microglia-activating antibody was tested in humans, before the human soluble-amyloid literature matured, before the receptor it uses as its exemplar acquired a rival ligand, and before human tissue studies identified what actually tags a synapse for removal in Alzheimer's disease. A theory that makes claims bearing on all five should be read against all five.

Sections 2 to 7 assemble the argument from its sources and press on it where it is weakest. Sections 8 to 11 test it against independent evidence. Section 12 grades every substantive claim. Sections 13 to 18 state the weaknesses, the refutation conditions and the practical consequences.

2. The Bacterial Template

2.1 What a bacteriocin has to do

Lactococcus lactis secretes nisin, a 3.4 kilodalton lantibiotic, when it is crowded. The problem nisin solves is the hardest version of a competitive problem: the cells being killed are genetically identical to the cell doing the killing. Whatever makes the neighbour die must not make the secretor die. There is no antigenic difference to exploit, no self/non-self discrimination available. The organism solves this with a gene cluster that couples three functions [5,6].

The first is **quorum sensing**. The cluster encodes a two-component system — a sensor histidine kinase and a response regulator — whose ligand is nisin itself [5,7]. Under sparse conditions nisin is produced at a trickle and never reaches the receptor's activation threshold. Under crowding, extracellular nisin crosses that threshold, activates the receptor, and the cluster switches on. The molecule reports the density of the population and then acts on it. Production and sensing are the same chemistry.

The second is **immunity**. The same switch that raises nisin production raises production of the immunity protein NisI, a surface lipoprotein that binds nisin, sequesters it locally, prevents it from aggregating into pore-forming assemblies near the producer's own membrane, and can also drive cell clustering that physically restricts access [6,8]. Some NisI is secreted, neutralising nisin at a distance. Self-protection is a distinct, genetically encoded, co-regulated arm of the same programme — not a passive consequence of the killer's constitution.

The third, and the one that carries the analogy, is **conformational duality**. Nisin's activities depend on its assembly state. At concentrations near the activation threshold it exists mainly as monomer and binds its receptor and its immunity protein. At higher concentration it oligomerises, binds the cell-wall precursor lipid II, aggregates that complex, blocks peptidoglycan synthesis, destabilises the membrane and forms pores [9]. A second, lipid-II-independent killing mechanism operates purely as a function of crowding and degree of oligomerisation, decreasing lipid packing density and increasing membrane permeability [10].

So: one molecule, one concentration gradient, two opposite outcomes, with the transition governed by self-assembly, and an immunity system that works precisely by *preventing local assembly*. The spatial structure falls out for free — the peptide is monomeric where it is dilute and oligomeric where it is concentrated, which means near the producer it protects and far from the producer it kills. This is the feature that makes a diffusible molecule into a competition signal rather than a

poison.

2.2 The homology claim, stated exactly

Huang's claim is not that amyloid-β is a bacteriocin. It is that amyloid-β possesses the same functional grammar, and that this grammar is what a competition signal requires.

The first premise is that amyloid-β is a genuine antimicrobial peptide. This is not Huang's claim but Robert Moir's and Rudolph Tanzi's, and it is well evidenced: synthetic and brain-derived amyloid-β has broad-spectrum antimicrobial activity against bacteria, yeast and viruses, protects mice and nematodes against infection, and entraps pathogens in fibrillar structures [11,12].

The class has since widened in ways that materially strengthen the premise, and both additions post-date the essay. Human amylin — the pancreatic peptide of type 2 diabetes, itself an amyloid-forming protein — was shown in 2025 to be a potent antimicrobial peptide, eliminating 99.9% of bacteria at low dose by a fibril-driven trapping mechanism, protecting human cells and *Caenorhabditis elegans* from infection, and acting *synergistically* with amyloid-β [13]. And in March 2026 the same lineage reported that tau is hyperphosphorylated in human neurons in response to viral infection, and that phosphorylated tau neutralises herpes simplex virus 1 by binding viral capsids directly [14].

That second result deserves a moment. Both of the proteins that define Alzheimer's neuropathology are now reported to be host-defence molecules whose canonically pathological behaviours — aggregation, hyperphosphorylation, microtubule destabilisation — are the mechanism of the defence. If that holds, the two hallmark lesions of the disease are the residue of an innate immune response, and the question shifts from why the brain makes these things to why it cannot stop.

This is a substantial independent strengthening of Huang's starting premise. It is important to say exactly what it does and does not do. Showing that amyloid-β is an antimicrobial peptide establishes that it belongs to the class from which the analogy is drawn. It does not establish that it does in a brain what nisin does in a colony. That second step needs its own evidence, and most of this paper is about whether it has it.

2.3 The wider precedent

Huang adds a supporting observation that is often overlooked and is stronger than it first appears: peptides with antimicrobial activity are pervasive in nervous systems, and several have well-characterised neural functions unrelated to infection.

Substance P, an eleven-residue neurotransmitter and neuromodulator, has potent antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*. Neuropeptide Y, which regulates feeding,

behaviour and metabolism, has potent antifungal activity. α-Melanocyte-stimulating hormone, a thirteen-residue peptide regulating appetite and sexual behaviour, is effective against *S. aureus* and *Candida albicans* at femtomolar to picomolar concentrations — far below those required of most antimicrobial peptides. In *Drosophila*, the antimicrobial peptide diptericin B regulates long-term memory [15], and the antimicrobial peptide nemuri increases arousability when deleted and drives prolonged sleep when overexpressed [16].

The mammalian cathelicidin LL-37 shows the same conformation-dependent inversion as nisin: as a monomer at low concentration it activates trophic signalling and *inhibits* pro-inflammatory activity in immune cells; as an oligomer at high concentration it does the opposite [17]. LL-37 is thus a second mammalian peptide with exactly the profile Huang attributes to amyloid-β, and it is a peptide nobody disputes is an antimicrobial.

The general claim — that the innate immune peptide repertoire has been repeatedly co-opted for neural signalling — is well supported and independently made [18]. This is the analogy's strongest surrounding context. If antimicrobial peptides are routinely repurposed as neural signals, then the proposal that one of them was repurposed as a competition signal is not exotic. It is the default expectation for a peptide of this class expressed in this tissue.

2.4 What would make the analogy load-bearing

An analogy earns its keep in a theory when it does work that the direct evidence cannot: when it predicts something, constrains something, or explains a feature that would otherwise be arbitrary.

The bacteriocin analogy has one such job, and it is the most important unsolved problem in the whole framework. **How does a diffusible peptide produce a selective outcome?** If amyloid-β simply damages synapses, it should damage them all. Competition requires that the losing terminal be harmed and the winning terminal spared, and the two may be micrometres apart on the same target cell.

Nisin solves this with the concentration gradient plus the immunity protein: the producer is protected by NisI and by the monomeric state of the peptide at its own surface; the competitor, further away but still within range, meets oligomer. If amyloid-β works this way, selectivity is geometric and no further machinery is needed.

That is what the analogy would buy. Section 7.4 argues that the numbers now available do not support the purchase, and Section 11.3 examines the alternative selectivity mechanism the 2024 review proposes in its place.

3. The Peptide With Two Faces

3.1 The table

The empirical core of the theory is a body of work, largely from other laboratories, showing that amyloid-β does opposite things at low and high concentration. The 2020 submission tabulates it, and the tabulation is worth reproducing in outline because the numbers matter a great deal later.

At low concentration — 100 to 200 picomolar, occasionally to about 2 nanomolar:

Domain	Effect
Presynaptic	Increases releasable and recycling synaptic vesicle pools and release probability [19,20]
Presynaptic	Increases miniature excitatory postsynaptic current frequency, decreases paired-pulse facilitation, increases docked vesicle number — effects abolished by α7 nicotinic receptor knockout [20]
Postsynaptic	Increases postsynaptic density length and plasticity-protein expression [20]
Plasticity	Enhances long-term potentiation; converts early into late LTP; rescues LTP in precursor-protein knockout slices [21,22,20]
Memory	Enhances fear-conditioning consolidation and water-maze performance; converts short-term into long-term memory [22,20]

At high concentration — 50 nanomolar to 1 micromolar:

Domain	Effect
Presynaptic	Reduces miniature current frequency and the recycling vesicle pool
Presynaptic	Inhibits calcium-triggered exocytosis; suppresses release via presynaptic phosphatidylinositol-4,5-bisphosphate depletion
Plasticity	Impairs LTP in slices and in vivo [23,24,25,22]
Memory	Impairs water-maze performance after twenty-minute pretreatment [22]

The structural correlate is the most elegant single observation in the set. At 100 picomolar, amyloid-β induces a *desensitised* conformation of the α7 nicotinic acetylcholine receptor that remains responsive to its cognate agonist; at 100 nanomolar it induces a resting-like conformation that no longer responds [26]. The same peptide, on the same receptor, produces two different

conformational states three orders of magnitude apart — and the sign of the functional consequence flips between them.

There is a second structural observation that supports the assembly-state reading directly: Aβ40 inhibits the oligomerisation of Aβ42 [27], so the ratio between the two species — not merely the amount of either — determines how much toxic assembly occurs. That is precisely the kind of graded control variable a competition system would need, and it is the variable that familial mutations move.

3.2 The trophic arm is not merely pharmacological

If the low-concentration effects were only what happens when you apply a peptide to a slice, they would be of limited interest. They are not. Endogenous amyloid-β is **required**.

Antibody depletion of endogenous amyloid-β, or pharmacological blockade of its production, impairs hippocampal long-term potentiation and contextual fear memory, and the deficit is rescued by picomolar exogenous peptide [28]. Neurons deprived of amyloid-β production die, and are rescued by the peptide [29]. Monomeric amyloid-β protects neurons, acting through the PI3K/Akt pathway [30].

This is the part of the literature the field has most consistently under-weighted. It means the peptide is not an unfortunate by-product with an incidental low-dose effect; it is a required participant in the machinery of synaptic plasticity, and any account of the disease must accommodate a normal function that the disease presumably disturbs.

3.3 What the duality does and does not establish

Three things are firmly established by this literature. Amyloid-β has a physiological signalling function. That function is concentration-dependent with opposite signs at the two ends. And the aggregation state — monomer versus oligomer — is at least part of what distinguishes them.

Two things are not.

First, concentration and oligomeric state are entangled in the source data. Several of the low-concentration effects are reported for preparations described as oligomeric at 200 picomolar [20], and several high-concentration effects for preparations described as monomeric [22]. The theory needs the two variables separable — it needs to say that conformation determines sign and concentration determines conformation — and the source literature does not cleanly permit that separation.

Second, high-concentration toxicity is not by itself a competition signal. A molecule that damages synapses at high concentration is not thereby a molecule that selects *which* synapses to damage. Selectivity is the entire content of the competition claim. It has to come from

somewhere: from receptors expressed differentially on winners and losers, from the local geometry of secretion, or from a co-signal that marks the loser. Huang proposes all three at different points. The receptor argument is examined in §5; the geometric argument remains a diagram rather than a measurement; the co-signal argument — phosphatidylserine — is the 2024 review's contribution and is examined in §11.3.

