The Switch and the Sieve

Ephexin5 and the neuroproteasome, reconsidered — what a decade of evidence did to two models of synaptic and proteostatic failure in Alzheimer's disease

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Two proposals were made about the Alzheimer dendrite: that a developmental repressor of synapse formation is re-applied in the adult brain, and that a proteasome at the neuronal surface holds newly made tau below the threshold at which it polymerises. A decade of evidence has revised them in opposite directions. This paper sets out both revisions, grades what each model is now entitled to claim, and argues that the two are one statement about the same compartment.

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Abstract

Two mechanistic proposals have been advanced for how a neuron in Alzheimer's disease loses its synapses and acquires its tangles without either event requiring amyloid to act directly upon it. The first holds that a developmental repressor of excitatory synapse formation, the RhoA guanine-nucleotide exchange factor Ephexin5, is re-expressed in the adult brain when amyloid-β strips the EphB2 receptor that normally licenses its destruction, and that the re-expressed protein collapses dendritic spines through RhoA. The second holds that a neuron-specific 20S proteasome resident in the plasma membrane — the neuronal membrane proteasome, latterly the neuroproteasome — degrades newly synthesised protein at the dendrite, that its abundance at the membrane is set by apolipoprotein E isoform and by age, and that when it fails, newly made tau aggregates.

Both proposals have been substantially revised by evidence published since they were framed, and the revisions run in opposite directions. The synaptic proposal has weakened where it was strongest. Ephexin5 is not a RhoA-selective exchange factor and not simply a brake: it activates Cdc42 as well as RhoA, the choice between them is set by the phosphorylation state of a single tyrosine, Y361, and downstream of neuronal activity the Cdc42 arm is *required* for the long-term spine growth that accompanies potentiation. The same residue that selects the substrate is the residue whose phosphorylation licenses the protein's own ubiquitin-dependent destruction, so abundance and activity are not independent variables and cannot be targeted independently. Human genetics has meanwhile supplied a natural experiment in chronic Ephexin5 loss: heterozygous loss-of-function mutations in *ARHGEF15*, the gene encoding Ephexin5, cause autosomal-dominant cerebral small-vessel disease with osteoporotic fracture, through RhoA/ROCK2 inactivation in vascular cells. The therapeutic prescription that the synaptic model originally implied — lower Ephexin5 — is now a phenocopy of a human vasculopathy and, in neurons, an ablation of the growth arm.

The proteostatic proposal has strengthened where it was weakest. The claim that apolipoprotein E isoform sets a threshold for tau aggregation through neuroproteasome abundance has moved from preprint to peer review, with a selective membrane-impermeant inhibitor, endogenous non-mutant tau, filaments raised in three days in mouse brain, and a graded genotype effect: neurons carrying ApoE4 aggregate tau after a small fraction of the inhibition that ApoE2 neurons tolerate. The claim is now the more falsifiable of the two, and the outstanding objection is structural rather than cell-biological — negative-stain electron microscopy cannot establish that the filaments adopt the Alzheimer fold, and cryo-electron microscopy has not yet been done.

This paper sets out both revisions, and then argues that the two proposals are less independent than they have been presented. Both are statements about protein levels in one compartment — the dendrite — that are set by degradation rather than by synthesis. Ephexin5's dendritic level falls in an activity-dependent, proteasome-dependent manner; the neuroproteasome is the

activity-dependent dendritic proteasome that degrades newly synthesised protein. No experiment has yet asked whether the second degrades the first. If it does, then apolipoprotein E4 — which lowers neuroproteasome surface abundance — supplies the mechanism that the synaptic model has always lacked for why the principal genetic risk factor should make spines more fragile, and the two proposals become one lesion with two readouts. That question is stated here as a falsifiable prediction, alongside eight others, together with the measurements that would settle each. A strength-of-evidence table grades every claim, and the therapeutic implications are re-derived from the revised models rather than the original ones.

1. Introduction: two proposals about one compartment

Alzheimer's disease is diagnosed by two lesions and predicted by a third. Plaques and tangles define the neuropathology; synapse loss defines the clinical syndrome. Terry and colleagues established in 1991 that neocortical synapse density is the strongest structural correlate of cognitive impairment (Terry et al., 1991), and DeKosky and Scheff had reached the same conclusion the previous year from frontal-cortex biopsy material in which post-mortem artefact is minimal (DeKosky and Scheff, 1990). Selkoe compressed the position into a title that has not needed amendment: Alzheimer's disease is a synaptic failure (Selkoe, 2002). Three decades later, positron-emission tomography of the synaptic vesicle glycoprotein SV2A measures that failure in living patients, and finds it widespread and early (Mecca et al., 2020).

The consequence for mechanism is specific. If the operative lesion is the removal of synapses, then a complete account of the disease must name the machinery that removes them — not the agent that initiates the process, which is a separate question, but the effector that executes it. And if the second lesion is a filament of tau assembled inside a neuron, a complete account must name the step at which soluble, natively unfolded tau becomes an insoluble polymer. Neither question is answered by the statement that amyloid-β accumulates. The two anti-amyloid antibodies that have cleared plaque from living brains and reached regulatory approval slow decline by roughly a quarter to a third in early symptomatic disease (van Dyck et al., 2023; Sims et al., 2023); they do not stop it. Whatever is doing the damage is downstream of the plaque, or beside it, and its identity is a matter of molecular specifics.

Two proposals developed over the past fifteen years address these two questions with unusual mechanistic concreteness, and they emerged from the same laboratory. The first concerns the structural collapse of the dendritic spine. Its claim is that the adult brain retains a developmental programme for repressing excitatory synapse formation, that the programme is held off by the continuous destruction of its central effector, and that amyloid-β re-activates the programme by removing the receptor that orders the destruction. The effector is Ephexin5, the product of *ARHGEF15*, a guanine-nucleotide exchange factor first characterised as selective for the small GTPase RhoA.

The second concerns proteostasis at the neuronal surface. Its claim is that neurons possess a class of 20S proteasome complexes associated with the plasma membrane, exposed to the extracellular space, and dedicated to the rapid destruction of proteins that have only just been

made; that this machinery is the dominant route of disposal for the activity-induced nascent proteome; and that when it is compromised — by apolipoprotein E4, by age — newly synthesised tau escapes disposal and polymerises. This complex was named the neuronal membrane proteasome and is now generally called the neuroproteasome.

Both proposals share three features that make them worth revisiting together. Both locate the lesion in the dendrite rather than the axon or the extracellular space. Both make protein *degradation*, not protein synthesis, the controlled variable. And both were formulated at a point when the supporting evidence was thinner than the models required — the first resting on a single amyloid-precursor-protein-overexpressing mouse line, the second on a preprint.

The intervening evidence has not been kind to them symmetrically. The synaptic proposal has been revised in a way that removes its therapeutic prescription and complicates its mechanism; the proteostatic proposal has been strengthened, sharpened, and published, and now carries a specific, quantitative, genotype-graded claim about the initiation of tau pathology. This paper sets out both revisions in detail, tests each model against the causal ordering that human neuropathology imposes, identifies the point at which the two intersect, and re-derives what each now implies for therapy. The aim is neither to defend nor to dismiss. It is to state what each model is now entitled to claim, what it is not, and what measurement would decide the difference.

2. The gap both proposals were built to fill

The amyloid cascade, as originally formulated, was a chain of implications rather than a chain of mechanisms. Amyloid-β accumulates; tau becomes hyperphosphorylated and aggregates; synapses are lost; neurons die; cognition fails. Each arrow in that sequence is a place where a mechanism should be, and for three decades most of them were unoccupied.

Some have since been filled. The synaptotoxic species was narrowed from fibrillar plaque to soluble oligomer: dimers isolated directly from Alzheimer brain impair long-term potentiation and memory at low nanomolar concentration (Shankar et al., 2008), and oligomeric amyloid concentrates at post-synaptic densities in a halo around plaques where excitatory synapse loss is greatest (Koffie et al., 2009). Receptors were identified. Cellular prion protein, the metabotropic glutamate receptor mGluR5, the paired immunoglobulin-like receptor B and its human orthologue LilrB2 each bind oligomeric amyloid with high affinity and each transduce a synaptic consequence (Kim et al., 2013). Effectors were identified: LilrB2/PirB engagement enhances cofilin signalling in mouse and in human Alzheimer cortex (Kim et al., 2013), and cofilin is the actin-severing protein whose dysregulation directly explains why a spine, which is an actin structure, should retract.

