
No Switch but the Endosome

The pruning receptor, the licensing architecture above cofilin, and the compartment in which both instructions have to end — two literatures on the loss of the dendritic spine that share a cell, a residue and a compartment, and do not share a single citation

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A signal ends when its ligand leaves or its receptor does. At this synapse the ligand does not leave, and the receptor is removed by the one compartment that fails before anything else in this disease can be seen. The instruction is not too strong. It is never withdrawn.

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Abstract

Two bodies of work describe the loss of an excitatory synapse in Alzheimer's disease, and they do not cite one another.

The first is a twenty-seven-year programme in developmental neuroscience. It established that neurons express class I MHC molecules under the control of their own activity; that an inhibitory immune receptor on their dendrites — PirB in the mouse, LILRB2 in the human — restrains spine density and plasticity for life; and that in Alzheimer's disease two pathological ligands, soluble amyloid- β oligomers and the complement fragment C4d, engage that receptor at the same two immunoglobulin domains that bind its physiological ligand, with the consequence that the neuron takes its own spines apart. The second is an architecture assembled from cell biology, human genetics and the reelin literature. It holds that the sign of the structural change at a spine is set above cofilin serine 3, at a tyrosine on each of two opposed transducers; that in both transducers the phosphorylation which activates the transducer is the phosphorylation which condemns it to the proteasome; and that the instruction is therefore terminated by destruction rather than by dephosphorylation.

The two accounts meet at one residue and are usually left there. This paper asks what happens when they are made to meet at the compartment instead, and reports three things.

The receptor's own termination step is endocytosis, and it was demonstrated nine years before the neuroscience arrived. In 2016 an immunology laboratory screening for receptors of the complement split product C4d identified Ig-like transcript 4 — the alternative name for LILRB2 — as a cellular receptor for C4d, and showed that engagement of surface ILT4 by soluble monomeric C4d results in the endocytosis of the ligand (Hofer et al., 2016). That result places the OFF switch of this receptor inside the early endosome. It is the same compartment in which the licensing transducers below it are disposed of, and the same compartment whose enlargement is the earliest disease-specific structural abnormality in sporadic Alzheimer's disease (Cataldo et al., 2000), whose sorting receptor is a causal human gene (Hung et al., 2021), and whose recycling failure is the mechanism by which the commonest risk allele silences the protective arm (Chen et al., 2010; Xian et al., 2018). The convergence is not thematic. Both instructions at this synapse are ended in one organelle, and that organelle fails first.

Both of the receptor's disease ligand claims rest on a preparation that is not the one in the tissue, and the second has an unanswered negative result that has not been noticed. That the amyloid arm is contested is known: in the only standardised comparison, LILRB2 bound synthetic synaptotoxic assemblies but showed no detectable binding to oligomers extracted from human Alzheimer brain (Smith et al., 2019). The complement arm has been treated as free of that objection. It is not. Hofer and colleagues reported that soluble ILT4 bound soluble monomeric C4d but that binding to C4d **covalently immobilised on a cell**

surface by actual complement activation could not be detected, and concluded that the biological activity of surface-oriented C4d depends on a receptor still to be identified. The 2025 paper that reports C4d as a LILRB2 ligand uses soluble recombinant C4d throughout — dot blots probed with a soluble receptor ectodomain, surface plasmon resonance, and a four-day cortical infusion — while its human anatomy reports the deposited pool. It does not cite the 2016 work. The two arms of the programme therefore share one objection, in the same shape, and the newer arm is not on this axis the better-evidenced one.

And the licensing tyrosine has a sign problem that only becomes visible when the two literatures are placed together. Three independent routes lower the phosphorylated fraction of Ephexin5 tyrosine 361 in the Alzheimer dendrite: amyloid drives the writing kinase EphB2 into the proteasome; the tyrosine phosphatase STEP61 accumulates because its own disposal fails; and — on the evidence assembled in Section 5 — the restraint receptor recruits SHP-1 and SHP-2 to that membrane, a limb already shown in neurons to dephosphorylate a third-party receptor tyrosine kinase. All three predict what is observed, that Ephexin5 protein accumulates, because the phosphorylated form is the degraded form. All three predict the opposite of what is observed for the sign, because dephosphorylation at that residue biases the exchange factor toward Cdc42 and spine growth. The accumulation is over-explained and the collapse is unexplained, and the measurement that separates the four available resolutions — the ratio of active RhoA to active Cdc42 in amyloid-bearing hippocampus — has not been reported.