There is also a result that complicates the simple picture in an interesting direction. Two-photon calcium imaging in amyloid models shows that soluble amyloid-β drives neuronal *hyperactivation*, not silencing, and that hyperactivation in turn drives more amyloid-β release — a vicious cycle in which the peptide's acute effect is excitatory [31]. That is compatible with a homeostatic-signal reading (activity generates the signal that should restrain it, and the restraint fails), but it sits awkwardly with the simple statement that high-concentration amyloid-β suppresses transmission.

3.4 The receptor problem

The theory requires high-affinity receptors that transduce the oligomer's punishment signal, and it names three: PirB (human LilrB2) [25], the Nogo receptor family, and the cellular prion protein [32]. Each has a real literature and each has been proposed to mediate oligomer effects on plasticity.

It also has to survive a sceptical result that Huang cites and does not evade. In 2019 Strittmatter's laboratory conducted a systematic, standardised, head-to-head comparison of the reported amyloid-β receptors for sufficiency, affinity and disease relevance, under uniform conditions [33]. The exercise was necessary because the field's receptor claims come from different laboratories using different peptide preparations, different assays and different definitions of binding, and the number of published receptors substantially exceeds the number that survive standardisation.

Any theory that leans on receptor specificity inherits that uncertainty. This one leans on it heavily, and §5.6 describes a 2025 result that makes the exposure concrete.

4. Competition as a Cell-Biological Programme

4.1 Flower, and the fitness fingerprint

Cell competition is a real and well-characterised phenomenon, worked out principally in *Drosophila*: within a tissue of individually viable cells, relatively less fit cells are actively eliminated by relatively fitter neighbours. Three features define it. The comparison is *local* — it requires direct interaction. It is *relative* — a cell that would survive perfectly well in one neighbourhood dies in another. And it is *active* — the winner does something to the loser, rather than simply out-growing it.

The molecular basis in flies is the Flower code. Flower is a calcium channel that regulates endocytosis, and it exists in isoforms displayed at the plasma membrane that mark a cell as winner or loser [34]. The genetics is unusually clean and unusually informative. Removing Flower from a subset of cells kills that subset; removing it from all cells does nothing. Overexpressing the loser isoform in a subset kills that subset; overexpressing it uniformly does nothing. The molecule therefore does not encode fitness. It encodes *relative* fitness, and it is read by the neighbours. A downstream gene, *ahuizotl* (*azot*), acts as the executioner of the comparison, and eliminating unfit cells through this pathway extends lifespan and maintains tissue health [35].

Two further features make Flower the theory's linchpin.

It is synaptic. In the nervous system, Flower localises to synaptic vesicles at the *Drosophila* neuromuscular junction, relocalises to the presynaptic zone upon vesicle fusion, and there regulates both clathrin-mediated endocytosis and activity-dependent bulk endocytosis [36,37]. The competition molecule sits on the release machinery and is deployed by release.

Endocytosis is where amyloid-β is made. β-Secretase acts in endosomes, and blocking clathrin-mediated endocytosis lowers interstitial amyloid-β in vivo [38]. Synaptic activity regulates interstitial amyloid-β, and the coupling is endocytosis-dependent [39,38].

The inference Huang draws is that this is not coincidence: the neural competition signal is manufactured by the neural competition machinery, on the same organelle, in response to the same trigger.

This is the most elegant step in the argument, and it should be labelled honestly. Flower's synaptic function and Flower's competition function have been demonstrated in different tissues by

different experiments. No experiment has shown that Flower-regulated endocytosis at a synapse produces amyloid-β, or that amyloid-β production is required for Flower-mediated competition, or that the mammalian Flower orthologue does either. The connection is architectural — the parts are in the right place — rather than demonstrated.

A related conservation result does strengthen the mammalian relevance. Expressing the human Flower isoforms in *Drosophila* neurons reveals functional conservation of the code itself: hFWE1 acts as the sole loser isoform and hFWE2 as a winner isoform [40]. The grammar, at least, crosses the phylum boundary.

4.2 The fly's executioners

The second half of the fly template is the elimination machinery, and it is closer to the mammalian brain than one might expect.

When a loser cell is culled in *Drosophila*, hemocytes — the fly's innate immune cells — secrete TNF in the vicinity of the loser; TNF induces the losing cell to expose phosphatidylserine on its outer membrane; exposed phosphatidylserine renders the cell sensitive to the antimicrobial peptide Defensin, which binds it and, together with other TNF effectors, provokes death; and the corpse is removed by hemocyte phagocytosis [41]. Comparable coordination between TNF and defensins is documented in mammalian cell death. Flower has an additional, mechanistically suggestive role in the immune system: it is required for cytotoxic granule endocytosis and for target-cell killing by T lymphocytes [42].

Three players, then: an innate immune cell, a cytokine, an antimicrobial peptide. The same three appear in activity-dependent axon competition in vertebrates — microglia, TNF, and (on Huang's proposal) amyloid-β.

This parallel is the strongest structural argument in the theory, and its force does not depend on resolving whether it reflects homology or convergence. What it establishes is that the *architecture is available*: nature does build competition systems out of exactly these components, and a nervous system that needed one would not have had to invent the parts.

4.3 Competition in the mammalian brain

Neural cell competition has become a field in its own right since the essay was written, which is a modest vindication of the framing. A 2025 review surveys competition across neural progenitors, neurons, astrocytes, oligodendrocytes and microglia, and frames it as a pervasive surveillance mechanism governing survival, arborisation, organisation and territorial colonisation, whose dysregulation may accelerate ageing and exacerbate neurodegeneration [43]. Retinal morphogenesis has been shown to depend on photoreceptors actively translocating to *avoid* spatial competition, with blockade producing apical congestion and lamination defects [44] — which establishes competition for space as a real constraint on developing neural tissue rather than an imported metaphor.

4.4 The sign problem

There is, however, a result from the laboratory that built the Flower code which points the other way, and no fair assessment can pass over it.

Eduardo Moreno's group expressed a secreted form of human amyloid-β42 in *Drosophila* and obtained a model that recapitulates neuronal death and impaired long-term memory — features conspicuously absent from mouse amyloid models. They found the death was cell-fitness-driven neuronal culling, dependent on Flower and *azot*: precisely the machinery Huang invokes. And then they found that this culling was **protective**. Removing the less-fit neurons delayed amyloid-induced brain damage and protected against cognitive and motor decline. Their conclusion, stated in the title, was that contrary to common assumption, neuronal death may have a beneficial effect in Alzheimer's disease [45].

The group has developed this consistently. A 2019 review set out the links between cell competition and Alzheimer's disease from that perspective [46], a 2021 review placed it within the broader competition literature [47], and in December 2025 they reported that dietary manipulation modulates *azot*-dependent competition and locomotor decline in the same model: a synthetic amino acid diet delayed competition activation until day 21, and that delay coincided with improved locomotion and delayed amyloid formation [40].

That last result is genuinely double-edged, and it should be read carefully rather than recruited. Delaying competition helped. But in the same study, *forcing* competition by expressing the human winner isoform hFWE2 in the amyloid model led to accumulation of unfit cells and worse locomotor phenotypes over time. So competition engaged at the right moment removes damage; competition engaged too hard or too early makes things worse.

That is close to a reconciliation, and it may be the correct one: competition is locally protective when it removes cells that cannot be repaired, and destructive when it is chronically over-engaged and removes cells that could have been. But the reconciliation is not made in Huang's documents,

which do not cite this work, and it changes the shape of the disease model if adopted. As the literature stands, the laboratory that owns the mechanism reports that engaging it in an amyloid model helps, and the theory that borrows the mechanism proposes that engaging it too hard is the disease. The sign of the effect is exactly what is at issue, and it is not settled.

5. The Loss-of-Function Genetics

This is the theory's strongest empirical leg, and it deserves careful statement because it is the part most likely to survive whatever happens to the rest.

5.1 The prediction, and why it is not trivial

If oligomeric amyloid-β is a punishment signal that eliminates losing axons, then removing the machinery that transduces it should cause losing axons to *survive*. Not merely to be less damaged — to persist, expand, and occupy territory they should have lost.

This is a directional and counterintuitive prediction. A pure toxicity model predicts that removing the toxin protects: less damage, fewer lost synapses, better outcomes. A competition model predicts something stranger — exuberance, disinhibited growth of structures that should have been eliminated, and a disordered map. The two predictions differ, and the second is the one that has been observed.

5.2 The precursor protein

The premise is that the precursor protein mediates the toxic effects of amyloid-β oligomers: in precursor-protein knockout animals the deleterious effects of oligomers on synaptic plasticity, learning and memory are prevented, and human brain-derived oligomers require the precursor protein to bind synapses and disrupt activity. That makes precursor-protein removal a usable proxy for removing the oligomer signal.

Three results follow the prediction.

Superior colliculus. Precursor-protein loss of function leaves unpruned retinal axons persisting beyond their normal target zone [48].

Somatosensory cortex. Whisker plucking induces axonal growth and pruning of long-range horizontal projections from neurons in surrounding intact whisker representations. Two-photon imaging shows that precursor-protein mutants fail to retract axonal terminals during this rewiring. The critical control is the sparse-deletion experiment: deleting the precursor protein from would-be retracting axons alone reproduces the failure, establishing a cell-autonomous requirement in the axon that should have lost [49]. This is the cleanest single result in the set, because cell-autonomy is what a competition signal — as opposed to a diffuse trophic environment — demands.

Neuromuscular junction. Double mutation of the precursor protein and its homologue APLP2 produces exuberant axonal terminal sprouting and defective synapses, the phenotype

expected when activity-dependent pruning fails [50].

5.3 A complication inside the precursor-protein story

A separate line of work, from Marc Tessier-Lavigne's laboratory, shows that the precursor protein binds death receptor 6 to trigger axon pruning and neuronal death via distinct caspases [51], and that the precursor protein and death receptor 6 function in the same pathway to control axonal pruning **independent of β-secretase** [48].

That last clause matters. If precursor-protein-dependent pruning proceeds without β-secretase, then it proceeds without amyloid-β, and the precursor-protein loss-of-function phenotypes cannot be attributed to loss of the peptide. They may be attributable to loss of the protein's own receptor function.

This does not dispose of Huang's argument — pruning is plainly not a single pathway, and the death-receptor-6 route and an amyloid-β route could operate in parallel or in different contexts. But it means the precursor-protein evidence, taken alone, is consistent with a theory in which amyloid-β plays no part at all. The weight has to be carried by PirB.

5.4 PirB, and the bidirectional test

PirB is the murine homologue of human LilrB2, which Carla Shatz's group identified as a nanomolar-affinity receptor for amyloid-β oligomers, signalling through enhanced cofilin activity — a signature also detectable in human Alzheimer's brain [25]. PirB restricts ocular dominance plasticity [52] and regulates dendritic spine density cell-autonomously [53].

The experiment that matters is the binocular zone. Monocular deprivation during the critical period expands the binocular zone in visual cortex, largely because the normally weaker ipsilateral input is disinhibited and grows. Two manipulations, in opposite directions, were performed on this readout.

Less signal. In PirB mutants the deprivation-induced expansion is *exaggerated* — the losing input grows more than it does in wild types [52].

More signal. In an amyloid-overexpressing model, where oligomeric amyloid-β is elevated, the binocular zone after monocular deprivation is *shrunken*, as though both winning and losing axons were being over-pruned. And that shrinkage is prevented by removing PirB [25].