What remained missing was the link between receptor occupancy and structural collapse in the specific, enzymatic sense: which exchange factor, acting on which GTPase, under which regulatory control. Amyloid oligomers "cause spine loss" is not a mechanism; it is a description awaiting one. The Ephexin5 proposal is an attempt to supply exactly that link, and its appeal lies in its economy — it does not require the disease to invent a destructive process, only to reinstate one the brain already possesses and normally suppresses.

The tau side of the cascade has an equivalent gap, and it is worse. Tau in the healthy neuron is soluble, natively unfolded, and largely axonal. In disease it becomes hyperphosphorylated, mislocalises to the somatodendritic compartment and into spines, and assembles into paired helical filaments with a defined cryo-electron-microscopic fold (Fitzpatrick et al., 2017). The mislocalisation step is reasonably well documented: amyloid oligomers cause localised calcium elevation and missorting of endogenous tau into dendrites (Zempel et al., 2010), and hyperphosphorylated tau accumulating within intact spines impairs glutamate-receptor trafficking without any neuron dying (Hoover et al., 2010). But *why the protein polymerises* — what tips a soluble monomer into a filament in a cell that has managed the same protein for decades — has been answered chiefly by appeals to seeding and to templated conversion, which explain propagation rather than origination. Something must make the first filament.

Both gaps are, at bottom, questions about protein quantity in a compartment. A spine collapses when the actin-severing arm of its regulatory machinery outruns the nucleating arm. A protein polymerises when its local concentration in a susceptible state exceeds what its chaperoning and disposal capacity can hold. Alzheimer's disease is a disease of an ageing neuron, and the ageing neuron's proteasome is demonstrably impaired: proteasome activity is reduced in Alzheimer brain (Keller et al., 2000), and recent work integrating kinetic assays, proteasome purification and transcriptomics across Braak stages finds that constitutive proteasome subunit genes are downregulated in neurons from the earliest stages (Jiang et al., 2025) — in tissue without overt tau aggregation — with the compensatory NRF1-driven response blocked by failed nuclear localisation. Proteasome failure in this disease is early, neuron-selective, and prior to the lesion it is usually invoked to explain.

That is the setting in which both proposals should be read. They are not competing accounts of one thing. They are two accounts of what happens in one compartment when the machinery that decides how much of a protein is present stops deciding correctly.

3. The first proposal as originally stated: a developmental brake, re-applied

3.1 The developmental physiology

Excitatory synapse formation in the developing brain is not simply promoted; it is also actively restrained, and the restraint must be lifted at the right time and place. Ephexin5 is the restraint. Identified in 2010 as a RhoA guanine-nucleotide exchange factor expressed highly in immature neurons (Margolis et al., 2010), it negatively regulates excitatory synapse development until ephrin-B binding to the EphB receptor tyrosine kinase triggers its phosphorylation, ubiquitination and degradation. The ubiquitin ligase that performs the tagging is Ube3A — the gene deleted or mutated in Angelman syndrome and duplicated in some autism-spectrum disorders — which gave the finding immediate relevance beyond synapse biology.

The architecture is worth stating precisely, because the revisions turn on it. Ephexin5 restrains spine formation through RhoA. EphB2 signalling phosphorylates Ephexin5 on a tyrosine within a regulatory motif conserved across the Ephexin family. Phosphorylation recruits Ube3A. Ube3A ubiquitinates Ephexin5. The proteasome destroys it. Removal of the restraint permits synaptogenesis. In the mature brain, on this account, Ephexin5 expression is low and the restraint is therefore absent by default.

A second regulatory input was later identified in the same laboratory. Protein kinase C epsilon acutely and specifically reduces dendritic spine number in immature neurons, and does so through the phosphorylation and activation of Ephexin5 (Schaffer et al., 2018) — a mechanism temporally restricted to immature neurons and, notably, opposite in sign to the same kinase's pro-synaptic role in the mature brain. Ephexin5 activity, then, is set by at least two kinases with different developmental profiles, one of which marks it for destruction and one of which activates it.

3.2 The disease claim

The disease claim has three components, each supported by a separate experiment.

The first is that amyloid removes the licensing receptor. Amyloid-β oligomers bind EphB2 and drive its depletion; restoring EphB2 expression in the dentate gyrus of an amyloid-overexpressing mouse reverses deficits in long-term potentiation, in NMDA-receptor-dependent function, and in memory (Cissé et al., 2011). This was reported by an independent group and is the sturdiest element of the chain.

The second is that Ephexin5 consequently accumulates. Amyloid-β acutely promotes Ephexin5 production in mature hippocampal neurons and in hAPP mice, and Ephexin5 expression is elevated in the hippocampi of human Alzheimer patients (Sell et al., 2017). That last observation is the model's only direct human anchor.

The third is that the accumulation is necessary for the phenotype. Genetic removal of Ephexin5 from hAPP mice eliminated hippocampal dendritic spine loss and rescued behavioural deficits; shRNA-mediated reduction of Ephexin5 in the dentate gyrus of presymptomatic adolescent hAPP mice was sufficient to protect them from later cognitive impairment (Sell et al., 2017). This is a loss-of-function rescue with a prevention arm, which is a stronger design than most reported in the field.

3.3 The prescription that followed

The therapeutic reading was immediate and was stated by the authors: because Ephexin5 is minimally expressed in the healthy adult brain, and because pathological elevation of Ephexin5 drives amyloid-induced memory impairment, strategies aimed at reducing Ephexin5 levels may represent an effective approach to treating Alzheimer's disease (Sell et al., 2017).

The logic is clean. A protein that is nearly absent from the healthy adult brain, elevated in disease, and necessary for the disease phenotype in an animal model is close to an ideal target: inhibiting it should have a wide therapeutic window, because there is little physiological function to disturb. Two subsequent bodies of evidence — one from synaptic physiology, one from human genetics — have made that inference untenable. They are the subject of the next two sections.

4. The first revision: Ephexin5 is a switch, not a brake

4.1 The dual-GTPase result

The proposition that Ephexin5 is a RhoA-selective exchange factor was already under strain in 2017, in a paper co-authored by the laboratories that had described it. Reducing Ephexin5 increased spine outgrowth and increasing it decreased outgrowth, consistent with a brake — but Ephexin5-GFP was found to be *elevated* on the dendritic shaft at the sites of future new spines before those spines appeared, and lowering Ephexin5 *inhibited* new spine outgrowth in response to both global activity increases and local glutamatergic stimulation. The authors concluded that Ephexin5 serves a dual role: a brake on overall spine outgrowth, and a necessary component of the site-specific formation of new spines (Hamilton et al., 2017). The same paper reported that increased neural activity produced a proteasome-dependent reduction of Ephexin5 in dendrites — a detail that will matter in section 9.

The mechanism of that duality was established in 2025 (Petshow et al., 2025). Ephexin5 activates both RhoA and Cdc42; in knockout brain, the activated pools of both GTPases fall by roughly seventy per cent. Live imaging of Förster-resonance-energy-transfer GTPase biosensors at single spines showed that during plasticity induced by high-frequency glutamate uncaging, Ephexin5 regulates the activation of Cdc42 but not of RhoA: knockout neurons showed about half the normal Cdc42 activation following stimulation, with RhoA activation unchanged. Substrate selection is therefore not a property of the enzyme but of its state.

The state is set by tyrosine phosphorylation. Phospho-tyrosine Ephexin5 falls developmentally, and chemical long-term potentiation reduces it by about three-quarters within minutes. That reduction is dephosphorylation, not degradation: it survives proteasome inhibition with MG132, and the loss of phospho-signal is a small fraction of total Ephexin5. Mutating the key tyrosine to phenylalanine — Y361F, which cannot be phosphorylated — enhances Cdc42 activation while leaving RhoA activation unchanged.

The functional consequence is the part that dismantles the original therapeutic prescription. Spines in Ephexin5-knockout neurons failed to sustain activity-driven growth: stimulated spines returned to approximately baseline volume, against roughly twofold sustained growth in wild-type. Re-expressing full-length Ephexin5 restored growth; re-expressing a catalytically dead exchange factor did not, so the rescue requires GEF activity and not merely the protein's presence. The

Y361F phosphomutant rescued growth in knockout neurons.