The paper ends with what follows for treatment, and the conclusion is narrow rather than encouraging. Every therapeutic route proposed on either side is either a level intervention on a timing problem, or a removal of restraint whose long-horizon cost has never been measured. The one route that is neither — inhibiting the proteolytic cleavage that turns this receptor's cytoplasmic tail into an inhibitor of the adaptor that delivers hydrolases to the lysosome — repairs the clock and spares the signal at the same time, and rests on a single unreplicated paper.

i. Introduction

1.1 Two accounts of one event

An excitatory synapse present on a cortical pyramidal neuron at fifty is absent at eighty, and the density of such synapses is the strongest structural correlate of cognitive impairment in Alzheimer's disease — a multivariate correlation of 0.96 against the Dementia Rating Scale in the study that established it, where plaque density contributed twenty-six per cent of the model's strength (Terry et al., 1991). Any account of the disease that means to reach the clinic has to say what removed the contact.

Two accounts do, in mechanistic detail, and they were built by people who have never read each other.

The first begins in 1998 with a screen that returned the wrong answer. Corriveau, Huh and Shatz blocked spontaneous retinal activity and looked for transcripts that changed; what fell were messenger RNAs encoding class I major histocompatibility complex molecules, which the brain was believed not to express (Corriveau et al., 1998). Twenty-seven years of work followed. Mice unable to present class I MHC fail to refine their retinal projections and lose long-term depression while gaining potentiation (Huh et al., 2000). Two genes out of the family's fifty account for most of the phenotype, and restoring one of them to neurons alone, in an animal whose immune system stays broken, rescues synapse elimination (Datwani et al., 2009; Lee et al., 2014). A receptor for these ligands, paired immunoglobulin-like receptor B, sits on cortical neurons, associates with synapses, forms complexes with the protein tyrosine phosphatases SHP-1 and SHP-2, and holds ocular-dominance plasticity down at every age (Syken et al., 2006). Its deletion raises spine density cell-autonomously (Vidal et al., 2016), and blocking it acutely in an adult with a soluble decoy recovers spines and acuity lost months earlier (Bochner et al., 2014). Only then did the programme turn to disease: PirB and its human orthologue LILRB2 were reported to bind soluble amyloid- β oligomers at the same two immunoglobulin domains that bind MHC class I (Kim et al., 2013), and, in 2025, to bind the complement fragment C4d at the same site — a fragment elevated fourfold in Alzheimer cortex and sufficient, infused into an adult mouse cortex for four days, to strip dendritic spines in a manner abolished in PirB-null animals (Brott et al., 2025).

The second account begins with a residue. A dendritic spine is a bag of actin, and the balance between severing and stabilisation of its filaments is set by cofilin-1 at serine 3. Phosphorylated cofilin cannot bind filamentous actin and the network is stable; dephosphorylated cofilin severs it (Bamburg et al., 2021). The direction of change at that residue in human Alzheimer tissue is

disputed and unresolved. The architecture assembled to explain the dispute holds that the mark is degenerate — two antagonistic Rho-family arms write it through the same kinase, with opposite structural outcomes — and that the information the field wants sits one layer up, on the transducers that select which GTPase is loaded. Two such transducers act on this cell with opposite signs: Ephexin5, a Rho-family exchange factor whose substrate selection is set by phosphorylation at tyrosine 361 (Margolis et al., 2010; Petshow et al., 2025), and Disabled-1, the adaptor through which the entire protective reelin signal passes (Hiesberger et al., 1999; Chai et al., 2009). Both are built to the same unusual design: the phosphorylation that activates the transducer is the phosphorylation that consigns it to the proteasome (Margolis et al., 2010; Bock et al., 2004). Transience at this control surface is therefore achieved by destruction rather than by dephosphorylation, and the temporal control of the spine's structural signalling is vested in its proteolytic and sorting machinery.