A two-directional test on a single readout, with the effect of the second manipulation requiring the receptor implicated in the first, is a strong design. This is the best evidence in the whole framework, and it is what an evaluator should reach for if asked what the theory has going for it.

5.5 The immune-molecule context

The PirB result sits inside a larger and long-established literature. Class I major histocompatibility molecules are required for CNS development and plasticity [54]; classical MHC-I molecules regulate retinogeniculate refinement and limit ocular dominance plasticity [55]; MHC-I promotes motor-neuron terminal pruning at the neuromuscular junction; and mutations in CD3ζ, a more widely expressed MHC-I receptor, produce defective eye-specific segregation.

In 2022 Shatz's group added the nonclassical MHC molecule Qa-1, expressed in layer 6 corticothalamic neurons, whose expression begins during the ocular dominance critical period, is regulated by neuronal activity, and whose loss perturbs plasticity — signalling through the CD94/NKG2 receptor pair expressed by microglia [56].

That paper deserves note for a reason beyond its general support of the framework. It identifies a neuron-to-microglia competition signal that is *not* amyloid-β, working through a receptor pair borrowed wholesale from the immune system, doing precisely the job Huang assigns to amyloid-β. The architecture Huang describes is real. Whether amyloid-β is its principal ligand is a separate question, and this is the first hint that the answer may be "one of several."

5.6 What loss of function does not establish — and the 2025 complication

Loss-of-function genetics identifies necessity of a *pathway*. It does not identify the ligand. PirB knockout tells us PirB is required for the pruning; it does not tell us what activates PirB in vivo.

In September 2025 that distinction became concrete and consequential. Shatz's group reported that C4d — a cleavage product of complement C4 previously regarded as functionless — binds LilrB2 and PirB with nanomolar affinity; colocalises with LilrB2 at excitatory synapses in human cerebral cortex, and with amyloid-β in Alzheimer's disease; rises with age and rises further in the disease; and, applied to mouse cortex, produces a significant decrease in dendritic spine density on layer 5 pyramidal neurons that is *completely prevented* by PirB knockout [57].

The receptor Huang uses as his exemplar of amyloid-β-mediated punishment therefore has a second high-affinity ligand, of complement origin, which is elevated in the disease and is sufficient on its own to drive spine loss through that receptor. Three readings are available, and the evidence does not yet choose between them.

1. **Convergence.** Amyloid-β and C4d converge on one receptor. This is compatible with Huang and arguably a strengthening: it would mean the punishment channel is served by more than one ligand, exactly as the fly template — TNF *plus* Defensin — suggests.
2. **Displacement.** C4d is the physiological ligand and amyloid-β an interloper. This is damaging: the pruning architecture would be complement-based, with amyloid-β binding a receptor that evolved for something else, and the developmental competition evidence would

no longer be evidence about amyloid-β.

3. **Sequential.** Both, at different times of life. Developmental pruning is complement-driven; amyloid-β's engagement of the same receptor is a feature of the aged or diseased brain.

A fourth consideration cuts across all three. LilrB2 signalling inhibits TREM2 function and suppresses microglial activity [58] — so the receptor at the centre of the punishment argument is also a brake on the phagocyte, which means engaging it has opposite consequences for the neuron and for the microglion. Any account of what amyloid-β does at this receptor has to specify which cell is being addressed.

Reading 3 is the most parsimonious given that C4d rises with age. It would preserve the disease relevance of amyloid-β–PirB signalling while removing the developmental competition claim from which the theory draws much of its authority — leaving the framework with a strong account of pathological pruning and a weaker claim to be describing a normal process.

6. The Adult Module: Activity, Amyloid-β, Glia, Cytokine

Axon competition is a developmental phenomenon. To make it a theory of a disease of late life, Huang argues that the same module is retained in the adult brain to serve homeostatic plasticity — the mechanism by which neurons scale synaptic strength up when activity falls and down when it rises [59].

6.1 The loop as proposed

The loop has four components, three of them independently established.

Activity drives amyloid-β production. Synaptic activity regulates interstitial fluid amyloid-β in vivo, and the coupling requires endocytosis [39,38]. Amyloid-β in turn depresses synaptic transmission: precursor-protein processing is coupled to synaptic function, and the peptide acts as an endogenous negative feedback that keeps hyperactivity in check [60].

Arc closes the loop postsynaptically. Arc/Arg3.1 is the activity-induced cytoskeletal protein that drives AMPA-receptor removal during homeostatic scaling [61], and it independently regulates an endosomal pathway essential for activity-dependent amyloid-β generation [62]. One protein, both jobs — which is either a striking coincidence or a sign that the two processes are one process.

Glial TNF sets synaptic gain. Glial TNF is required for synaptic scaling: chronic activity blockade raises glial TNF, which drives AMPA-receptor insertion and strengthens synapses [63,64]. TNF is also required for one component of experience-dependent plasticity in developing visual cortex [65] and for terminal elimination at the vertebrate neuromuscular junction [66]. A TNF receptor superfamily member, Fn14, is required for experience-dependent retinogeniculate refinement [67].

Monomeric amyloid-β restrains glial cytokine release. This is the step Huang supplies and the one that closes the circuit. If activity raises amyloid-β, and monomeric amyloid-β suppresses glial TNF, then amyloid-β is the messenger that tells the glial cell how active the circuit is — and glial TNF is the effector that adjusts synaptic gain accordingly.

The architecture is coherent, and the fourth component is the theory's own contribution. Section 7 is about the attempt to demonstrate it.

6.2 Microglia as the third party

The framework also requires microglia to be genuine participants in activity-dependent competition rather than bystanders, and here the evidence is strong and independent. Complement C1q and C3 tag synapses for microglial engulfment during developmental refinement [68], and microglia sculpt postnatal circuits in an activity- and complement-dependent manner [69]. Microglial P2Y12 is necessary for ocular dominance plasticity [70]. Sensory lesioning induces microglial synapse elimination through ADAM10 and fractalkine signalling [71]. And noradrenergic signalling in the wakeful state inhibits microglial surveillance and constrains synaptic plasticity — meaning the microglial contribution is gated by arousal state [72].

That last result is worth flagging because it connects the module to the sleep argument in §6.4 by a mechanism the source documents do not draw out: if norepinephrine suppresses microglial surveillance during waking, then the microglial arm of the competition module is licensed to operate mainly during sleep.

6.3 A 2024 refinement that matters

The TNF component has since been sharpened in a way that partly redirects the model, and it is important enough to state at length.

Stellwagen's laboratory showed in 2024 that the glial source of TNF for homeostatic plasticity is specifically the **astrocyte**, not the microglion. Hippocampal cultures depleted of microglia still raise TNF after activity deprivation and still express scaling. Slice cultures with conditional deletion of TNF from microglia express scaling normally. Slice cultures with conditional deletion of TNF from astrocytes do not. Astrocytes sense falling activity through glutamate spillover, which reduces NF-κB signalling and TNF transcription; chronic activity blockade raises TNF in an NF-κB-dependent manner [73].

This is not a refutation. Huang's figures say "glia," and he explicitly notes that astrocytes behave similarly to microglia in cytokine regulation and likely perform similar functions. But it has a real consequence: the cell that runs the homeostatic arm of the module is not the cell that his disease model places at the centre. A theory that derives *microglial* hyperactivity from the failure of a loop whose effector is *astrocytic* has a gap in the middle of it, and closing it requires either showing that monomeric amyloid-β restrains astrocytes too (untested) or accepting that the developmental/homeostatic argument and the disease argument run through different cells.

The same group's review of how much of this literature remains in reduced preparations is candid [74], and its 2025 activity-regulated screen shows that TNF is one of a number of immune signalling molecules under activity control, with interferon-γ emerging as a second modulator of synaptic function [75]. The module is real; it is more populated than the four-component version implies.

6.4 Sleep

The 2024 review adds sleep as the brain state in which the module runs, and this is among its better-supported sections.

Amyloid-β tracks the sleep–wake cycle. Interstitial amyloid-β rises with wakefulness and falls with sleep, under orexinergic control; chronic sleep restriction increases plaque formation and a dual orexin receptor antagonist decreases it [76]. Sleep increases the clearance of interstitial solutes including amyloid-β [77]. In humans, a single night of sleep deprivation measurably increases amyloid burden in hippocampus and thalamus [78].

Amyloid-β oligomers induce sleep. This is the more novel direction. In zebrafish, exogenous long amyloid-β oligomers dampen neuronal activity and increase sleep, specifically by increasing the number of sleep bouts rather than lengthening them — that is, by boosting sleep *initiation*. The effect is prevented by prion-protein mutation and blocked by inhibiting mGluR5 or Fyn [79], implicating exactly the receptor complex proposed to mediate the oligomer's synaptic effects.

Sleep scales synapses down, and the mechanism overlaps. Homer1a drives homeostatic scaling-down of excitatory synapses during sleep: it accumulates at the postsynaptic density under adenosine and is removed by norepinephrine, then activates ligand-independent mGluR1/5 signalling that removes surface AMPA receptors [80]. Ultrastructural reconstruction shows the axon–spine interface shrinks by roughly a fifth across the sleep period, in proportion to synapse size and sparing the largest synapses [81].

The assembled claim is that amyloid-β oligomers, sleep, mGluR5 and Homer1a form one system in which the peptide both induces the state and specifies which synapses are weakened within it. The individual links are well evidenced. The assembly is the author's, and the crucial junction — that amyloid-β oligomers regulate the *selectivity* of sleep-dependent scaling — is proposed rather than shown.

It is nonetheless the most attractive unexplored prediction in the framework, because it is testable in a single experiment: measure sleep-dependent synaptic scaling and its size-dependence in animals with and without the proposed oligomer receptors.

7. The 2024 Experiment: A Receptor for the Monomer

From 2020 onward, the theory's most exposed claim was that monomeric amyloid-β restrains glial inflammatory activity. Nothing in the literature specified how. The 2024 *eLife* paper is the attempt [4], and it is the only primary experimental test of the framework by its author. It deserves detailed treatment.

7.1 What was done

The entry point was not amyloid at all. It was a developmental phenotype.

Deleting *Ric8a* — which encodes a chaperone and guanine-nucleotide exchange factor required for the stability of heterotrimeric G-protein α subunits — from dorsal forebrain progenitors using *Emx1-Cre* produced neuronal ectopia in lateral cortex. The lesion sequence was characterised carefully: laminin debris accumulated at embryonic day 12.5 while the basement membrane was still intact; focal breaches appeared at E13.5, some without ectopia; by E14.5 ectopia was always associated with breaches; radial glial fibres subsequently extended beyond the breach sites. Cajal-Retzius cells, reelin expression and preplate splitting were normal, and neuronal migration and laminar markers were normal outside the ectopic regions. The mechanism was therefore excessive basement-membrane *degradation*, not defective maintenance, and Gαi proteins were severely depleted in mutant cortices.

The cell-type dissection was thorough and, unusually, negative everywhere it was expected to be positive. Deleting *Ric8a* from Cajal-Retzius cells (*Wnt3a-Cre*), excitatory neurons (*Nex-Cre*), inhibitory neurons (*Dlx5/6-Cre*), neural progenitors (*Nestin-Cre*) or early forebrain progenitors (*Foxg1-Cre*) produced no ectopia. The responsible cell was non-neural. *Emx1-Cre*, it turned out, is active in microglia.