Ephexin5 is therefore *required* for the structural plasticity that accompanies potentiation. It is not a brake that the adult brain has switched off. It is a switch that the adult brain keeps and throws, and the throwing is what learning-associated spine growth depends on.

4.2 One residue, two jobs

The residue at which the switch is thrown is Y361 — the same tyrosine, within the same conserved regulatory motif, whose phosphorylation was characterised in 2010 as the event that recruits Ube3A and consigns Ephexin5 to the proteasome (Margolis et al., 2010; Petshow et al., 2025).

This coincidence has not, to our knowledge, been drawn out, and it has a consequence for every intervention proposed on this pathway. Phosphorylation at Y361 does two things at once: it biases the exchange factor toward RhoA, and it marks the exchange factor for destruction. Dephosphorylation likewise does two things: it releases the Cdc42-directed activity, and it protects the protein from Ube3A-dependent turnover. Abundance and activity are not independent variables in this system. They are two readings of one covalent modification.

Several things follow.

First, the phenotype "Ephexin5 is elevated" is ambiguous on its own. A cell with elevated Ephexin5 may have lost the kinase input that marks it for destruction, in which case the accumulated protein is hypo-phosphorylated at Y361 and, by the 2025 model, Cdc42-biased. Or it may have gained a phosphorylation input that is not coupled to Ube3A recruitment, in which case the accumulated protein is RhoA-biased. These two states have opposite structural consequences for the spine, and current measurements do not distinguish them, because the antibodies and assays used to report "Ephexin5 levels" report total protein.

Second, the disease model as stated contains a tension that has not been resolved. Its premise is that amyloid depletes EphB2. EphB2 is the kinase that phosphorylates Y361. Loss of the kinase should therefore *lower* the phosphorylated fraction — which explains the accumulation, since the phospho-form is the degraded form, but which predicts, on the 2025 model, a Cdc42-biased and therefore growth-promoting pool. The observed phenotype is spine loss. Something must restore the RhoA bias in disease that the loss of EphB2 removes, or the sign of the model is wrong.

Third, there is at least one candidate for that something, and it is testable. Protein kinase C epsilon phosphorylates and activates Ephexin5, and it does so in a manner that suppresses spines (Schaffer et al., 2018). Src-family kinases are plausible alternatives, and Fyn in particular is mistargeted to the post-synaptic density in a tau-dependent manner in Alzheimer models (Ittner et al., 2010), placing an active tyrosine kinase at exactly the compartment in question. If a tyrosine kinase other than EphB2 phosphorylates Y361 without licensing Ube3A recruitment — because the

ligase requires a co-incident EphB2-dependent signal that the disease has removed — then the Alzheimer neuron would hold a pool of Ephexin5 that is simultaneously abundant and RhoA-locked. That is the state the original model requires and the state no one has yet measured.

4.3 The measurement that would settle it

The experiment is straightforward and has not been done: quantify the phospho-Y361 fraction of Ephexin5, not total Ephexin5, in human Alzheimer hippocampus stratified by Braak stage and in amyloid-bearing mouse models, with parallel measurement of active RhoA and active Cdc42 by pulldown in the same tissue.

Three outcomes are possible, and each decides something.

If the phospho-Y361 fraction is elevated and Cdc42 activity is not, the original model survives the revision intact, and the therapeutic target becomes the kinase responsible rather than the exchange factor.

If the phospho-Y361 fraction is reduced and Cdc42 activity is elevated, the model's sign is wrong: Ephexin5 accumulation in disease would be a growth-directed, plausibly compensatory response to synaptic loss rather than its cause, and the rescue seen on genetic deletion would require reinterpretation — deletion would be removing a failed repair attempt whose collateral cost exceeds its benefit.

If neither fraction moves and total protein rises, then the disease-relevant variable is bulk abundance acting through mass action on both GTPases, and the model becomes a quantitative rather than a qualitative claim.

No published dataset answers this. It is the single most informative measurement available on this pathway, and it requires no new reagents beyond a validated phospho-Y361 antibody.

4.4 Angelman syndrome as the natural control

Angelman syndrome is the reciprocal experiment, performed by nature. Loss of Ube3A should stabilise Ephexin5 (Sell and Margolis, 2015), and if Ephexin5 were simply a RhoA-directed brake, the predicted consequence would be severe spine loss. The observed consequence in Angelman models is not spine loss.

The 2025 substrate-switching model resolves this without special pleading: in the developing brain, where phospho-tyrosine Ephexin5 is a shrinking fraction and activity is high, accumulated Ephexin5 is Cdc42-biased and therefore stabilising rather than destructive. The resolution is satisfying, but it is also a warning. It demonstrates that in a real human disorder, a large increase in Ephexin5 protein produced a phenotype opposite in sign to the one the brake model predicts. The disease model in Alzheimer's asks us to believe that a comparable increase in Ephexin5 protein, in a

different cellular context, produces the predicted sign. That may well be true. It is not, at present, shown — and Angelman syndrome establishes that the inference from abundance to sign is not safe.

5. What human genetics now says about *ARHGEF15*

5.1 A natural experiment in chronic Ephexin5 loss

In 2023 the gene encoding Ephexin5 acquired a Mendelian human phenotype. *ARHGEF15* was identified as a causal gene for autosomal-dominant hereditary cerebral small-vessel disease: a heterozygous non-synonymous mutation co-segregated completely in two families, and a further non-synonymous mutation and a stop-gain mutation were found in two sporadic cases. Every mutation carrier also had severe osteoporosis, and some had osteoporotic fractures. In vitro, the mutations produced RhoA/ROCK2 *inactivation* and consequent F-actin disorganisation in vascular smooth-muscle and endothelial cells, and osteoblast dysfunction through inhibition of Wnt/β-catenin signalling. A transgenic mouse carrying one of the variants developed small-vessel-disease pathology and behavioural phenotypes with severe osteoporosis. The authors' conclusion is explicit: these are loss-of-function mutations, and loss of function causes the disease (Ding et al., 2023).

The relevance to the Alzheimer proposal is direct and unfavourable. Cerebral small-vessel disease is itself a leading cause of vascular dementia and of both ischaemic and haemorrhagic stroke. The intervention the synaptic model recommends — chronic, systemic reduction of Ephexin5 function — now has a human phenotype attached to it, and the phenotype is a dementing cerebrovascular disease with skeletal fragility.

This is a different and stronger objection than the pleiotropy concern that was raised when *ARHGEF15* was known merely to be expressed in endothelium. Expression outside the brain is a reason for caution about delivery. A dominant loss-of-function disease is a demonstration that the drug's mechanism, run chronically in a whole human, produces a defined illness. The distinction between the two objections is the distinction between a hypothetical off-target effect and a documented on-target one.

5.2 The direction of the effect is the surprise

The detail most worth dwelling on is the direction. In neurons, the Alzheimer proposal casts RhoA activation by Ephexin5 as the destructive event, and its suppression as therapeutic. In vessels and bone, *ARHGEF15* loss-of-function causes disease *through RhoA/ROCK2 inactivation*. The same axis, suppressed, is pathogenic in one tissue and proposed as protective in another.

There is nothing incoherent in this. Rho-family signalling is context-specific, and a set-point that is too high in a spine may be load-bearing in a smooth-muscle cell. But it converts the therapeutic problem from one of delivery into one of dose and direction simultaneously, and it removes the argument that made Ephexin5 attractive in the first place: that a protein nearly absent from healthy adult tissue can be inhibited with impunity. *ARHGEF15* is not dispensable in the adult human. One functional copy is not enough.

5.3 What the genetics does not say

Two negative points should be stated plainly, because the human-genetic case for this pathway has occasionally been overstated.

ARHGEF15 is not an established Alzheimer risk locus. It does not appear among the loci reported by the large genome-wide association studies of Alzheimer's disease and related dementias (Bellenguez et al., 2022). The absence of a common-variant signal does not refute a mechanism — most executor genes in most diseases carry no association signal, because executors are downstream of the variance that association studies detect — but it does mean that the pathway's human support is confined to a single report of elevated protein in Alzheimer hippocampus (Sell et al., 2017), without an independent replication that we could identify.