1.2 The point of contact everyone sees, and why it is the wrong one

The obvious meeting place is cofilin serine 3. The receptor account terminates there — ligand binding to the D1D2 domains recruits phosphatase activity through the receptor's inhibitory motifs and drives cofilin dephosphorylation past the physiological range (Kim et al., 2013). The licensing account is *about* that residue. It should be a clean weld.

It is not, and Section 2 argues that it cannot be, because the residue is a degenerate variable: it is the shared output of a contractile arm, a protrusive arm and a protective arm, and no measurement made at it can report which produced it. Two careful laboratories have measured opposite directions in human Alzheimer cortex and both are probably right (Kim et al., 2013; Rush et al., 2018). A weld made at that residue would join two accounts at their least informative point.

This paper takes the other route. It asks not where the two accounts *arrive* but where their instructions are *ended*, and finds that they are ended in the same organelle by the same machinery, and that the machinery is the earliest thing in this disease to fail.

1.3 What this paper asks

Four questions organise what follows.

Where does the receptor's signal end? Section 4 answers it, from a 2016 immunology paper that the neuroscience literature has not read.

Does the complement arm rest on firmer ground than the amyloid arm? Section 3 answers it, and the answer is not the one the field has settled on.

What resets the licensing tyrosines? Section 5 identifies a candidate that has been sitting in the founding paper of the receptor programme since 2006 and has never been pointed at these

substrates, and Section 6 shows that supplying it makes an existing sign problem worse rather than better — which is diagnostic.

And what does the combination change about the therapeutic proposals on either side? Section 9.

Sections 7 and 8 do the housekeeping the combination makes possible: four questions the receptor programme names as open, and where the answers to them already sit; and one experiment that both literatures independently identify as decisive and that no one has run.

A note on what is claimed. This is a paper about the execution of synaptic loss, not about what starts the disease. It does not explain who develops Alzheimer's disease, why particular neurons fail first, or the substantial fraction of dementia not attributable to the pathologies conventionally measured. Section 12 states the boundary and Section 10 states what would refute the argument. Two of its central observations — the endocytic termination step and the unanswered negative on surface-oriented C4d — are readings of published primary results and are not in doubt as readings. The inferences drawn from them in Sections 4.5, 5.3 and 6.3 are inferences, and are graded as such in Section 11.

2. The Residue, and Why It Cannot Carry the Join

2.1 One mark, three writers

Cofilin is switched at serine 3 by LIM-domain kinases and reset by the slingshot phosphatases and chronophin (Bamburg et al., 2021; Kang and Woo, 2019). The complication is upstream of the kinase.

The Rho-family GTPases that control spine actin do not form one pathway. RhoA activates Rho-associated kinase, which phosphorylates LIM-domain kinase on its activation-loop threonine; the structural output is spine shrinkage. Rac1 and Cdc42 activate p21-activated kinase, which phosphorylates the *same* LIM-domain kinase on the *same* threonine; the structural output is spine growth. Both arms raise phospho-serine-3, and they mean opposite things.

To these must be added a third writer with a third meaning. Reelin, signalling through ApoER2, Disabled-1, Src-family kinases and phosphatidylinositol-3-kinase, phosphorylates n-cofilin at serine 3 and thereby stabilises the actin cytoskeleton (Chai et al., 2009). That is a protective input writing in the same direction as the pathological contractile one.

The consequence is not a sampling problem. Even a perfectly compartment-resolved measurement, made at a single synapse with no averaging, would not say which arm produced the mark. The degeneracy is in the variable.

2.2 A correction the two literatures make necessary

This has a specific consequence for how one published result is usually cited, and it should be stated plainly because it changes what the receptor account can claim.