Microglial *Ric8a*. Microglia-specific deletion (*Ric8a:Cx3cr1-Cre*) produced hyper-responsive microglia — elevated TNF, IL-1β and IL-6 on lipopolysaccharide or poly(I:C) stimulation — but no ectopia on its own. Adding an immune stimulus produced the phenotype: 10 of 19 microglia-specific mutants given lipopolysaccharide at E11.5–12.5 developed ectopia, against 0 of 32 controls. Combining the microglial and neural deletions produced severe ectopia in all six animals examined. A second insult, or a second deficit, was required.

Microglial precursor protein. Deleting the amyloid precursor protein from microglia produced a parallel result: elevated TNF, IL-1β, IL-6 and MCP1 from fresh peritoneal

macrophages on stimulation, with increased cytokine transcription; and ectopia in 6 of 31 mutants given lipopolysaccharide, against 0 of 81 controls.

The amyloid experiments. Wild-type microglia treated with monomeric amyloid-β40 during lipopolysaccharide or poly(I:C) stimulation showed potent suppression of TNF, IL-6, IL-1β and MCP1 secretion, and suppression of IL-6 and IL-1β transcription. The tested range was 50 to 500 nanomolar, and suppression of TNF and IL-6 was significant at the lowest concentration tested. In precursor-protein-null microglia and in precursor-protein-null peritoneal macrophages the suppression was abolished. In APLP2-null microglia it was preserved, establishing specificity to the precursor protein rather than to the wider family. In *Ric8a*-null microglia, suppression of TNF and IL-6 was abolished while suppression of IL-1β was preserved — a partial dependence the authors report as such and interpret as evidence that heterotrimeric G proteins mediate only part of the signalling. Oligomeric preparations, added in revision as a control, were pro-inflammatory.

The effector. Pharmacological suppression of inflammation (an Akt inhibitor plus a Stat3 inhibitor, given at E12.5) nearly eliminated the ectopia and suppressed astrogliosis. MMP9 was expressed in a sparse microglia-like population at E13.5; MMP9 protein was elevated in mutants (35.7 ± 1.7 versus 24.8 ± 0.2 arbitrary units, $p = 0.002$) and gelatinase activity was elevated (3.72 ± 1.86 versus 1.00 ± 0.06, $p = 0.028$), with MMP2 activity unchanged. Both a broad-spectrum MMP inhibitor and an MMP9/13-selective inhibitor reduced ectopia number and size, and the anti-inflammatory treatment reduced MMP9 activity to control levels.

7.2 What it means

Assembled, the paper proposes a pathway: monomeric amyloid-β → amyloid precursor protein → Ric8a-stabilised Gαi → suppression of microglial cytokine transcription and secretion → restrained MMP9 → intact basement membrane.

Three things make this consequential.

It supplies the theory's missing mechanism. Before this, "monomeric amyloid-β is anti-inflammatory" was an inference assembled from scattered observations — that non-fibrillar amyloid-β lacks pro-inflammatory effects, that monomers activate PI3K/Akt, that amyloid-β inhibits T-cell activation under monomer-promoting conditions. Now there is a candidate receptor, a candidate transducer, and a candidate effector, with genetic epistasis between them and an in vivo phenotype.

It makes the precursor protein a receptor for its own product. That is an unusual architecture and it revives a claim that has been dormant for three decades. In 1993, Nishimoto and colleagues reported in *Nature* that the amyloid precursor protein complexes with the brain GTP-binding protein Go [82]. The result was never comfortably assimilated: the precursor protein has the topology of a receptor but no accepted ligand, and a G-protein coupling with no ligand and

no function is hard to build on. If the 2024 finding holds, the missing ligand is the protein's own cleavage product, and the missing function is restraint of innate immunity. Whether or not the specific pathway survives, that is a productive hypothesis about a thirty-year-old orphan result.

It names MMP9 as the executioner. This connects the framework to a large literature on matrix proteases in brain disease and to human data: plasma MMP-9 tracks disease severity in Alzheimer's disease with a sex difference [83], and the plasma MMP-9/TIMP-1 ratio has been proposed as a biomarker [84]. It also supplies a mechanism by which a microglial state change becomes structural damage — the gap in most inflammation-centred accounts, which stop at cytokines.

7.3 What it does not show

The paper's own reviewers pressed hard on the central point and the record is public.

The in vivo phenotype is a *Ric8a* phenotype and a precursor-protein phenotype. No experiment shows monomeric amyloid-β activating this pathway in a living brain. One reviewer stated the objection bluntly: there is no proof that amyloid-β is the activating signal in vivo, the title mentions only amyloid-β, and the abstract is overwhelmingly about amyloid-β while the amyloid evidence is a single figure of cell culture. The authors conceded the point explicitly, stating that they do not currently have evidence that in the developing cortex amyloid-β monomers play a role in inhibiting microglia. They also note that the precursor protein has other ligands that could be responsible for the developmental phenotype.

Other specific criticisms stand on the record. The monomeric state of the peptide preparations was not independently verified after addition to culture medium — a non-trivial omission given amyloid-β's strong tendency to polymerise — though oligomer controls showing opposite effects were added in revision. The ectopia in precursor-protein mutants was inconsistent, appearing in a minority of animals and often in only one hemisphere, which prevented meaningful MMP9 analysis in that genotype. Gel zymography was queried as a quantification method. Whether *Emx1-Cre* is genuinely active in microglia was questioned. And the claim that the precursor protein and Ric8a act in one pathway was argued to rest on phenotypic similarity rather than direct evidence.

None of this makes the result wrong, and the genetics within the cultured system is clean. It does mean the paper establishes an in vitro pathway and an in vivo phenotype and links them by inference.

7.4 The concentration problem

There is a further difficulty, which the review process did not raise and which bears on the theory rather than on the paper.

The concentrations at which monomeric amyloid-β40 suppressed microglial cytokines were **50, 200 and 500 nanomolar**, with significant suppression of TNF and IL-6 at the lowest concentration tested.

Now return to the summary table in §3.1, and note where 50 nanomolar falls in it. It is the exact bottom of the *high-concentration* band — the row that reads "50–500 nM Aβ40 reduces the frequency of miniature currents." The concentration at which monomeric amyloid-β begins to restrain a microglion is the concentration at which amyloid-β begins to suppress synaptic transmission.

The trophic neuronal effects, meanwhile, occur at 100 to 200 *picomolar*. The two protective actions the theory requires — trophic support of the neuron and restraint of the microglion — are therefore separated by a factor of roughly 250 to 500, and the lower bound of the microglial effect has not been probed: no concentration below 50 nanomolar was tested.

This matters, and the reason should be stated precisely rather than dismissed or overstated.

The bacteriocin analogy works because in bacteria **concentration drives conformation**. Nisin is monomeric near the producing cell and oligomerises as local concentration rises, so a single concentration gradient generates two opposite activities at two distances from one source. That is what converts a diffusible molecule into a competition signal with spatial structure, and it is the specific problem — selectivity — that §2.4 identified as the analogy's job.

In the amyloid case as now assembled, the variable that separates protective from destructive is not concentration but **conformation**, and conformation is held constant experimentally by the preparation method. This is entirely compatible with the observations: the peptide can perfectly well have a monomeric anti-inflammatory action with an EC50 in the high nanomolar range and a monomeric trophic action with an EC50 in the picomolar range. Different receptors, different affinities, same ligand. But it is not the nisin architecture. It is two separate receptor systems that happen to share a ligand and a conformational requirement.

Three consequences follow.

The spatial-gradient model loses its support. The 2020 figures depict a two-layered cloud around a secreting terminal, with monomer near the membrane and oligomer at distance. On the concentrations now reported, a gradient carrying enough monomer near the membrane to restrain a microglion — 50 nanomolar at the very least — would be several hundred-fold above the neuronal trophic range everywhere within the cloud, and squarely inside the range that impairs plasticity.

The quorum-sensing language stops mapping. Quorum sensing depends on a single threshold at which a reporter concentration triggers a coordinated switch. A system with two

protective thresholds several hundred-fold apart, one of them coinciding with the onset of the destructive effect, is not reporting one variable.

The most testable in vivo prediction becomes harder to formulate. Interstitial amyloid-β in the healthy rodent brain is in the low nanomolar range at most, and free monomer considerably below that — below the lowest concentration at which the microglial effect has been demonstrated. Either the in vivo effect operates at concentrations not yet tested, or it operates in microenvironments where local concentration is much higher than bulk interstitial fluid, or it does not operate.

None of this touches the finding. It touches the analogy the finding was recruited to support, and it suggests the framework would be stronger if it dropped the concentration axis and argued the conformational one directly — at the cost of losing its account of selectivity, which would then have to be carried entirely by the phosphatidylserine mechanism of §11.3.

8. The Disease Model

8.1 The claim

The 2020 and 2023 statements put the disease model in one sentence: defects in the amyloid-β-mediated anti-inflammatory feedback pathway, arising from different primary perturbations in different forms of the disease, converge on chronic microglial hyperactivity, and that is what Alzheimer's disease is.

The mechanism of convergence is monomer depletion. Aggregation removes monomer from the parenchyma. Monomer restrains microglia. Therefore aggregation disinhibits microglia. Disinhibited microglia raise cytokines. Cytokines drive tau pathology, and also raise precursor-protein cleavage and amyloid production, which aggregates further. The loop closes and runs away.

The model is explicitly a two-entrance model.

In familial disease the entry is genetic. Mutations raise production or the Aβ42:Aβ40 ratio; aggregation follows; monomer is consumed; the brake is released. This preserves the genetic evidence that makes the amyloid cascade compelling while reinterpreting what the aggregation does.

In sporadic disease the entry may be at the other end. A primary defect in the anti-inflammatory arm — genetic (the microglial risk genes), epigenetic (innate immune memory laid down by infection, sleep-disordered breathing, head injury, ageing), or metabolic — raises cytokines first. Cytokines then raise precursor-protein cleavage and amyloid production, which aggregates, which depletes monomer, which disinhibits further.

The second route is the framework's most distinctive structural claim, because it makes amyloid pathology a *consequence* of inflammation in most sporadic disease while keeping it causal in familial disease — and it explains why the two look alike at autopsy despite arriving from opposite directions.

One terminological caution should be entered here and carried forward. "Microglial hyperactivity" was a serviceable term in 2020 and is no longer sufficient. Single-cell work has since resolved microglia into distinct states — the disease-associated phenotype defined by a TREM2-dependent transcriptional programme [85], and the lipid-droplet-accumulating phenotype of the aged brain, which is simultaneously *defective* in phagocytosis and *elevated* in reactive oxygen

species and cytokine output [86]. A model whose central lesion is "too much microglial activity" has to say which activity, since the states that matter are not simply more or less of one thing. The lipid-droplet phenotype is the sharpest case: on any one-dimensional activity axis it is both hyperactive and hypoactive at once.

8.2 The evidence for depletion the model cites

The critical human observation is a neuropathological study finding that soluble Aβ40 falls from roughly half of total brain amyloid-β in normal controls, to 8% in pathological ageing, to 2.7% in Alzheimer's disease [87]. On the standard reading this simply reflects growth of the insoluble pool. On Huang's reading it is the depletion of a functional species. Both readings are consistent with the data; the difference is which quantity is taken to be doing the work.