Second, the *ARHGEF15* small-vessel-disease phenotype is not evidence that Ephexin5 participates in Alzheimer's disease. It is evidence about what happens when Ephexin5 function is lost. It bears on the therapy, not on the pathophysiology.

6. Where the synaptic proposal sits in the causal order

6.1 The evidence base is narrower than the claim

The in vivo evidence for the Ephexin5 arm rests, so far as the published record shows, on a single mouse line: hAPP mice overexpressing human amyloid precursor protein, from one laboratory, with the genetic-deletion rescue, the shRNA prevention arm and the amyloid-injection experiment all performed in that system or in cultured hippocampal neurons treated with oligomeric amyloid.

This matters more than it once did. Amyloid-precursor-protein overexpression models are now known to generate phenotypes that do not derive from amyloid-β. Because they overproduce the full complement of APP fragments and not only Aβ, they carry artefacts attributable to the other products and to the overexpression itself — the reason knock-in models carrying humanised *App* with pathogenic mutations at endogenous expression levels were developed (Saito et al., 2014). A phenotype that appears in an overexpressing line and has not been sought in a knock-in line has an unquantified probability of being an artefact of the model. Whether Ephexin5 is elevated in *App* knock-in mice, and whether its deletion rescues spine loss there, is not addressed in the published literature we could identify. It is a cheap experiment and it is the obvious next one.

The human anchor is likewise single-source: elevated Ephexin5 in Alzheimer hippocampus, reported once. There is no published independent replication in a second cohort, no stratification by Braak stage, no cell-type resolution establishing that the elevation is neuronal rather than vascular — a question with unusual force here, given that *ARHGEF15* is expressed in cerebral endothelium and that Alzheimer brain carries a substantial burden of small-vessel pathology.

6.2 The proposal is a claim about execution, not about onset

Even granting every element, the Ephexin5 model is gated on amyloid. Its first step is amyloid-driven EphB2 depletion. Nothing in it explains why amyloid accumulates, and its authors did not claim otherwise.

That places it late. The tangle pathology of Alzheimer's disease begins, in the systematic autopsy series, not in the hippocampus but in the brainstem: pre-tangle tau appears in the noradrenergic neurons of the locus coeruleus in individuals in their third decade, decades before cortical amyloid deposition is detectable (Braak and Del Tredici, 2011; Braak et al., 2011), and locus coeruleus neuron number falls progressively across Braak stages (Theofilas et al., 2017). Whatever

begins the disease is operating in a compartment and at a time that the Ephexin5 model does not address.

This is not a criticism of the model; a theory of execution need not be a theory of onset. But it constrains the therapeutic reading. An intervention aimed at an amyloid-gated executor is an intervention for the symptomatic and immediately pre-symptomatic period, when the executor is running. It is not a prevention strategy, and the shRNA experiment that protected presymptomatic adolescent hAPP mice should not be read as one: in a line that produces amyloid from birth, "presymptomatic adolescent" is not the human presymptomatic period. It is early in a compressed and artificial course.

6.3 What the model still gets right

Three of its features survive every revision above, and they are substantial.

It identifies a physiological programme rather than a novel toxicity. Spine repression through a Rho exchange factor is a mechanism the brain uses; the disease claim is that it is used in the wrong context. Programmes reinstated out of context are efficient, self-limiting in their molecular requirements, and produce no inflammatory signature of their own — which is consistent with the fact that a great deal of synapse loss in this disease occurs without a corresponding local immune signature. The neuron uses its own destructive machinery this way elsewhere: caspase-3, the canonical executioner of apoptosis, is activated within dendritic spines early in an amyloid model, where it drives long-term depression, spine loss and memory impairment without killing the cell (D'Amelio et al., 2011).

It is a *neuron-autonomous* mechanism. Much of the recent work on synapse elimination in Alzheimer's disease has been glial: complement tagging and microglial engulfment, with C1q, C3 or CR3 knockout each rescuing amyloid-independently (Hong et al., 2016). Ephexin5 requires no third cell. As will be argued in section 10, the field now has both kinds of mechanism converging on the same actin machinery, and the existence of a neuron-autonomous arm has direct consequences for how much benefit a purely anti-microglial therapy can be expected to deliver.

And it is falsifiable in a way most synaptic-loss models are not, because it names an enzyme, a substrate, a regulatory residue and a licensing ligase. The revisions described in section 4 were possible precisely because the model was specific enough to be wrong in an informative way.

7. The second proposal as originally stated: a proteasome in the membrane

7.1 The complex

Short-term proteasome inhibition affects processes — neurotransmission, calcium signalling — on timescales too fast to be explained by the accumulation of undegraded proteins. That observation motivated the search that produced the neuronal membrane proteasome: a nervous-system-specific 20S proteasome complex closely associated with the neuronal plasma membrane, exposed to the extracellular space, and catalytically active. Selective inhibition with a cell-impermeant inhibitor blocked the production of extracellular peptides and attenuated activity-induced calcium signalling; the peptides themselves were sufficient to induce neuronal calcium signalling (Ramachandran and Margolis, 2017).

Three features distinguish this complex from the canonical 26S proteasome. It is uncapped — a 20S core without the 19S regulatory particle — and therefore operates without ATP and without ubiquitin recognition. It is membrane-associated, with its catalytic chamber oriented so that products are released outside the cell. And its outputs are not merely disposed of: they act as signals.

7.2 The nascentome

The substrate specificity was defined next. During neuronal stimulation, the neuronal membrane proteasome degrades a large fraction of ribosome-associated nascent polypeptides — proteins caught in the act of being made. Deep-coverage mass spectrometry identified the substrates, which include the products of immediate-early genes such as *Fos* and *Npas4*. Turnover of nascent chains, and not of full-length proteins, proceeded independently of canonical ubiquitylation (Ramachandran et al., 2018).

The functional proposal that follows is a homeostatic one: activity drives synthesis, and the same activity drives a co-translational disposal arm that decides how much of what was just made survives. The two arms are coupled, and the coupling is what sets the amplitude of the response.

7.3 Outward signalling and circuit-level function

Two further results extended the model beyond cell biology. Neuronal-activity-dependent peptides produced by the complex promote NMDA-receptor-dependent calcium influx, sustained CREB phosphorylation and downstream induction of immediate-early and other activity-regulated genes, dependent on NMDA receptors and independent of AMPA receptors or voltage-gated sodium channels (Türker et al., 2024). And in intact *Xenopus laevis* tadpole brain, acute inhibition of the complex rapidly increased spontaneous activity and produced hypersynchrony across tectal neurons, abolished learning-dependent improvement in visuomotor behaviour, and degraded basal performance after enriched visual training (He et al., 2023).

The last of these is the most important for the disease argument, because it converts the proposal from a biochemical curiosity into a statement about circuit homeostasis: a neuron that cannot dispose of what it has just made becomes hyperactive and desynchronised, and the animal cannot learn.

8. The second revision: from preprint to a graded claim about tau

8.1 What was published

The proposition connecting this machinery to Alzheimer's disease existed as a preprint from 2022 and has now been published, with a change of emphasis and a change of numbers.

The published claim identifies the neuron-specific plasma-membrane proteasome — the neuroproteasome — as a determinant of tau proteostasis. Selective inhibition of neuroproteasome function rapidly triggers the *de novo* formation of endogenous, sarkosyl-insoluble tau paired helical filaments in primary neurons and in mouse brain, which share biochemical and ultrastructural features with filaments from human Alzheimer brain. Neuroproteasome abundance at the plasma membrane is differentially modulated by apolipoprotein E isoform in the order E2 > E3 > E4, and declines with age. ApoE4 neurons accumulate tau aggregates after modest neuroproteasome disruption; ApoE2 neurons resist (Paradise et al., 2026).

The experimental design deserves description, because its strength lies in what it does *not* require. The inhibitor is a membrane-impermeant conjugate of epoxomicin, which restricts inhibition to the surface-exposed pool and leaves the cytosolic 26S proteasome untouched. The tau is endogenous, non-mutant, and in the in vivo arm is human tau expressed from the humanised locus of a knock-in line. No seed is applied. No pathogenic mutation is required. Filaments appear in hippocampus within three days of injection — faster than the roughly week-long course typical of seeded aggregation. Co-application of cycloheximide abolishes the effect, which places the requirement squarely on new synthesis rather than on the conversion of an existing soluble pool. Reported thresholds scale with genotype: neurons carrying ApoE4 aggregate tau after approximately twenty per cent inhibition of the surface pool, ApoE3 neurons at around sixty per cent, ApoE2 neurons only at about eighty-five per cent, with surface neuroproteasome abundance reduced by roughly a third in ApoE4 and approximately doubled in ApoE2 relative to ApoE3 (Paradise et al., 2026).