Rush and colleagues reported elevated phospho-cofilin-1 in the post-synaptic-enriched synaptosome fraction of cortical samples from APP/PS1 mice and from human Alzheimer cases; that amyloid oligomers induced rapid actin *stabilisation* and *increased* phospho-cofilin within thirty minutes in primary cortical neurons; that cofilin phosphorylation was necessary and sufficient for amyloid-induced synaptic impairment via actin stabilisation, occurring before the formation of cofilin–actin rods; and that the Rho-kinase inhibitor fasudil prevented the actin stabilisation, the synaptic impairment and the synaptic loss by blocking cofilin phosphorylation (Rush et al., 2018).

That paper is routinely cited as independent corroboration that the cofilin axis is dysregulated in Alzheimer's disease. It is more than that and less than that. It is a measurement in human Alzheimer cortex of the **opposite direction** to the one the receptor account reports, made by a laboratory with no shared authorship, with a pharmacological rescue attached. The 2018 paper opens by stating that how amyloid- β affects the actin cytoskeleton "remains unknown and contentious," and does not cite the receptor result. Reading it as corroboration of the node while passing over the contradiction of the sign is the commonest error in this area, and it matters because the receptor account's mechanistic specificity is often defended by the claim that it terminates in a named residue on a named protein.

2.3 What survives, and it is the structure rather than the phosphosite

The defence survives if it is re-based.

Cofilin-actin rods are directional in a way the phosphosite is not. They form spontaneously in neurons overexpressing *active* cofilin, so activation by dephosphorylation is sufficient to induce them; they require oxidation of cofilin to disulfide-linked dimers; they sequester cofilin, block transport and exacerbate mitochondrial membrane-potential loss; and they are present in human Alzheimer brain and not in normal brain, most prominently in neurites contacting amyloid deposits (Minamide et al., 2000; Bamburg and Bernstein, 2016; Bamburg et al., 2021). A rod is a readout that carries its own sign. A phospho-serine-3 signal is not.

The practical rule that follows applies to every experiment proposed later in this paper. **Where a directional claim about this pathway is to be made, the endpoint must be the rod, the GTPase load, or the governing tyrosine — never the mean phospho-serine-3 signal.** Section 8 applies the rule to an experiment that both literatures independently nominate as decisive and that both specify with the wrong readout.

3. The Ligand Problem, Stated Twice

3.1 The amyloid arm's unanswered negative

This is known and is stated here only because the second instance has its shape.

Smith, Kostylev, Lee and Strittmatter compared the reported amyloid- β receptors under standardised conditions — the same assays, the same amyloid preparations, controlled and confirmed cell-surface expression (Smith et al., 2019). Of fifteen reported receptors, three showed direct binding to synaptotoxic assemblies of synthetic amyloid: cellular prion protein, Nogo receptor 1, and LILRB2. Then the human material. Binding studies using soluble amyloid oligomers extracted from human Alzheimer brain revealed strong affinity for cellular prion protein, weak affinity for NgR1, and **no detectable affinity for LILRB2**; and hippocampal neurons lacking both NgR1 and LILRB2 showed a smaller reduction in oligomer binding than neurons lacking prion protein alone.

The senior author's competing interests are disclosed in the paper and are a reason to want independent replication rather than a reason to discount a controlled negative. No such replication has appeared in seven years. The shape of the objection is worth naming precisely, because it recurs: *the receptor binds the synthetic preparation and has not been shown to bind the species present in the tissue.*

3.2 The complement arm has one too

The 2025 C4d result has been treated — including in careful readings — as untouched by that objection, on the reasonable ground that it concerns a different ligand established with different methods. That is right as far as it goes. It does not follow that the complement arm is unchallenged, and it is not.

In 2016, Hofer and colleagues screened a cDNA library from human monocyte-derived dendritic cells, expressed in murine thymoma cells, against recombinant human C4d (Hofer et al., 2016). They identified two receptors. One was ILT5v2. The other was **Ig-like transcript 4** — the alternative designation for LILRB2, and the same receptor the 2025 paper reports, as that paper itself acknowledges when it notes that LILRB2 is "also referred to in NCBI as ILT4" (Brott et al., 2025). Both receptors also interacted with the split products C3d, C4b, C3b and iC3b, while C4d did not bind the classical complement receptors.