A supporting animal observation: in models of cerebral amyloid angiopathy, early parenchymal plaque formation diverts amyloid away from blood vessels — that is, an aggregate acts as a sink that depletes the soluble pool available elsewhere.

8.3 What the model explains that a pure cascade does not

Four things, and they are not trivial.

The plaque–cognition dissociation. Plaque burden correlates weakly with cognitive status [88], and regional hypometabolism is unrelated to regional plaque burden [89]. On a deposit-driven account this is an embarrassment managed by appeal to tau. On a depletion account it is expected: what matters is residual monomer, and two people with identical deposits can differ in how much soluble peptide they retain.

Resistance despite extreme amyloid load. The APOE3-Christchurch homozygote who resisted autosomal-dominant Alzheimer's disease for roughly three decades despite extraordinarily high amyloid burden [90] is anomalous on a deposit account and unsurprising on a functional-species account.

Why anti-amyloid trials have underperformed. Huang's 2020 statement — that most anti-amyloid agents target monomers as well as larger aggregates, and may not only fail to restore anti-inflammatory signalling but unwittingly compromise it further — is the model's sharpest prediction and the one most exposed to falsification. Section 10 tests it.

Why tau pathology is always accompanied by amyloidosis in sporadic disease. The tau hypothesis has no principled explanation for the invariable co-occurrence. The depletion model supplies one: whatever raises the cytokines that drive tau also raises precursor-protein cleavage and amyloid production, so the two are yoked by a shared upstream driver rather than by a direct causal arrow between them.

8.4 The tau arm

The claim that microglial cytokine signalling drives tau pathology is well supported and has strengthened since 2020. IL-1β signalling drives tau hyperphosphorylation and aggregation via p38 MAPK, and fractalkine-receptor deficiency exacerbates it [91]. NLRP3 inflammasome activation drives tau pathology, with inflammasome blockade reducing tau hyperphosphorylation by altering kinase and phosphatase activity [92]. Microglia drive apolipoprotein-E-dependent tau-mediated neurodegeneration [93]. TREM2 function impedes tau seeding in neuritic plaques [94], and partial versus complete TREM2 loss have differential effects on microglial injury response and tauopathy [95]. Clearance of senescent glia prevents tau-dependent pathology and cognitive decline [96]. In human three-dimensional culture, adding microglia to a neuron–astrocyte system increases cytokine secretion and induces neuronal loss [97], and the Aβ42:Aβ40 ratio — not total amyloid-β — drives tau pathology [98].

This arm is the best-evidenced part of the disease model. It is also the least distinctive: it is shared with every inflammation-centred account of the disease and does not require the competition framework. What the competition framework adds is a reason why the inflammation begins — the withdrawal of a physiological brake — rather than an appeal to inflammation as a primitive.

8.5 The route from risk factors to microglial state

The 2020 essay devotes considerable space to how genetic and non-genetic risk converges on microglial activity, and this material has largely disappeared from the later statement, which is a loss.

The genetic argument is straightforward and well supported: late-onset risk genes are enriched in microglial pathways [99], and many of them — TREM2, APOE, CD33, the endosomal trafficking genes — normally suppress or shape microglial inflammatory activity, so loss of function releases it.

The cholesterol argument is more original. Microglial cholesterol synthesis is part of the pro-inflammatory programme, and SREBP2 activation has several feedforward links to inflammation: it promotes NLRP3 translocation to mitochondria-adjacent sites, binds inflammatory gene promoters directly, and generates mevalonate, which induces trained immunity through mTOR activation and histone modification. Because astrocytes synthesise the bulk of brain cholesterol and cholesterol does not readily cross the blood–brain barrier, failure of astrocytic supply raises microglial synthesis and thereby microglial inflammatory tone. This is a specific and testable route from a lipid phenotype to a microglial state, and it is the framework's best explanation for why cholesterol-metabolism genes appear so prominently among risk loci.

The trained-immunity argument supplies the link for non-genetic risk: peripheral inflammatory stimuli induce innate immune memory in microglia that alters disease pathology months later [100],

and because microglia are long-lived, an exposure can leave a lasting epigenetic mark. This is the framework's account of how infection, sleep-disordered breathing and head injury raise risk decades before onset.

None of this is unique to the competition theory, and all of it would survive the theory's failure. But it is the part of the 2020 essay that engages most directly with epidemiology, and the 2024 statement is poorer for dropping it.

8.6 The apolipoprotein E addition, and the paradox it creates

The 2024 review adds apolipoprotein E as a second self-protection system, in explicit parallel to the bacterial immunity protein [3]. The parallel is drawn carefully: bacteria engaging in competition upregulate immunity proteins that bind the antimicrobial peptide and impede its aggregation near the producing cell, and Huang proposes that apolipoprotein E does the same job for amyloid-β.

The supporting case is real. Purified apolipoprotein E binds amyloid-β; kinetic studies consistently show it slows the growth of toxic oligomeric species; electron microscopy shows it prevents oligomer formation; it may promote formation of filaments or high-molecular-weight assemblies that are less toxic; the related protein clusterin sequesters oligomers similarly. In vivo, removing apolipoprotein E reduces plaque compaction — plausibly deleterious, since compaction sequesters diffusible oligomers — and raises soluble brain amyloid-β. Apolipoprotein E also promotes amyloid-β degradation by glia through neprilysin and cholesterol modulation, is a ligand for TREM2 [101], and suppresses inflammatory activation of microglia and macrophages.

Then comes the complication. Apolipoprotein E promotes transcription of the precursor protein and secretion of amyloid-β monomers in human neurons — a *further* protective route on this model, since it raises the trophic species — and on the evidence cited, the ε4 allele is the **most** potent of the three alleles at doing so [102]. Huang flags this as surprising and it is: the model's central protective mechanism is executed best by the allele that confers the greatest risk. His accommodation is that chronic ε4-driven elevation of precursor protein and amyloid-β may itself be the source of risk — which converts a protective mechanism into a pathogenic one by changing the time constant, and is not independently supported. The wider ε4 literature does not settle the matter in either direction: the allele produces widespread molecular and cellular alterations across every major brain cell type in human induced-pluripotent-stem-cell models [103], and its effects can be reversed by a small-molecule structure corrector [104] — which locates the pathogenic property in the protein's conformation rather than in any one of its activities.

A third strand, developed at length, proposes that *neuronal* apolipoprotein E does the opposite job from astrocytic apolipoprotein E — that it sits in a gene regulatory network with MHC-I, Tap2, C1qa, interleukin-4, Stat1 and RORβ that promotes competitive elimination, and that this is why apolipoprotein-E-expressing and RORβ-expressing neurons are selectively vulnerable.

The result is a system in which one gene is protective in astrocytes and destructive in neurons, in which the risk allele performs the protective function best, and in which the sign of every effect depends on cell type, concentration and allele. Each individual claim has support. But the framework loses falsifiability at this point: for almost any observed effect of apolipoprotein E, one of these arms accommodates it. This is where the theory's explanatory reach most clearly outruns its constraint, and §14 states falsifiers explicitly because the source documents do not.

8.7 The DNA-damage arm

The 2024 review adds one further self-protection mechanism worth recording because it is genuinely novel and largely untested: that the precursor protein's *intracellular* cleavage product participates in DNA-damage repair, protecting the competing neuron from the reactive oxygen species that activity-dependent plasticity generates.

The chain is: genotoxic agents induce precursor-protein cleavage releasing the intracellular domain and its partner FE65 in a γ-secretase-dependent manner; the intracellular domain promotes nuclear translocation of FE65; FE65 binds the Tip60–TRRAP histone acetyltransferase complex, which mediates histone H4 acetylation and repair-protein loading at damage sites; and FE65 also stabilises the Bloom syndrome helicase, which promotes homologous recombination at actively transcribed genes.

If this holds, the precursor protein produces two products serving one purpose: an extracellular peptide that arbitrates the competition and an intracellular fragment that repairs the collateral damage the competition inflicts on the winner. It is an attractive symmetry. It is also the least tested claim in the framework, and the review extends it further — to mitochondrial DNA repair, and to a proposal that nuclear phospho-tau in tauopathies may be a DNA-repair response — on inference alone.

9. The Human Evidence That Arrived Afterwards

The most striking development since the 2020 essay is that a separate research programme, working from human biomarker data and with no reference to competition, antimicrobial peptides or microglia, arrived at the same central inference: that losing the soluble monomer matters more than gaining the aggregate.

9.1 The observations

In 598 amyloid-positive participants in the Alzheimer's Disease Neuroimaging Initiative, cerebrospinal soluble Aβ42 was higher in those with normal cognition (864 pg/ml) than in mild cognitive impairment (769) or dementia (617), and the relationship held within every tertile of amyloid PET burden. The adjusted effect size for soluble Aβ42 exceeded that for PET burden in distinguishing normal cognition from dementia (0.82 versus 0.40) and mild impairment from dementia (0.60 versus 0.26). Each standard deviation increase in Aβ42 was associated with roughly sixfold greater odds of normal cognition versus dementia. Higher soluble Aβ42 also tracked better neuropsychological performance and larger hippocampal volume [105].

The finding was then reproduced longitudinally in a genetic cohort. Among 108 amyloid-positive carriers of *APP*, *PSEN1* or *PSEN2* mutations followed for a mean of 3.3 years, higher cerebrospinal Aβ42 predicted lower risk of clinical progression (adjusted relative risk 0.36; 95% CI 0.19–0.67) better than lower PET burden did (0.81; 0.68–0.96). The Aβ42 level required to predict low risk rose as amyloid burden rose — as though a threshold of residual soluble peptide had to be maintained against an increasing sink [106].

9.2 The interpretation

Espay and colleagues have built these observations into an explicit loss-of-function programme: soluble amyloid-β consumption [107], the proteinopenia hypothesis [108], and in November 2025 a therapeutic proposal in *Brain* to *restore* Aβ42 and γ-secretase function rather than reduce them [109].

Their stated case has five parts: that cerebrospinal soluble Aβ42 in Alzheimer's disease is about half that of healthy individuals and drops further at dementia onset in genetic forms and in Down syndrome; that roughly 90% of pathogenic *PSEN1* mutations *reduce* γ-secretase activity and Aβ42 production; that lower γ-secretase activity correlates with lower soluble Aβ42, earlier onset, worse cognition and faster progression; that higher soluble Aβ42 associates with preserved cognition and delayed dementia in both sporadic and familial amyloid-positive disease; and that monomeric Aβ42

supports memory in the manner of a neuropeptide.

A mechanistic result from a third direction points the same way. Human Aβ42 — but not murine Aβ42, and not the human p3 fragment — inhibits γ-secretase by product feedback, causing accumulation of unprocessed substrates including precursor-protein, p75 and pan-cadherin C-terminal fragments, and inducing p75-dependent neuronal death [110]. Elevated Aβ42 in the endolysosome would thereby shut down a signalling enzyme with dozens of substrates. That is a loss-of-function toxicity distinct from both aggregation toxicity and monomer depletion, but it is on the same side of the ledger: what hurts is the failure of a normal signalling process, not the presence of a deposit.

9.3 What convergence is worth

Two independent programmes, with different data, different vocabularies and different theoretical commitments, converging on "the soluble species is the functional one and its loss is what hurts" is meaningful. Independent arrival at the same conclusion from different evidence is the ordinary way an idea earns credibility, and it is worth more than either programme accumulating further evidence of its own kind.