Two points of scholarly hygiene. The preprint expressed the genotype effect as a fold-shift in aggregation threshold — approximately twenty-five-fold relative to ApoE3 and approximately two-hundred-fold relative to ApoE2 — whereas the published account expresses it as the fraction of inhibition required. These are different quantities and are not interchangeable; the fold-shift figures should not be carried forward, and any secondary source reporting a fifty-fold shift relative to

ApoE3 has compounded the error. And the two accounts differ in what they claim to have made: the preprint reported tau *aggregates*, the published paper reports paired helical *filaments*. The upgrade is consequential, and it is where the principal outstanding objection lies.

8.2 Why this is a better class of claim than it was

Three things changed with publication, and each raises the model's standing.

The mechanism became an initiation mechanism rather than a permissive one. A model in which apolipoprotein E4 "impairs proteostasis" is a risk-factor model. A model in which a defined, selective, acute perturbation is *sufficient* to produce filaments of endogenous tau in wild-type-sequence protein, in three days, in vivo, without seeding, is a candidate account of how the first filament forms. Alzheimer's disease has not had many of those.

The genotype effect acquired a shape. Apolipoprotein E4 has been connected to tau before — most forcefully by the demonstration that ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse tauopathy model (Shi et al., 2017) — and the epidemiology has hardened to the point where ApoE4 homozygosity has been argued to constitute a distinct genetic form of the disease (Fortea et al., 2024). What has been missing is a neuron-autonomous, quantitative mechanism by which the isoform sets tau risk. Surface abundance of a tau-degrading proteasome, ordered E2 > E3 > E4, is such a mechanism, and it has the correct shape: the protective allele is not merely the absence of the risk allele but an active gain, mirroring the way the protective *APOE3* Christchurch variant behaves in the one human case of near-complete resistance to autosomal-dominant Alzheimer's disease that has been documented in detail (Arboleda-Velasquez et al., 2019).

And the model became explicitly age-dependent. Neuroproteasome membrane abundance declines with age. That is the correct dependency for a disease whose overwhelming risk factor is age, and it converts the genotype effect into a two-factor threshold model: the surface pool falls with age in everyone, and where a given individual's threshold sits is set by isoform.

8.3 The dendritic locus

A companion study, currently a preprint and to be treated as such, localises the process. Using a method for visualising the subcellular site of endogenous messenger-RNA translation with single-molecule sensitivity and without modifying the nascent chain, it reports that despite broad distribution of *Mapt* messenger RNA, tau is translated almost exclusively in dendrites, and that about one third of newly synthesised tau is co- or peri-translationally degraded there by the neuroproteasome. Failure of that degradation leads to protein-synthesis-dependent accumulation of somatodendritically mislocalised tau aggregates (Konrad-Vicario et al., 2025, preprint).

If that result survives review, it closes a gap that has been open for fifteen years. Somatodendritic mislocalisation of tau is one of the best-documented early events in the disease: amyloid oligomers cause localised calcium elevation and missorting of endogenous tau into dendrites, hyperphosphorylated tau within intact spines impairs receptor trafficking without neuronal death, and the dendritic pool of tau is the pool that targets Fyn to the post-synaptic density and thereby confers amyloid toxicity (Zempel et al., 2010; Hoover et al., 2010; Ittner et al., 2010). All of that literature treats dendritic tau as *mislocalised* — as protein that arrived where it should not be. The new result proposes instead that dendritic tau is where tau is made, that a third of it is normally destroyed on the spot, and that the disease phenotype is a failure of local disposal rather than a failure of local exclusion. That is a different account of the same observation, and it is testable against the old one.

8.4 What is not established

Four objections stand, and they should be stated at their full strength.

The filament identity is not structurally proven. Negative-stain electron microscopy resolves helical periodicity but cannot establish that a filament adopts the Alzheimer fold, and the Alzheimer fold is the definition of a paired helical filament in the modern, cryo-electron-microscopic sense (Fitzpatrick et al., 2017). Until cryo-electron microscopy is performed on these filaments, the claim that the model produces Alzheimer-type tau filaments rests on morphology and biochemistry. The authors have acknowledged this and stated an intention to perform the structural work; the absence of filaments in tau-knockout material argues that the material is tau, which is a different question from whether it is a paired helical filament.

The structural basis of membrane association is unresolved. The 20S proteasome is a hydrophilic barrel with no obvious means of embedding in a lipid bilayer, and how the complex is held at the membrane with its chamber facing outward remains, at the level of structure, unexplained. A multipass transmembrane glycoprotein of the GPM6 family has been proposed as the anchor; the proposal has not been established to the standard the claim requires. This is the most frequently voiced reservation about the entire neuroproteasome concept and it is a fair one: an unexplained topology is a reason for caution, not for dismissal, but it is a reason.

It is not known whether the disease-relevant variable is catalytic activity or membrane localisation. Apolipoprotein E4 reduces the amount of complex at the surface; the inhibitor blocks the activity of the complex at the surface. These are treated as equivalent perturbations, and they may not be. A complex that is present but inactive and a complex that is absent are different states for any function that depends on the complex's physical presence — scaffolding, peptide release, membrane organisation — rather than on its proteolysis.

And independent replication is outstanding. Both the neuroproteasome concept and the tau result originate from a small number of closely connected laboratories. The concept is now more than eight years old and has been extended in vivo in a second species by a partly independent group (He et al., 2023), which is meaningful; the tau result is months old.

9. The point at which the two proposals meet

The two proposals have been presented, including by the laboratory that produced both, as complementary but distinct: one explains spine loss downstream of amyloid, the other explains tau aggregation downstream of apolipoprotein E. We think they are less independent than that, and the argument runs through a detail that has been available since 2017 without being connected.

9.1 Ephexin5 is a protein whose dendritic level is set by activity-dependent proteasomal degradation

The 2017 spine-outgrowth study reported, alongside its main result, that increased neural activity produced a *proteasome-dependent reduction in the levels of Ephexin5 in neuronal dendrites* (Hamilton et al., 2017). That is a specific claim: the controlled variable is dendritic Ephexin5; the control is proteolytic; the trigger is activity.

The neuroproteasome is a proteasome that is dendritic, activity-regulated, and specialised for the destruction of protein that has just been made. The coincidence of properties is close enough to be worth stating as a hypothesis: **the neuroproteasome is a candidate for the protease that clears Ephexin5 from the activated dendrite.**

We are careful about what this is. It is not shown. Ephexin5 was not among the nascent substrates reported in the neuroproteasome proteomics (Ramachandran et al., 2018), though absence from a published substrate list is weak evidence given coverage limits, and the reported inhibition experiment identified more than two hundred and fifty proteins accumulating in the soluble fraction without exhaustive enumeration. Ephexin5's characterised degradation route is ubiquitin- and Ube3A-dependent (Margolis et al., 2010), which is the canonical 26S route and not the neuroproteasome's; but the neuronal dendrite plainly contains both machines, and a protein may have more than one disposal route with different kinetics and different triggers. The specific proposal here is that the *activity-dependent, rapid* component of dendritic Ephexin5 turnover — the component reported in 2017 — is neuroproteasomal, while the *EphB2-licensed, Ube3A-dependent* component is canonical.

9.2 Why it would matter

If the hypothesis is right, three things that are currently asserted without mechanism acquire one.

It would explain why apolipoprotein E4 should make spines fragile. The claim that ApoE4 promotes Ephexin5-dependent spine collapse has been made in synthetic accounts of this literature, but it has been an assertion of association rather than a mechanism. If ApoE4 reduces the surface neuroproteasome pool by roughly a third, and if that pool clears dendritic Ephexin5 after activity, then the ApoE4 dendrite holds more Ephexin5 after every episode of activity than the ApoE3 dendrite does — before amyloid enters the story at all. The genotype would set the resting level of the executor.