Three results in that paper bear directly on the neuroscience.

Engagement of the surface receptor by soluble C4d causes endocytosis.

"Interaction between cell surface-resident ILT4 and soluble monomeric C4d resulted in endocytosis of C4d." Section 4 builds on this.

Binding to the surface-immobilised form was not detected. "Surprisingly, binding of soluble ILT4 to C4d covalently immobilized to a cellular surface following classic complement activation could not be detected."

And the surface form is nevertheless bioactive, through something else. C4d immobilised to a solid phase via its intrinsic thioester conferred a dose-dependent inhibition of TNF- α and IL-6 secretion in monocytes activated by Fc cross-linking, of up to fifty per cent relative to baseline, and attenuated intracellular calcium flux. The authors' conclusion is explicit: ILT4 is a scavenger-type endocytotic receptor for **soluble monomeric** C4d, whereas the attenuation conferred by physiologically oriented surface C4d "appears to be dependent on a yet to be identified C4d receptor."

3.3 Two pools, and which one each experiment used

The distinction the 2016 paper turns on is not a technicality, and the 2025 paper states it itself. Upon complement activation, C4 is processed to C4b, exposing an internal thioester which enables **a small fraction** of C4b to bind covalently to nearby proteins or carbohydrates "while the majority of C4b remains soluble"; subsequent cleavage generates C4d, "which can be membrane-bound or soluble" (Brott et al., 2025). Within the primary sequence of C4d the reactive thioester binds covalently to nearby surfaces, which is what makes it a durable marker of where complement fired (Kowalska et al., 2024). There are two pools, they are chemically distinct, and only one of them is welded to a synapse.

Now set the 2025 experiments against that distinction.

Result	C4d species used	Receptor species used
Dot blot: strong sLilrB2 binding to C4d; C4 and C4b barely above background; no C4a	Purified protein spotted on nitrocellulose	Soluble Fc-tagged LilrB2 ectodomain
Dot blot: sPirB binds C4d, weakly C4 and C4b	As above	Soluble myc-tagged PirB ectodomain
Surface plasmon resonance, $K_D \sim 3$ nM; no LilrB1 binding; mapped to D1D2	Soluble recombinant	Immobilised ectodomain
Cell-based binding, ~ 37 nM on LilrB2-HEK293, ~ 56 nM PirB	Soluble recombinant	Cell-surface receptor
Neuronal culture binding, reduced but not abolished in PirB-null (residual attributed to neuropilin)	Soluble recombinant	Cell-surface receptor
Minipump, ~ 10 μg over four days, spine loss within ~ 800 μm, abolished in PirB-null	Soluble recombinant	Cell-surface receptor in vivo
Array tomography: $\sim 30\%$ of human excitatory synapses carry C4d; ~ 3-fold excitatory selectivity; C4d-LilrB2 colocalisation enriched near plaques	Deposited, in situ	Cell-surface receptor in situ
Western blot: C4d protein ~ 4-fold elevated in Alzheimer prefrontal cortex	Tissue pool, both forms	—

Every binding measurement and the entire causal demonstration use soluble C4d. The human anatomy — the row that carries the claim to relevance — reports the deposited pool and is a colocalisation rather than a binding measurement. The one published attempt to test whether the receptor engages C4d in the deposited configuration returned a negative, in an independent laboratory, nine years earlier, and is not cited.

3.4 How much this does and does not overturn

It would be easy to overstate this, and the honest reading is bounded on four sides.

The geometries differ, and the 2016 negative is the weaker kind. Hofer and colleagues probed surface-immobilised C4d with a *soluble* receptor ectodomain. A soluble monomeric probe failing to bind is a weaker result than a cell-surface receptor failing to bind, because it forgoes avidity. At a real synapse the receptor is membrane-anchored and can cluster, and the ligand is presented at high local density on a fixed surface; the avidity available in that configuration is not available to a soluble probe. The negative may be an artefact of the assay's valency.