Three qualifications are owed.

The two accounts differ on why monomer matters. For Espay's group it is a neuropeptide supporting neuronal function directly. For Huang it is principally a brake on glia. Those are different mechanisms with different predictions — for instance, about whether monomer restoration would help in a brain with no microglia — and the human data speak to neither.

The human data are correlational. The first study is cross-sectional; the second is observational. Reverse causation is not excluded: a brain degenerating faster may produce less amyloid-β, rather than a brain with less amyloid-β degenerating faster. Neuronal loss reduces the cells that make the peptide.

The measured quantity is several steps from the theoretical one. Cerebrospinal Aβ42 falls as amyloid is sequestered into plaque, so residual soluble Aβ42 partly indexes how much has aggregated — which is precisely the confound at issue. And "soluble Aβ42 in cerebrospinal fluid" is not "monomeric Aβ42 in brain parenchyma at a synapse."

10. The Trials as an Adjudication

Between 2023 and 2026, four sets of clinical results became available that bear on the model's central therapeutic prediction. Read as a set they constitute the closest thing to a natural experiment on the monomer question that this field has produced.

10.1 Antibodies that bind the monomer

Solanezumab binds the mid-domain of soluble monomeric amyloid-β. In the A4 trial, 1,169 people with preclinical Alzheimer's disease — cognitively normal, amyloid-positive, aged 65 to 85 — were randomised to solanezumab at up to 1,600 mg every four weeks or placebo, and followed for 240 weeks. The primary cognitive endpoint showed no benefit: mean change −1.43 with drug versus −1.13 with placebo, difference −0.30 (95% CI −0.82 to 0.22, p = 0.26). Amyloid PET rose in both arms, by 11.6 centiloids on drug and 19.3 on placebo [111].

This is the single most informative negative result available on the monomer question. It was the best-designed test of early monomer removal that will ever be run: the right target, the right population, before symptoms, over four and a half years. It produced nothing, with a point estimate on the wrong side of zero.

Crenezumab binds both monomers and oligomers. In the Alzheimer's Prevention Initiative trial in Colombia, 252 cognitively unimpaired members of the *PSEN1* Glu280Ala kindred — the largest known autosomal-dominant Alzheimer's kindred, with near-certain onset before 65 — were randomised to crenezumab or placebo, with dose escalated during the trial, and followed for five to eight years with final data collection in 2022 and full publication in *Lancet Neurology* in February 2026. Ninety-four percent completed. The trial did not demonstrate significant benefit on either of its dual primary endpoints [112].

Two antibodies that engage the monomer; no benefit in either, in the two populations — preclinical sporadic and presymptomatic autosomal-dominant — where an intervention on the earliest process should have had its best chance.

10.2 Antibodies that spare the monomer

Lecanemab preferentially targets soluble aggregated amyloid-β with activity across oligomers, protofibrils and fibrils [113], and **donanemab** targets pyroglutamate-modified amyloid-β found only in established plaque. Both slowed decline in phase 3. Lecanemab reduced decline on the Clinical Dementia Rating–Sum of Boxes by 27% at 18 months [114]. Donanemab, in 1,736 participants, produced a 3.25-point difference on its primary integrated rating scale in the low/medium-tau population and 2.92 points in the combined population, with 23 of its 24 gated outcomes statistically significant [115]. Aducanumab's selectivity for aggregated over monomeric forms is documented structurally and kinetically [116]. The contrast is the point. The agents that spare the monomer while removing aggregate produced effects; the agents that bind the monomer did not.

10.3 The size of the effect, and the 2026 dispute

Honesty requires stating that the effects in question are small and that their clinical meaningfulness is under active challenge.

A Cochrane review published in April 2026 assessed amyloid-β-targeting monoclonal antibodies in mild cognitive impairment and mild dementia, covering 17 randomised trials and 20,342 participants across seven antibodies, with GRADE certainty assessment of cognition, dementia severity, functional ability, imaging abnormalities, serious adverse events and mortality [117]. Its assessment prompted a formal rebuttal in July 2026 from a large international group of clinicians and researchers, who argued that the review was seriously flawed [118].

This dispute does not resolve the monomer question either way — it concerns the magnitude and interpretation of the aggregate-clearing arm, not the sign of the monomer arm. But a paper that cites the positive trials in support of a theory owes the reader the information that their interpretation is contested.

10.4 The antibody that activated microglia

The fourth result is the most directly diagnostic, because it tests the model's other half.

AL002 is a humanised agonistic antibody against TREM2, designed to *increase* microglial activity. The preclinical rationale was strong: anti-TREM2 antibody induced microglial proliferation and reduced pathology in an amyloid model [119], and TREM2 is both a major risk locus and a receptor for amyloid-β [120] and for apolipoproteins [101], required for synapse elimination and normal connectivity [121].

The INVOKE-2 phase 2 trial randomised 381 participants with early Alzheimer's disease to AL002 at 15, 40 or 60 mg/kg or placebo, intravenously every four weeks for 48 to 96 weeks. Target engagement was confirmed in the central nervous system: cerebrospinal soluble TREM2 fell and

osteopontin rose. The trial missed its primary endpoint at every dose, with least-squares mean differences versus placebo at week 96 of −0.31, +0.13 and −0.17 on the Clinical Dementia Rating–Sum of Boxes, all non-significant. The most frequent treatment-emergent adverse events were MRI changes resembling amyloid-related imaging abnormalities [122]. Colonna and Holtzman, whose laboratories built much of the TREM2 field, published a reassessment titled "Rethinking TREM2 as a target for Alzheimer's disease after the INVOKE-2 trial failure" [123].

On Huang's model, chronic microglial hyperactivity is the core lesion. Agonising microglia in symptomatic patients should not help, and might harm. It did not help, in a trial that demonstrably hit its target.

10.5 Reading the four together

The pattern is: bind the monomer, nothing; spare the monomer and clear the aggregate, something; activate the microglion, nothing.

That is the pattern Huang's model predicts. It is not the pattern a simple amyloid-cascade model predicts — on a pure cascade account, removing the peptide in any form, and especially before deposition, should help, and solanezumab in preclinical disease should have been the most successful trial in the field's history rather than one of its cleanest nulls.

The inference must nonetheless be held loosely, for reasons that are individually sufficient to break it.

Solanezumab may have failed on pharmacokinetics, brain penetration or dose rather than on target biology; its peripheral sink effect may never have meaningfully lowered brain monomer. Crenezumab's trial was small, long, in a single kindred, with a mid-trial dose escalation and an unusual endpoint. Lecanemab and donanemab differ from the monomer-binders in target engagement *in tissue* as well as in species selectivity, and their modest benefit is straightforwardly explained by plaque removal without reference to monomer at all. AL002's failure is explained at least as economically by TREM2 agonism being the wrong lever on microglia as by microglial activation being the lesion — Colonna and Holtzman argue essentially this. And four trials with different molecules, populations, endpoints and durations are not a factorial design.

What can be said is narrower and still worth saying: **no clinical result to date contradicts the monomer-sparing principle, and the one trial that directly tested monomer removal in the ideal population produced nothing.** For a prediction made in 2020, that is a respectable record.

11. Who Actually Removes the Synapse

The theory's claim is that amyloid-β oligomers tag weak synapses and recruit glia to remove them. This is where the framework's stakes are highest, because synapse loss remains the best structural correlate of cognitive decline in this disease — better than plaques or tangles [124]. Three years of human tissue work now bear directly on it.

11.1 The human evidence for glial synapse removal

Human astrocytes and microglia contain more synaptic protein in Alzheimer's disease than in non-disease controls; proximity to amyloid-β plaques and the *APOE* ε4 genotype exacerbate this; cultured human and mouse astrocytes and microglia phagocytose patient-derived synapses more than control synapses; and inhibiting MFG-E8 — a bridging molecule that opsonises exposed phosphatidylserine — rescues the elevated engulfment of disease synapses without affecting control synapse uptake [125].

That last detail is the fly template, in human tissue: an eat-me lipid, a bridging opsonin, a phagocyte.

A second study sharpened the picture considerably. In 40 post-mortem brains matched for tau stage (Braak III–IV) but divergent in antemortem cognition, brains from people with dementia — but not resilient brains with the same tau burden — showed 33–43% loss of synaptic elements and markedly increased internalisation of mature synapses by microglia (13.3% versus 2.6% in resilient brains and 0.9% in controls) and by astrocytes (17.2% versus 3.7% and 2.7%). The synapses being taken were enriched for tau oligomers. And all of this occurred in visual cortex, a region with no tangle deposition at that Braak stage [126].

Two things follow, and they cut in different directions for the theory. The engulfment mechanism is real in human brain, and it tracks *dementia* rather than pathology burden — which is exactly the resilience-relevant variable that deposit-driven models struggle with, and which a signalling-imbalance model handles naturally. But the tag identified on the removed synapses is **tau oligomer**, not amyloid-β.

11.2 The complement arm

Complement C1q and C3 mediate developmental synapse elimination [68,69] and are re-engaged in disease. C1q-dependent excitatory and inhibitory synapse elimination by astrocytes and microglia occurs in amyloid models [127]; the synaptic proteome changes in tauopathy, and tau-induced synapse loss is rescued by C1q antibodies [128]; and C3 is activated in human Alzheimer's brain and required for neurodegeneration in both amyloid and tau models [129].

Complement is therefore an executioner with human-tissue support, developmental precedent, therapeutic tractability — and, after the 2025 C4d result [57], a direct molecular link to the very receptor the punishment-signal argument depends on.

11.3 The phosphatidylserine loop

The 2024 review's most mechanistically attractive proposal concerns phosphatidylserine, and it is the framework's best answer to the selectivity problem.

Phosphatidylserine normally resides in the inner membrane leaflet and is externalised as an eat-me signal. Its exposure on pre- and postsynaptic membranes is developmentally regulated, coincides with the period of activity-dependent pruning, and is required for microglial engulfment of supernumerary synapses — blocking the interaction with microglial phosphatidylserine receptors compromises pruning [130].

Separately, phosphatidylserine-like lipids in the outer leaflet *accelerate* amyloid-β aggregation while phosphatidylcholine-like lipids slow it; the extent of surface phosphatidylserine exposure determines a cell's susceptibility to amyloid-β toxicity; and phosphatidylserine incorporated into the outer leaflet of a bilayer triggers rapid amyloid-β oligomerisation at subnanomolar concentrations, inducing extensive pore formation.

The proposed loop: a weakening synapse externalises phosphatidylserine → local phosphatidylserine nucleates amyloid-β oligomerisation *at that membrane* → the oligomer damages the membrane and amplifies the eat-me signal, since oligomers themselves enhance phosphatidylserine exposure → receptors that read phosphatidylserine (complement, the TAM receptor kinases, TREM2 [120,121]) are engaged → the synapse is removed.

This is genuinely self-amplifying, spatially local, and selectivity-generating. It is the first mechanism in the framework that would explain how a diffusible peptide produces a *selective* outcome — and it does so without needing the concentration gradient that §7.4 argued is unavailable. If the framework were rebuilt around this mechanism rather than around the nisin gradient, it would be more robust.