It would predict a specific interaction between the two arms. On this account, amyloid-driven EphB2 loss and apolipoprotein-E4-driven neuroproteasome loss are two independent lesions in the disposal of one protein, one removing the licensing signal and the other removing capacity. Their effects on dendritic Ephexin5 should be at least additive and plausibly synergistic, which would give a molecular reading of the well-established clinical observation that amyloid and *APOE4* interact.

And it would unify the compartment. Both proposals would become statements about the same thing: the dendrite's capacity to dispose of newly made protein. Tau and Ephexin5 are both made in the dendrite — tau, on the new evidence, almost exclusively there — and both are, on this reading, held below a pathogenic level by local degradation rather than by restrained synthesis. The disease would consist in the failure of one disposal compartment, with two readouts: a filament, and a spine.

9.3 The experiments

Three experiments would test it, in ascending order of cost.

Apply the membrane-impermeant neuroproteasome inhibitor to mature hippocampal neurons and measure dendritic Ephexin5 by immunocytochemistry and by biochemical fractionation, with and without chemical long-term potentiation. If the activity-dependent fall in dendritic Ephexin5 is abolished by surface-restricted inhibition, the hypothesis is supported. If it survives surface-restricted inhibition but is abolished by MG132, the canonical proteasome is responsible and the hypothesis is refuted.

Measure Ephexin5, total and phospho-Y361, in the ApoE2, ApoE3 and ApoE4 knock-in neurons already generated for the tau work. The prediction is an inverse ordering to neuroproteasome surface abundance: Ephexin5 highest in ApoE4.

Cross the *ARHGEF15*-null line onto an *App* knock-in background — replacing the amyloid-overexpressing line the original rescue used — and ask whether the spine and behavioural rescue reproduces at endogenous amyloid-precursor-protein expression. This is the replication the synaptic proposal most needs on its own terms, and it becomes considerably more interesting if performed across apolipoprotein E genotypes.

9.4 The third leg: general proteasome failure

There is a wider context that neither proposal has incorporated and that strengthens both. Proteasome function is impaired in Alzheimer brain, and the impairment is early, intrinsic and neuron-selective. Kinetic assay, purification of intact 26S complexes, in-gel activity assays and proteomics of post-mortem tissue converge on reduced proteolytic capacity that persists after purification — implicating defects within the complex rather than merely its environment — with proteasomes co-purifying with aggregation-prone substrates including tau, and with constitutive proteasome subunit genes progressively downregulated along the Braak axis (Jiang et al., 2025), apparent at the earliest stages, in tissue without overt tau aggregation. Neurons are disproportionately affected. The compensatory transcriptional response that should follow is blocked: expression of the transcription factor NFE2L1 rises, but NRF1 fails to localise to the nucleus.

Both proposals are, in this light, specific instances of a general failure that begins before the lesions do. That is an argument for taking them seriously and an argument against treating either as *the* mechanism. If the neuron's whole degradative apparatus is losing capacity from the earliest stage, then the interesting question is not whether a particular protein escapes disposal but which proteins escape first, and why those. Tau and Ephexin5 are two answers. There will be others.

10. Downstream: the arms converge on one actin machine

A separate reason for scepticism about single-target therapy on this pathway has nothing to do with Ephexin5's regulation and everything to do with what it shares with its competitors.

A dendritic spine is an actin structure. Its volume is a balance between filament nucleation and filament severing, and the severing is done by cofilin, whose activity is suppressed by phosphorylation through LIM-domain kinase and restored by dephosphorylation (Bamburg and Bernstein, 2016). Rho-family GTPases control this balance: RhoA acts through Rho-associated kinase to LIM-domain kinase and thence to cofilin, while Cdc42 and Rac1 drive nucleation and growth.

At least four distinct upstream arms in Alzheimer's disease converge on that machine.

Amyloid oligomers acting through LilrB2/PirB enhance cofilin signalling — demonstrated in mouse and detected in human Alzheimer cortex — and PirB is required for the deleterious effect of oligomers on hippocampal long-term potentiation and contributes to memory deficits in a transgenic model (Kim et al., 2013).

The complement fragment C4d, a high-affinity LilrB2 ligand, is elevated in ageing and further in Alzheimer's disease, colocalises with LilrB2 at excitatory synapses in human cortex, and reduces dendritic spine density on cortical pyramidal neurons — an effect completely prevented by knockout of PirB (Brott et al., 2025). This is a neuron-autonomous elimination signal converging on the same receptor as amyloid.

Complement-tagged synapses are engulfed by microglia, and knockout of C1q, C3 or CR3 each rescues synapse loss amyloid-independently (Hong et al., 2016) — a glial arm whose terminal effector is phagocytic rather than cytoskeletal, but which acts on the same object.

And the Ephexin5 arm, on its original reading, drives RhoA and thereby the same LIM-kinase-to-cofilin axis. The step from Ephexin5 to ROCK to LIM-kinase to cofilin in Alzheimer neurons has not been demonstrated directly and should be labelled as inference from canonical Rho signalling rather than as an established chain in this disease.

The consequence is a redundancy argument, and it is not a comfortable one for any single-target programme. Four arms converging on one effector means that blocking any one of them leaves the effector reachable by the others. It predicts partial efficacy for any monotherapy on

this pathway, which is what the field has generally observed. And it argues that the more efficient point of intervention may be the shared effector rather than any individual arm — with the immediate objection that cofilin and the Rho-kinase axis are required for normal structural plasticity, so that a therapy at the convergence point has the same problem as a therapy at Ephexin5, only more so.

There is one asymmetry worth noting. The arms are not equally reachable. The complement arm has agents in clinical development; the LilrB2 arm is an extracellular receptor with an unusual property, in that the same receptor is inhibitory on myeloid cells and instructive on neurons, so blockade is predicted both to prevent neuron-autonomous spine collapse and to release a brake on microglial clearance. The Ephexin5 arm is intracellular, enzymatic, pleiotropic, and — as section 5 established — attached to a dominant human loss-of-function disease. On tractability alone it is now the least attractive of the four.

11. Two proposals, two epochs

Placing each proposal on a timeline is the most consequential thing that can be done with them, because it determines who could be treated and when.

The synaptic proposal is amyloid-gated. Its first step requires amyloid-β to deplete EphB2, so it cannot begin before there is enough soluble oligomer in the relevant compartment to do so. In the human course, that is late: it follows amyloid deposition, which follows the brainstem tau pathology that appears in the third decade by a considerable interval. The Ephexin5 arm is therefore a mechanism of the symptomatic and immediately prodromal period. It executes; it does not initiate.

The proteostatic proposal has the opposite time signature. Its two determinants are apolipoprotein E genotype, which is fixed at conception, and age, which is monotonic. Neither requires amyloid. A neuron carrying ApoE4 begins life with a smaller surface neuroproteasome pool than a neuron carrying ApoE3, and that pool declines with age in both. On this model the threshold for tau filament formation is crossed when the declining pool meets the genotype-set requirement, and nothing in the account requires an amyloid intermediate.

That is a claim with real consequences, and it should be stated at its strongest and then qualified. At its strongest: this is a candidate mechanism for tau pathology arising before, and independently of, amyloid — which is what the human autopsy record has appeared to demand since pre-tangles were documented in the locus coeruleus of young adults with no cortical amyloid (Braak and Del Tredici, 2011). The mechanism is age- and genotype-scaled, neuron-autonomous, and requires only that a neuron make tau and lose disposal capacity.

The qualification is that no one has looked at the locus coeruleus. Neuroproteasome abundance has not been measured in noradrenergic brainstem neurons at any age; whether these cells are early or late in the age-related decline is unknown. It is an attractive candidate for early failure — these are cells with very long, thinly myelinated, extensively branched projections and correspondingly heavy demands on protein synthesis and delivery — but that is a plausibility argument, not a measurement, and should be treated as a hypothesis to be tested rather than as part of the model. The measurement is straightforward: quantify surface neuroproteasome in locus coeruleus, entorhinal cortex and hippocampus across the adult age range, stratified by apolipoprotein E genotype, in post-mortem tissue without tau pathology.