The orientation may differ too. C4d adsorbed to nitrocellulose, C4d immobilised on a chip for surface plasmon resonance, and C4d thioester-linked to a cell-surface acceptor present different faces of the molecule to a receptor. The 2016 paper's own contrast — the same protein binds when soluble and does not when thioester-linked to a cell — is most simply explained by the covalent linkage occluding or reorienting the binding surface, which is a chemically specific prediction rather than a general doubt.

Nothing here touches the developmental work, which is the securest part of the receptor programme and makes no claim about complement.

And nothing here touches the demonstration of sufficiency. Recombinant soluble C4d infused into an adult cortex removed spines, and the effect was abolished in PirB-null animals. That is a real causal result about a real ligand species, and the 2016 finding of a soluble-C4d-ILT4 interaction with endocytosis independently corroborates that the soluble form engages this receptor.

What the objection does establish is narrower and still substantial. **The species for which binding is demonstrated and the species for which elevation in human tissue is demonstrated are not the same species, and the one attempt to bridge them failed.** The programme's amyloid arm and its complement arm therefore carry the same unanswered question in the same form, and the frequent summary that the newer arm is the better-evidenced one does not survive on this axis. It may still be true on other axes — the sufficiency experiment has no counterpart in the amyloid arm, and the human anatomy is better — but it is not true of the binding claim, which is what both arms are named for.

3.5 The experiment, and it is one afternoon of work

Activate complement on a cell surface or a synaptosome preparation, generate C4d in situ by the physiological route, and test binding by **cell-surface** LILRB2 rather than by a soluble ectodomain — with soluble recombinant C4d as the positive control in the same assay. If deposited C4d is bound by the clustered surface receptor, the 2016 negative was a valency artefact and the arm is repaired. If it is not, then the pool that is elevated fourfold in Alzheimer cortex is not the pool that engages this receptor, the human anatomy is a colocalisation of two things that do not interact, and the mechanism has to be rebuilt around the soluble pool — which, as Section 9 argues, changes the therapeutic target from a durable deposit to a diffusible product and changes which drug classes can reach it.

3.6 A note on priority

The 2025 paper describes C4d as having been "considered an orphan ligand without an *in vivo* function." That is defensible about *in vivo* function and about the nervous system. It is not accurate about receptor identification: the same receptor was reported as a C4d receptor in 2016, in a journal of general biology, by a group working on transplant immunology. The receptor's placement in cortex, the anatomy, the age curve, the elevation in disease and the causal spine experiment are all genuinely new. The binding partnership is a rediscovery, and the earlier report contains a result that the later one needs to answer.

4. Termination: Where the Instruction Ends

4.1 A receptor signal ends when the ligand leaves or the receptor does

This is elementary and it is the hinge of the paper.

A signal delivered by a diffusible ligand to a surface receptor is terminated in one of two ways. Either the ligand's local concentration falls, and occupancy falls with it; or the receptor is removed from the membrane by internalisation and is then either recycled to the surface or delivered through the multivesicular body to the lysosome for destruction. Which of the two operates determines what kind of lesion can break the signal.

For the ligands at issue here, the first route is weak and the second is documented.

C4d is generated at the surface where the cascade fired and, in its deposited form, is covalently attached there; it does not diffuse away, and no enzymatic pathway for removing it from a neural surface has been described. Its soluble form is a stable terminal degradation product with no further processing step in the cascade. Amyloid oligomers accumulate where they accumulate. Neither is a ligand whose concentration falls on a physiological timescale in a diseased cortex.

The second route is demonstrated. Cell-surface ILT4 engaged by soluble monomeric C4d **endocytoses the ligand**; the authors characterise the receptor as a scavenger-type endocytotic receptor (Hofer et al., 2016). Whatever else this receptor does when C4d binds, it internalises.

So the OFF switch of this arm is the endosome.