It is also, at present, an assembly of separately demonstrated components rather than a demonstrated loop. The critical experiment — showing that blocking phosphatidylserine-nucleated

amyloid-β oligomerisation at a synapse spares that synapse from engulfment — has not been done.

11.4 The synthesis

Read together, the last three years suggest that the executioner is a committee: complement C1q, C3 and C4d; MFG-E8 bridging to exposed phosphatidylserine; the TAM receptor kinases; TREM2; and MMP9 at the matrix. Amyloid-β oligomers plausibly participate — they activate both the classical and alternative complement pathways, they bind TREM2, they accelerate on phosphatidylserine-containing membranes, they bind PirB — but the direct human evidence for the tag on a removed synapse currently points at tau oligomers and at exposed phosphatidylserine, not at amyloid-β.

The most recent authoritative survey of the field frames the whole problem as one of dysregulated microglial phagocytosis, notes that most known genetic risk maps onto phagocytic machinery — including *LILRB2* — and draws the same double-edged conclusion the competition framework requires: microglial phagocytosis of amyloid aggregates is beneficial, restricting subsequent tau pathology, whereas microglial phagocytosis of synapses and neurons is detrimental in later disease [131].

That is Huang's structure — one machine, two signs, timing decides which — arrived at from an entirely different direction and without his framework. It is a good illustration of the general point that the theory's architecture is more robust than its specific ligand claims.

12. Strength of Evidence

The table below grades each substantive claim. Grades: **Established** (multiple independent laboratories, interventional evidence, replicated); **Supported** (good evidence, limited replication or partly indirect); **Plausible** (consistent with evidence, not directly tested); **Speculative** (proposed, no direct test); **Contested** (evidence points both ways).

#	Claim	Grade	Basis and principal limitation
1	Amyloid-β is an antimicrobial peptide	Established	Interventional in mouse and nematode; class widened by amylin and phospho-tau
2	Antimicrobial peptides are widely co-opted for neural signalling	Established	Multiple peptides, multiple species, independent literature
3	Amyloid-β has opposite effects at low and high concentration	Established	Several laboratories, electrophysiology and behaviour, both directions
4	Endogenous amyloid-β is required for normal plasticity and memory	Established	Depletion impairs, picomolar peptide rescues; production blockade kills neurons
5	The two faces are separated by conformation	Supported	Consistent across preparations; concentration and conformation entangled in source data
6	The two faces are separated by concentration on a single axis	Contested	Neuronal trophic effects at 100–200 pM; microglial anti-inflammatory effects at 50–500 nM. Not one axis
7	The nisin quorum architecture applies to amyloid-β	Speculative	Structurally apt, but the two protective thresholds are several hundred-fold apart and no spatial gradient has been measured in tissue
8	Precursor-protein loss of function spares would-be losing axons	Established	Three systems including cell-autonomous sparse deletion
9	Those phenotypes are attributable to loss of amyloid-β	Contested	Precursor protein prunes via death receptor 6 independently of β-secretase
10	PirB loss of function spares would-be losing axons	Established	Bidirectional test on one readout, with receptor dependence of the second direction

#	Claim	Grade	Basis and principal limitation
11	Amyloid-β oligomers are the physiological ligand for PirB in pruning	Contested	C4d binds LilrB2/PirB at nanomolar affinity, rises in disease, drives spine loss PirB-dependently
12	Immune molecules generally mediate activity-dependent competition	Established	MHC-I, Qa-1/CD94-NKG2, complement, TNF, fractalkine, P2Y12
13	Flower couples competition to synaptic endocytosis and thus to amyloid-β production	Plausible	Both halves demonstrated separately; the junction is not
14	The Flower code is conserved to humans	Supported	Human isoforms function as winner/loser in fly neurons
15	Cell competition operates in the mammalian brain	Supported	Growing literature; mammalian mechanism less defined than fly
16	Engaging competition in an amyloid model is harmful	Contested	Culling is *protective* in the fly amyloid model; forcing competition worsens outcome over time
17	Activity drives amyloid-β production via endocytosis	Established	In vivo microdialysis, pharmacological and genetic
18	Amyloid-β acts as negative feedback on excitatory activity	Supported	Established for depression of transmission; complicated by evidence of oligomer-driven hyperactivation
19	Glial TNF sets synaptic gain in homeostatic plasticity	Established	Interventional; source now specified as astrocyte, not microglion
20	Monomeric amyloid-β suppresses microglial cytokine output	Supported	Clean in vitro genetics with precursor-protein and APLP2 controls; single laboratory; not independently replicated
21	The pathway runs precursor protein → Ric8a/Gαi → MMP9	Supported	Genetic epistasis in culture, pharmacological rescue in vivo; partial (IL-1β is Ric8a-independent)
22	Monomeric amyloid-β restrains microglia in the living brain	Speculative	Not shown; authors concede this explicitly
23	The precursor protein is a G-protein-coupled receptor for amyloid-β	Plausible	Revives a 1993 result; needs direct binding, structure and pharmacology
24	MMP9 is the effector linking microglial state to structural damage	Supported	Genetic and pharmacological in development; human data correlational

#	Claim	Grade	Basis and principal limitation
25	Amyloid aggregation depletes a functional soluble pool	Supported	Neuropathology and human biomarker cohorts; correlational, reverse causation not excluded
26	Loss of soluble Aβ42 tracks clinical state better than deposit	Supported	Two cohorts, one longitudinal and genetic; independently interpreted the same way by another group
27	Microglial cytokine signalling drives tau pathology	Established	Many laboratories, interventional; not distinctive to this theory
28	Chronic microglial hyperactivity is the core convergent lesion	Plausible	Coherent with genetics and with INVOKE-2; "hyperactivity" underspecified relative to modern state taxonomies
29	Risk factors converge on microglial state via cholesterol and trained immunity	Plausible	Each link supported; the chain is not tested end to end; dropped from the 2024 statement
30	Targeting the monomer is therapeutically inert or harmful	Supported	Two monomer-binding antibodies null in ideal populations; two monomer-sparing agents positive; not a designed comparison
31	Activating microglia will not help symptomatic disease	Supported	INVOKE-2 null with confirmed target engagement
32	Amyloid-β oligomers tag the synapses glia remove in human brain	Contested	Human engulfment established; the identified tags are tau oligomers and phosphatidylserine
33	Phosphatidylserine and amyloid-β form a self-amplifying eat-me loop	Plausible	Components separately established; loop not demonstrated; best available answer to selectivity
34	Astrocytic apolipoprotein E protects by suppressing oligomerisation	Supported	Kinetic and in vivo evidence; in vivo effects complex and stage-dependent
35	Apolipoprotein E ε4 confers risk through this pathway	Contested	ε4 is reported *most* potent at the protective step of raising monomer secretion
36	Neuronal apolipoprotein E drives a competition gene network	Speculative	Correlational transcriptomics plus one tau rescue; network assembled across studies
37	Amyloid-β oligomers induce sleep	Supported	Zebrafish, with prion-protein and mGluR5/Fyn dependence; one species

#	Claim	Grade	Basis and principal limitation
38	Amyloid-β oligomers specify the selectivity of sleep-dependent scaling	Speculative	Components established; the junction is proposed only
39	The precursor-protein intracellular domain protects the winner via DNA repair	Speculative	Biochemical chain plausible; no test in a competition context
40	Precursor-protein overexpression suppresses tangles via excess monomer	Speculative	Internally consistent; a simpler rival explanation exists (murine tau does not aggregate)

13. Where the Theory Is Weak

13.1 The axis problem

Set out in §7.4 and recorded as claims 6 and 7. The framework's organising image — one molecule, one concentration gradient, two opposite outcomes, spatial selectivity for free — does not survive contact with the numbers the framework's own experiment produced. The theory is about conformation, and it would be stronger, not weaker, restated that way. What it would lose is its account of selectivity, which would have to be carried by the phosphatidylserine mechanism instead — a trade this evaluation regards as favourable, since that mechanism is more specific and more testable.

13.2 Homology or analogy

The bacteriocin comparison is invoked at two different strengths in different passages. Sometimes it is an analogy: amyloid-β has the same functional grammar. Sometimes it is a claim about descent: the precursor protein and its peptide "may be part of an ancient mechanism employed in cell competition," subsequently co-opted during the evolution of metazoans and nervous systems.

The evolutionary claim is much stronger and much less supported. There is no sequence homology between amyloid-β and lantibiotics. The shared properties — amphipathicity, self-assembly, conformation-dependent membrane activity — are properties that unrelated short amphipathic peptides converge on because they follow from physics. The precursor protein's antiquity is real, but antiquity establishes that it had *some* ancient function, not this one. The iron-export activity of full-length precursor protein, which Huang cites as consistent with a primordial self-protection role, is equally consistent with several other stories.

Nothing in the theory's empirical content requires the evolutionary claim, and it carries a real cost: it makes the framework look like an origin story, and origin stories are what this field is least able to adjudicate.

13.3 The mouse-tangle argument has a simpler rival

Huang offers an ingenious explanation for a real puzzle: precursor-protein-overexpressing mice do not develop neurofibrillary tangles because overexpression raises basal monomeric amyloid-β, which suppresses microglial inflammation, which is required for tau pathology. He notes that soluble Aβ40 in 5xFAD cortex is roughly five times control, and derives a testable prediction — that raising microglial inflammatory activity in these animals should promote tau pathology.

That prediction is well supported. Enhancing inflammation in these models does exacerbate tau: autophagy-gene deletion that increases microglial inflammation produces tau hyperphosphorylation and accelerated neuronal death; APOE4 homozygosity increases microglial activation and site-specific tau phosphorylation in 5xFAD; TREM2 knockout or the R47H variant facilitates tau seeding and spreading in APP/PS1 animals [94]; membrane-anchored CX3CL1 deficiency increases inflammatory cytokines and neuronal tau phosphorylation [91]; interleukin-1β overexpression increases tau phosphorylation despite reduced amyloid burden; and IL-1 receptor blockade attenuates tau pathology.

But the argument as a whole has a much simpler rival. Mice do not develop tangles with amyloid pathology alone principally because murine tau differs from human tau in isoform composition and aggregation propensity — which is why the field introduced mutant human tau to get tangles at all, and why 3xTg and similar models exist. Huang's explanation and the standard explanation predict identical outcomes in every experiment so far performed. Where two explanations of a negative result predict identically, the one requiring fewer new assumptions should be preferred until a discriminating experiment exists.

One is available in principle: humanised-tau knock-in mice with graded precursor-protein overexpression. The monomer explanation predicts an inverse relationship between soluble Aβ40 and tangle formation; the isoform explanation predicts none.

13.4 In vivo silence on the central claim

The claim that gives the theory its therapeutic edge — that monomeric amyloid-β holds glia in check — has been demonstrated only in culture, by one laboratory, at concentrations at or above the estimated interstitial range and never below 50 nanomolar, and the authors have stated on the record that they lack in vivo evidence. This is the single most important gap in the programme, and §14 places the corresponding falsifier first.

13.5 Breadth without constraint

The 2020 essay claims compatibility with the amyloid cascade, the tau hypothesis, the neuroinflammation hypothesis and the antimicrobial protection hypothesis, and offers an accommodation for each. Some of this is earned: a framework whose currency is a regulatory loop can genuinely contain several accounts of where the loop breaks, and the two-entrance structure of §8.1 is a real contribution rather than a hedge.