There is a second, subtler consequence. If tau filament formation is set by a threshold on disposal capacity rather than by exposure to a seed, then two phenomena that are usually treated as puzzles become expectations. The first is the poor correspondence between amyloid burden and

tangle burden across individuals — expected, if the two lesions are governed by different variables. The second is the strong dependence of tau pathology on neuronal activity: activity stimulates the physiological release of tau (Pooler et al., 2013), and enhances tau propagation and pathology in vivo (Wu et al., 2016). On the disposal model, activity is doubly implicated, since activity is also what drives the nascent synthesis that the neuroproteasome exists to trim. A neuron that fires more makes more tau and must dispose of more tau. A neuron that fires more with a reduced disposal capacity is exactly the substrate the model predicts.

Table 1 — The two proposals compared on the variables that matter for therapy

Variable	Synaptic proposal (Ephexin5)	Proteostatic proposal (neuroproteasome)
Lesion explained	Dendritic spine loss	*De novo* tau filament formation
Compartment	Dendritic spine / shaft	Dendritic plasma membrane
Controlled variable	Abundance and substrate-selectivity of one exchange factor	Surface abundance of a degradative complex
Upstream requirement	Amyloid-β, via EphB2 depletion	None; apolipoprotein E isoform and age
Position in the course	Executor; symptomatic and prodromal	Candidate initiator; lifelong, threshold-crossing
Genetic anchor in humans	*ARHGEF15* loss-of-function causes small-vessel disease; not an Alzheimer risk locus	*APOE* is the largest common risk factor; effect ordered E2 > E3 > E4
Human tissue evidence	Elevated protein, single report	Isoform-graded surface abundance; age decline
Principal unresolved objection	Sign of the effect, given substrate switching	Structural identity of the filaments; membrane topology
Direction of the revision	Weakened; prescription inverted	Strengthened; claim sharpened

12. Strength of evidence

The claims made across both proposals differ widely in how well they are supported, and a reader is entitled to see that difference set out rather than inferred from hedging in the prose. The following grading is applied throughout this paper. **Established** denotes a claim supported by direct experiment with an appropriate control, replicated or from more than one system. **Supported** denotes a claim resting on direct experiment from a single system or a single group, without independent replication. **Inference** denotes a claim assembled from established components but not itself tested. **Open** denotes a claim that is proposed here or elsewhere and not yet addressed by any published experiment.

Table 2 — Strength of evidence for the principal claims

Claim	Grade	Basis and limit
Synapse loss is the strongest structural correlate of cognitive decline	Established	Autopsy and biopsy series; corroborated in vivo by SV2A imaging
EphB2 is depleted by amyloid-β and its restoration rescues cognition in a mouse model	Established	Independent group; rescue design
Ephexin5 is degraded following EphB-dependent phosphorylation via Ube3A	Established	Biochemistry with ligase identification
Ephexin5 protein is elevated in Alzheimer hippocampus	Supported	Single report; no independent cohort; no cell-type resolution
Ephexin5 deletion rescues spine loss and behaviour in hAPP mice	Supported	One overexpressing line, one group; not tested in *App* knock-in
Ephexin5 activates Cdc42 as well as RhoA	Established	Pulldown in knockout brain plus single-spine biosensor imaging
Substrate selectivity is set by tyrosine phosphorylation at Y361	Established	Phosphomutant rescue with catalytically dead control
Ephexin5 is required for activity-dependent long-term spine growth	Established	Knockout plus structured re-expression rescue
Y361 is both the selectivity switch and the degradation licence	Inference	Each half established separately; the coupling is not itself tested

Claim	Grade	Basis and limit
The Alzheimer dendrite holds Ephexin5 that is abundant *and* RhoA-biased	Open	Requires phospho-Y361 measurement in disease tissue; not published
***ARHGEF15* loss-of-function causes cerebral small-vessel disease with osteoporosis**	Established	Co-segregating families, sporadic cases, cellular mechanism, mouse model
***ARHGEF15* is not an established Alzheimer risk locus**	Established	Absent from large genome-wide association studies
Neurons possess a catalytically active 20S proteasome at the plasma membrane	Supported	Multiple papers, small number of connected groups; topology unexplained
The complex degrades activity-induced nascent polypeptides ubiquitin-independently	Supported	Deep proteomics with substrate identification
Its inhibition alters circuit activity and blocks learning in vivo	Supported	Independent laboratory, second species
Selective inhibition induces sarkosyl-insoluble endogenous tau filaments in three days	Supported	Membrane-impermeant inhibitor; cycloheximide-sensitive; single group
Those filaments adopt the Alzheimer paired-helical fold	Open	Negative-stain morphology only; cryo-electron microscopy not yet performed
Surface neuroproteasome abundance is ordered E2 > E3 > E4 and declines with age	Supported	In vitro, in vivo and human post-mortem; single group
Tau is translated almost exclusively in dendrites, with a third degraded locally	Open	Preprint; not yet peer-reviewed
Proteasome capacity falls early and neuron-selectively in Alzheimer brain	Established	Multi-modal human post-mortem study across Braak stages
The neuroproteasome clears activity-induced dendritic Ephexin5	Open	Proposed here; each premise published, the junction untested
Amyloid, C4d and Ephexin5 arms converge on cofilin	Inference	Cofilin convergence established for the first two; the Ephexin5 chain is canonical but not shown in this disease

13. Therapeutic reassessment

13.1 The Ephexin5 prescription must be rewritten

The 2017 recommendation — reduce Ephexin5 levels — is no longer supportable in that form, for three independent reasons, any one of which would be sufficient.

Reducing the protein removes the growth arm along with the collapse arm. Ephexin5-knockout neurons cannot sustain activity-driven spine growth, and the deficit is rescued only by catalytically competent exchange factor (Petshow et al., 2025). A drug that lowers Ephexin5 in a patient whose remaining synapses depend on activity-driven structural plasticity is removing a component of the repair capacity at the same time as it removes a component of the damage.

Chronic reduction has a human phenotype, and it is a dementing one. Heterozygous loss of function causes cerebral small-vessel disease with osteoporotic fracture (Ding et al., 2023), through the inactivation of the same RhoA/ROCK2 axis that the neuronal argument proposes to suppress. Any systemic agent that lowers Ephexin5 function is, mechanistically, titrating a patient toward a Mendelian vasculopathy — in a population already carrying a substantial burden of cerebrovascular disease.

And the sign of the neuronal effect is not secure. Section 4.3 sets out why the disease state of the Y361 switch is unmeasured, and why the model's prediction and the substrate-switching model's prediction currently point in opposite directions.

What replaces it is narrower and harder. If the disease-relevant lesion is a switch stuck in the RhoA position rather than an excess of protein, then the object of intervention is the switch: an agent that biases substrate selection toward Cdc42 without depleting the enzyme — functionally, a small-molecule mimic of the Y361F state — or an agent that restores the activity-driven dephosphorylation that potentiation normally produces. Neither exists. Both would require structural work on the inhibitory-helix-to-DH-domain interface that the phosphomutant work has now localised, which is at least a defined starting point. The alternative of neuron-restricted degradation — targeted protein degradation delivered under a neuronal promoter — solves the tissue-selectivity problem created by the small-vessel phenotype but not the intraneuronal problem created by the growth arm, since it removes the protein rather than biasing it.

The honest position is that the Ephexin5 arm is presently a target with an identified enzymology, a defined regulatory residue, a documented human loss-of-function syndrome, an unresolved sign, and no viable chemical matter. That combination argues for further biology rather

than for a drug programme.

13.2 Downstream, at ROCK

Blocking the effector rather than the exchange factor is the obvious alternative and has independent motivation: pharmacological inhibition of ROCK2 suppresses amyloid-β production in an Alzheimer mouse model (Herskowitz et al., 2013), and Rho-kinase II phosphorylation of the sorting receptor LR11/SORLA alters amyloid-β production (Herskowitz et al., 2011) — so the axis has an amyloid-processing rationale as well as a cytoskeletal one.

The difficulty is a symmetry that has not been remarked upon. The human *ARHGEF15* syndrome is caused by RhoA/ROCK2 *inactivation* in vascular cells. A systemic ROCK inhibitor reproduces, pharmacologically and in the same tissue, the biochemical state that the Mendelian disease produces genetically. That is a specific, mechanistically grounded reason to expect cerebrovascular liability from chronic ROCK inhibition in this indication, and it is stronger than a generic caution about a pleiotropic kinase. It argues for isoform selectivity, for central restriction, and for careful vascular monitoring in any trial.