4.2 The transducers below it end the same way

The licensing architecture reaches the same conclusion from the other direction, and the result there is older and better established.

Ephexin5 restrains excitatory synapse development until ephrin-B binding to the EphB receptor tyrosine kinase triggers its phosphorylation, ubiquitination by Ube3A, and proteasomal degradation; the removal of the restraint is what permits synaptogenesis (Margolis et al., 2010). The relevant point is not that the brake is switched off but that it is *removed from the cell*. Independently, dendritic Ephexin5 falls after increased neuronal activity in a proteasome-dependent manner (Hamilton et al., 2017); the controlled variable is dendritic abundance and the control is proteolytic.

The protective transducer is built the same way. Reelin treatment targets Disabled-1 for degradation by the ubiquitin–proteasome pathway; tyrosine phosphorylation of Disabled-1, but not phosphatidylinositol-3-kinase activation, is required for that targeting; genetic deficiency in the Disabled-1 kinase Fyn prevents the degradation; the degradation depends on ApoER2 and the very-low-density lipoprotein receptor in a gene-dose-dependent manner; and pharmacological blockade of the proteasome prevents the formation of a proper cortical plate, so the destruction step is a required part of the signalling rather than an epiphenomenon of it (Bock et al., 2004). Disabled-1 protein *rises* in Fyn-deficient mice, which is the signature of an unsignalled pathway rather than an amplified one (Arnaud et al., 2003; Bock and Herz, 2003).

A second, reelin-independent disposal route exists for at least one isoform: Cdk2-mediated serine phosphorylation of the early Disabled-1 isoform promotes its ubiquitination and proteasomal degradation, and inhibition of protein phosphatase 1 or 2A increases its instability (Gao and Godbout, 2011). That work is in chick retinal progenitors and concerns the isoform lacking the Src-family sites, so it does not bear directly on the mature pyramidal neuron; it is noted because it places protein phosphatase 2A — an enzyme with multiple documented abnormalities in Alzheimer's disease (Torrent and Ferrer, 2012) — on the turnover of this adaptor as well as on tau.

4.3 One compartment, and it fails first

Put the two together and the structural claim is short.

The receptor arm is terminated by endocytosis. The transducer arm is terminated by ubiquitin-dependent proteolysis. Both are services of the same endolysosomal and proteasomal apparatus, in the same dendritic compartment of the same cell. And that apparatus carries the earliest and best-authenticated lesion in the disease.

Enlargement of the rab5-positive early endosome is the earliest known disease-specific structural abnormality in sporadic Alzheimer's disease: present in neocortical pyramidal neurons at preclinical stages when Alzheimer-like neuropathology is still restricted to the entorhinal region; present in Down syndrome pyramidal neurons from twenty-eight weeks of gestation; accompanied by elevated rab4 and translocation of rabaptin-5, implying that both uptake and recycling are engaged; minimally influenced by normal ageing; accentuated by inheritance of the *APOE* ϵ 4 allele; and — the control that makes the timing argument work — **normal in advanced familial disease caused by presenilin mutation**, which establishes that the abnormality is not a consequence of amyloid deposition (Cataldo et al., 2000).

The human genetics carry the direction of causation without a model organism. Loss-of-function variants in *SORL1*, the gene for the sorting receptor that delivers cargo to the retrieval machinery, are causal for Alzheimer's disease; in isogenic human neurons, haploinsufficiency alone enlarges endosomes while complete loss adds lysosomal and autophagic

failure, and the endolysosomal dysfunction is relieved by lowering amyloid precursor protein, placing presenilin-1, the precursor protein and SORLA in one pathway (Hung et al., 2021). In human iPSC-derived microglia, loss of SORLA decreases lysosomal degradation through altered trafficking of lysosomal enzymes; phagocytic uptake of fibrillar amyloid and of **synaptosomes** is increased while degradation is reduced, so both accumulate undigested (Mishra et al., 2025). The cell tasked with clearing synaptic material acquires the same lesion as the cell whose synapses are being lost.