But compatibility with everything is not a virtue in a theory; it is the absence of a constraint. The apolipoprotein E section of the 2024 review is where this becomes acute (§8.6): protective in one cell type, destructive in another, with the risk allele best at the protective function. Since the source documents state no refutation conditions, §14 states them.

13.6 The two versions are not one theory

The 2020/2023 statement and the 2024 statement share a premise and diverge in most of what is built on it. The first is a theory of microglial disinhibition following monomer depletion, with cholesterol metabolism and trained immunity supplying the route from risk factors to microglial state, and an argument about animal models attached. The second is a theory of apolipoprotein E, DNA-damage repair, phosphatidylserine, spine classes and sleep, in which microglial hyperactivity is barely mentioned and cholesterol and trained immunity are absent.

Nothing is retracted; the second simply proceeds elsewhere. A reader who encounters only one has an incomplete and in places misleading picture of what is being claimed, and the programme would benefit from a consolidated statement of which components remain load-bearing.

13.7 What the theory does not address

Three omissions are worth naming, not as objections but as boundaries.

Selective vulnerability of specific regions. The framework explains cell-type vulnerability through apolipoprotein E and RORβ expression, but says nothing about why the locus coeruleus and entorhinal cortex are affected first, or why the pattern of spread follows the routes it does.

Mixed pathology. Most dementia in the oldest old involves vascular disease, TDP-43 and α-synuclein alongside Alzheimer changes. A theory of amyloid-β signalling has nothing to say about this, which limits how much of the clinical territory it can claim.

The individual time course. The model describes a runaway loop but offers no account of why the loop takes two decades in one person and five years in another, beyond the general appeal to residual monomer.

14. What Would Refute It

Six conditions, stated so that the theory can lose.

1. Monomeric amyloid-β does not restrain microglia in a living brain. Direct test: conditional deletion of the precursor protein or *Ric8a* from microglia in adult mice, with measurement of cytokine output and microglial state under a defined challenge; plus intracerebroventricular or intraparenchymal delivery of verified monomeric peptide at interstitial concentrations. Failure to reproduce the cultured effect in vivo, at physiological concentration, would remove the theory's mechanistic core.

2. The anti-inflammatory effect is not conformation-specific. If preparations verified as oligomeric at the end of incubation suppress cytokines as effectively as verified monomeric preparations, the duality on which the entire framework rests is an artefact of preparation rather than a property of the molecule.

3. Restoring the monomer does not help. If a γ-secretase modulator or non-aggregating peptide analogue raises brain soluble Aβ42 into the normal range in an animal with established pathology and produces no benefit on microglial state, tau pathology or cognition, the depletion arm fails. This is now an explicit programme in another laboratory [109] and constitutes an independent test.

4. PirB-dependent pruning is complement-driven and amyloid-independent. If C4d accounts for the PirB-dependent spine loss, and selectively blocking the amyloid-β–PirB interaction leaves developmental pruning intact [57], the theory's best genetic evidence is reassigned to another ligand.

5. Competition is protective, not destructive, in a mammalian amyloid model. The fly result [45] should be tested in mouse, using the human Flower isoforms now shown to be functionally conserved [40]. If enhancing competition protects and blocking it harms, the disease model has the sign wrong.

6. The order is wrong in the earliest human disease. If cytokine elevation and microglial activation can be shown to *follow* rather than precede measurable monomer depletion in people at the earliest stages, the causal sequence is inverted. Serial cerebrospinal soluble Aβ42 alongside inflammatory markers in autosomal-dominant mutation carriers approaching estimated onset would address this directly.

15. Predictions and the Experiments That Would Settle Them

Beyond the falsifiers, the framework generates positive predictions worth testing.

Measure the concentration–response of the microglial effect properly. A full dose–response for verified monomeric Aβ40 and Aβ42 on microglial cytokine output, from 1 picomolar to 1 micromolar, with monomeric state verified at the *end* of the incubation, would establish whether the effect has any presence at physiological concentrations. This is the single most informative cheap experiment available, and its outcome determines whether §7.4's objection is fatal or merely tidy.

Test whether astrocytes carry the same receptor. Since astrocytes, not microglia, supply the TNF for homeostatic scaling [73], the module as drawn requires monomeric amyloid-β to restrain astrocytes. Whether it does is unknown and is a one-experiment question.

Spare the monomer by design. An antibody or degrader engineered to clear aggregates while leaving the monomer untouched should outperform one that clears both, matched for aggregate removal. The existing clinical comparison is confounded; a designed one would not be.

Establish the precursor protein as a receptor. Direct binding of monomeric amyloid-β to the precursor-protein ectodomain with a measured affinity, demonstration of nucleotide exchange on Gαi downstream, and pharmacological interruption of the coupling would move claim 23 from plausible to established — and would finally give the 1993 Go result [82] a context.

Look for MMP9 as the human effector. If the pathway operates in human disease, cerebrospinal or parenchymal MMP9 activity should track inversely with soluble Aβ42 *within* amyloid-positive individuals, independently of deposit burden. The plasma data are suggestive [83,84] but the within-person relationship has not been examined.

Test the monomer as a resilience marker. If residual monomer is what separates the resilient from the demented at matched pathology, then in cohorts of the kind that produced the human engulfment data [126], soluble Aβ42 should be higher in resilient brains at matched tau stage. This is testable in existing banked material and would be the most direct human test of the depletion claim available.

Test the sleep-selectivity prediction. Measure sleep-dependent synaptic scaling and its size-dependence [81,80] in animals lacking the proposed oligomer receptors. If scaling loses its

selectivity, the boldest claim in the 2024 review is supported.

16. Therapeutic Consequences

The framework's practical output is narrower than its explanatory reach, and better for it.

Do not remove the monomer. This is the principle, stated in 2020, before the four trials that now bear on it. It is not merely "target oligomers," which the field already said; it is the stronger claim that removing the monomer may be actively harmful because it removes a brake. Every trial result since is consistent with it, and one — solanezumab in preclinical disease — is a clean null in the population where a cascade model predicted the largest effect.

Restoring the monomer is a coherent strategy. If depletion is the lesion, replacement is the treatment. On this account, γ-secretase *inhibitors* are exactly wrong, modulators that shift cleavage toward shorter species are wrong, and agents that raise soluble Aβ42 — or non-aggregating peptide analogues — are right. This is now an explicit programme in another laboratory [109], which makes it an independent test of Huang's mechanism rather than merely a restatement of it.

Do not agonise microglia in symptomatic disease. INVOKE-2 is consistent with this [122,123], though a single failed mechanism is not a general law, and the same trial is equally consistent with TREM2 being the wrong lever.

Timing determines the sign of the intervention, and the framework says why. If the peptide's normal job is to arbitrate competition, then acting on it is acting on a physiological process, and the direction of benefit should depend on when in the process one intervenes. Removing amyloid-β early removes a brake; removing aggregates late removes a driver. This is a principled account of why the same target can reverse sign across disease stage — something a cascade model has to treat as a dosing or window problem. It also predicts that the therapeutic window for aggregate removal and the window for monomer restoration are different windows, and possibly non-overlapping.

MMP9 is a druggable node with a clean rationale. The 2024 work makes MMP9 the effector between microglial state and structural damage, and matrix protease inhibitors exist. The hazard is real and historically demonstrated: matrix proteases have essential physiological functions, and broad-spectrum inhibition has failed repeatedly in oncology. Selectivity would be the whole problem.

A measurement recommendation follows. If the theory is even partly right, trials should report soluble monomeric Aβ42 as an outcome, not only as a baseline covariate or a

target-engagement check. At present a trial can lower plaque, lower monomer, and record only the first.

17. Limitations of This Assessment

This evaluation reads the theory from four documents and the peer-review record of one of them. It has not had access to unpublished work, and a laboratory's published output lags its actual position, sometimes by years.

The judgements about relative evidential weight in §12 are the author's. Another reader weighting the fly genetics, the human biomarker data or the trial pattern differently would grade several rows differently, and the grading scheme itself is a convenience rather than a metric.

The concentration objection in §7.4 is an inference from comparing a summary table in one document with the methods of another. The arithmetic is straightforward but the comparison assumes the two sets of experiments are commensurable, and receptor systems in different cell types genuinely can differ in affinity by hundreds of fold without anything being wrong. What is claimed is narrower than "the finding is wrong": it is that the *nisin architecture*, and specifically its account of spatial selectivity, does not survive the comparison.

The trial argument in §10 compares four trials that were not designed to be compared, differing in molecule, population, endpoint, duration and era. Its conclusion is deliberately stated as a pattern that is not contradicted rather than a result that is established.

Finally, this is an assessment of a theory of what amyloid-β is for, and of a disease model derived from it. It is not an assessment of the disease. Alzheimer's disease is heterogeneous, most dementia in the oldest old is mixed, and no single-mechanism account — this one included — should be expected to cover the whole clinical territory.

18. Conclusion

The most useful thing about this body of work is that it asks the right question first. Almost every theory of Alzheimer's disease begins with pathology and reasons backwards toward physiology. This one begins with physiology — what is a peptide with these properties *for*? — and lets the disease model fall out as a corollary. Whatever happens to the specific claims, that ordering is the correct one for a molecule as old, as abundant and as tightly regulated as this.

The answer offered is that amyloid-β is a competition signal: the molecule an axon uses to protect itself and to mark its rivals. The supporting architecture is genuine. The loss-of-function genetics is strong, directional, and predicts the counterintuitive right thing — remove the signal and the loser survives, cell-autonomously. The concentration duality is real, replicated, and includes the under-weighted finding that the peptide is *required* for normal plasticity. The cell-competition machinery the theory borrows from is real, is conserved to the point that human Flower isoforms function in fly neurons, and has become a field in its own right. And the general shape of the argument — one machine, two signs, timing decides which — is now being arrived at independently by people working on microglial phagocytosis who have never cited it.

Three things are not established and two are contradicted. The claim that gives the theory its edge — that monomeric amyloid-β holds glia in check in a brain — exists in culture, in one laboratory, at concentrations at or above the physiological range, and its author says so on the record. The bacteriocin analogy, on which the framework's account of selectivity depends, does not survive the arithmetic of the concentrations now reported. The apolipoprotein E extension has grown past the point where it constrains anything. The laboratory that owns the competition machinery reports that engaging it in an amyloid model is protective, which is the opposite sign from the one the disease model needs. And the human tissue studies that have established glial synapse engulfment in this disease identify the tag on the engulfed synapse as tau oligomer and exposed phosphatidylserine, not amyloid-β.

Against that, two developments since 2020 have moved substantially in the theory's favour, and neither was available when it was written. A separate human-biomarker programme, working from cerebrospinal data with no reference to competition, antimicrobial peptides or microglia, has independently concluded that the loss of soluble monomer matters more than the gain of aggregate — and has moved to proposing that it be restored. And the clinical record now shows that the two antibodies that bind the monomer produced nothing in the two populations where they should have worked best, that the two that spare it produced small effects, and that the one antibody built to activate microglia produced nothing at all with its target demonstrably engaged.

None of that proves the theory. What it means is that the sharpest practical thing in it — *do not remove the monomer* — was written before the evidence that now supports it. That is the only kind of prediction that counts, and it is more than most theories of this disease have managed.

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