13.3 The neuroproteasome inverts the usual pharmacology

The proteostatic proposal presents an unusual therapeutic geometry, and it is worth being explicit about it because it is the opposite of what the field is tooled for.

Every existing proteasome drug is an inhibitor. The therapeutic requirement here is the reverse: to *increase* the amount of catalytically competent complex at the neuronal surface, or to slow its age-related loss. There is no established pharmacology for that. The tractable handles, in ascending order of speculativeness, are: the trafficking step that delivers the complex to the membrane and the anchor that retains it, which is the least characterised and therefore the most likely to yield a target once the anchor is settled; the apolipoprotein E axis itself, where agents that shift ApoE4 toward ApoE3-like behaviour are already in development for other reasons and would, on this model, raise the surface pool as a consequence; and the extracellular peptide output of the complex, which on the outward-signalling results is itself a functional signal (Ramachandran and Margolis, 2017; Türker et al., 2024), raising the possibility of replacing a lost output rather than restoring the machine that makes it.

The negative recommendation is firmer than any of the positive ones, and it should be stated. Systemic proteasome inhibition — an established class in oncology — is, on this model, a mechanism for inducing tau filament formation. The published experiment is precisely that: selective inhibition of the surface pool produces sarkosyl-insoluble filaments in three days (Paradise et al., 2026). Whether clinically used proteasome inhibitors reach the surface-exposed neuronal pool at therapeutic exposures is a question about pharmacokinetics rather than about mechanism, and it is answerable. It should be asked.

13.4 Who, when, and measured how

Three practical consequences follow from the revisions, independent of which agent is chosen.

The two proposals imply different trial populations. The proteostatic mechanism is genotype-graded and age-graded, and its natural population is *APOE4* carriers in mid-life — the group in whom the threshold model predicts the earliest crossing and in whom homozygosity has been argued to constitute a distinct genetic form of the disease (Fortea et al., 2024). The synaptic mechanism is amyloid-gated and its natural population is amyloid-positive symptomatic patients, which is the population already being enrolled.

The endpoint for any anti-elimination therapy should be synaptic density. SV2A positron-emission tomography measures the operative lesion in living patients (Mecca et al., 2020), sits closer to cognition than atrophy, and sits closer to the mechanism than amyloid or tau burden. A trial powered on synaptic density tests the therapy and the model at once, which a cognitive endpoint does not.

And the redundancy argument of section 10 predicts partial effect sizes for any single arm. If four upstream arms converge on one actin effector, a trial designed around a single arm should be powered for a fraction of the total elimination signal, not for its abolition — and its failure, if it fails, should not be read as refuting the mechanism.

14. Predictions

The following are stated so that they can be checked. Each is falsifiable with existing methods, and for each we name the result that would count against it.

1. **Phospho-Y361 Ephexin5 is elevated relative to total Ephexin5 in Alzheimer hippocampus.** Falsified by a reduced or unchanged phospho-fraction with elevated total protein, which would invert the sign of the synaptic model.

2. **Active RhoA is elevated and active Cdc42 unchanged or reduced in the same tissue.** Falsified by elevated active Cdc42, which would recast Ephexin5 accumulation as a growth-directed response.

3. **Ephexin5 elevation reproduces in *App* knock-in mice at endogenous expression, and its deletion rescues spine loss there.** Falsified by absence of elevation in knock-in animals, which would assign the original finding to amyloid-precursor-protein overexpression.

4. **Membrane-impermeant neuroproteasome inhibition abolishes the activity-dependent fall in dendritic Ephexin5.** Falsified if the fall survives surface-restricted inhibition but is abolished by a cell-permeant inhibitor, which would assign the turnover to the canonical proteasome and refute the junction proposed in section 9.

5. **Dendritic Ephexin5 is highest in ApoE4 and lowest in ApoE2 neurons, inversely to surface neuroproteasome abundance.** Falsified by no ordering, or by an ordering in the same direction as neuroproteasome abundance.

6. **The filaments produced by neuroproteasome inhibition adopt the Alzheimer paired-helical fold by cryo-electron microscopy.** Falsified by a distinct fold, which would leave the cell biology intact but sever the model from human tauopathy.

7. **Surface neuroproteasome abundance in human brain declines earliest in the locus coeruleus among the regions that develop tau pathology first.** Falsified by an absent or reversed regional gradient. This is the weakest of the predictions and is offered as a hypothesis rather than an expectation.

8. **Neuroproteasome inhibition raises the levels of the synaptic Rho-family exchange factors, Ephexin5 among them, in the accumulating soluble fraction.** Falsified by their absence from a well-powered proteomic re-analysis of the existing inhibition datasets. This is the cheapest test of section 9 and requires no new experiment, only re-interrogation of data already collected.

9. **Combined amyloid exposure and ApoE4 genotype raise dendritic Ephexin5 more than either alone.** Falsified by additivity indistinguishable from either single factor, or by occlusion.

15. Limitations

The argument of this paper has four principal weaknesses, and they should be weighed against its claims.

The junction proposed in section 9 is a hypothesis constructed from two published observations that were made for different purposes. Its premises are individually sound — dendritic Ephexin5 falls in an activity- and proteasome-dependent manner; the neuroproteasome is an activity-regulated dendritic proteasome for newly made protein — but the inference that the second explains the first is exactly the kind of assembly that looks compelling in prose and fails in an experiment. It is offered as a prediction with a stated test, and it should be read at that grade and no higher.

The critique of the synaptic proposal leans on a single 2025 study for its central mechanistic claim. That study is careful, uses independent methods, and includes the structured rescues that the inference requires; but it is one paper from one laboratory, and the field's history with this exchange factor is one of successive revisions. It may itself be revised.

The tau claim is very new. A result published within months, from a small number of connected laboratories, carrying an acknowledged structural gap, is not yet a settled fact. This paper has graded it as supported rather than established for that reason, and the grading should be revisited when cryo-electron microscopy and independent replication arrive.

And the temporal placement in section 11 rests on the autopsy-derived staging of the disease. That staging is strong evidence about the order in which lesions appear and weak evidence about causation; a lesion that appears first is not thereby the cause of what follows. The argument that the proteostatic proposal is better positioned as an initiator than the synaptic proposal is an argument about compatibility with the observed order, not a demonstration of initiation.

16. Conclusion

Two proposals were made about the Alzheimer dendrite. One said that a developmental brake on synapse formation is re-applied in the adult brain, and that removing the brake would be therapeutic. The other said that a proteasome at the neuronal surface disposes of newly made protein, and that when apolipoprotein E4 and age reduce it, tau polymerises.

A decade of evidence has treated them differently. The brake turned out not to be a brake. It is a switch, thrown at a single tyrosine, that selects between an arm that collapses spines and an arm that grows them — and the growing arm is required for the structural plasticity that potentiation depends on. The residue that throws the switch is the residue that licenses the protein's own destruction, so its abundance and its activity cannot be manipulated separately. And the one human genotype that reveals what chronic loss of this protein does produces a dementing cerebrovascular disease with skeletal fragility. The prescription that followed from the original model would, if delivered systemically, phenocopy that disease while removing a component of the neuron's repair capacity. The model's descriptive content — that a physiological programme is running in the wrong context, neuron-autonomously, without an inflammatory signature — survives. Its therapeutic content does not.

The proteasome proposal moved the other way. It acquired a selective tool, an endogenous non-mutant substrate, a three-day in vivo timecourse, a cycloheximide-sensitive requirement for new synthesis, an ordered genotype effect running the right way across all three apolipoprotein E isoforms, and an age dependency. It now names a candidate mechanism for the initiation of tau pathology that requires no amyloid intermediate, which is what the human record has been asking for. Its unfinished business is structural rather than cell-biological: whether the filaments it makes are the filaments the disease makes is a question for cryo-electron microscopy, and until that is done the model's link to human tauopathy is morphological.

The more interesting possibility is that these are not two proposals. Both concern the disposal of newly made protein in one compartment. Ephexin5's dendritic level is set by activity-dependent proteolysis; the neuroproteasome is the activity-dependent dendritic protease for newly made protein; and no one has asked whether the second sets the first. If it does, the largest genetic risk factor for the disease acquires a direct mechanistic route to spine fragility that it has never had, the two lesions become two readings of one failure, and the compartment — not the molecule — becomes the object of therapy. That question is answerable with reagents that already exist, and in one case with data that have already been collected.

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