And the commonest genetic risk factor acts on this arm by a trafficking mechanism that is reversible by a trafficking intervention. Apolipoprotein E4 reduces neuronal surface expression of ApoER2, and of the NMDA- and AMPA-type glutamate receptors co-endocytosed with it, by **sequestration in intracellular compartments**, critically reducing reelin's ability to enhance synaptic glutamate-receptor activity (Chen et al., 2010). The receptor is not absent, mutated or blocked by a competitor; it is in the wrong place. Pharmacological and genetic inhibition of NHE6, the principal proton-leak channel of the early endosome, completely reverses that recycling block and restores reelin's modulation of excitatory synapses (Xian et al., 2018).

4.4 The receptor disables its own disposal route

There is one further result, and once the compartment is the subject rather than the residue, it stops being an oddity and becomes the sharpest thing in the receptor programme's recent literature.

Han and colleagues reported that PirB is proteolytically cleaved upon amyloid exposure — in Alzheimer patients, in primary neurons and in APP/PS1 mice — and that the resulting C-terminal fragment accumulates in the Golgi apparatus by retrograde transport, binds the GAT domain of GGA3, disrupts Golgi transport, **impairs lysosomal maturation**, and compromises anterograde synaptic-vesicle transport. Inhibiting the cleavage, or overexpressing the GGA3-GAT domain, restored Golgi function, reduced plaque burden and tau phosphorylation, and rescued memory deficits (Han et al., 2026).

What GGA3 does makes the consequence specific rather than general. The Golgi-localised, γ -ear-containing, ARF-binding proteins bind the mannose-6-phosphate receptors at the Golgi and have an essential role in lysosomal enzyme sorting, cooperating with the AP-1 adaptor to package those receptors into clathrin-coated vesicles (Doray et al., 2002); GGA3 specifically directs the trans-Golgi-network export of the cation-independent mannose-6-phosphate receptor, in a cycle counterbalanced by PACS-1-mediated retrieval and regulated by casein kinase 2 (Scott et al., 2006). Depletion within this adaptor family causes missorting and secretion of lysosomal enzymes such as cathepsin D (Hida et al., 2007). The mannose-6-phosphate receptor is the vehicle by which newly made acid hydrolases reach the endosome. Jam its export adaptor and hydrolases are not delivered, and a lysosome without hydrolases cannot mature — which is what the cathepsin D maturation assays in the 2026 paper report.

So the chain, stated as the two literatures jointly imply it:

> The pathological ligand engages the restraint receptor. The engaged receptor is cleaved. Its cytoplasmic tail travels retrogradely to the Golgi and binds the adaptor that exports the hydrolase-delivery receptor. Hydrolases are not delivered. The lysosome does not mature. And the lysosome is the terminal step of the only route by which either the receptor or the transducers below it can be removed.

The receptor, when engaged, degrades the machine that would dispose of it. That is a feed-forward loop of a particular and unpleasant kind: it is not that the signal is too strong, but that transducing it consumes the cell's capacity to end it. On this reading the 2026 finding is not, as it has been read, a curious non-canonical side-effect. It is the mechanism by which chronic occupancy of this receptor becomes irreversible.

Three cautions belong with that. It is a single 2026 study and has not been replicated. The effect may be a general consequence of accumulating any undegraded membrane-protein fragment in the Golgi, in which case the specificity to GGA3 is incidental — the control is a comparable cleaved tail from an unrelated surface protein. And the direction of the loop is inferred; nobody has measured receptor turnover before and after the cleavage is blocked.

4.5 The statement of the convergence

Assembled, the argument of this section is one sentence with four supports.

Both instructions at this synapse are ended in the endolysosomal system, and that system is the earliest, best-authenticated and most human-genetically anchored lesion in the disease. The receptor's own termination is endocytic (Hofer et al., 2016). The transducers' termination is ubiquitin-proteasomal and, for the receptor limb of the protective arm, endosomal (Margolis et al., 2010; Bock et al., 2004; Chen et al., 2010). The compartment is enlarged before any deposit, in a manner independent of amyloid (Cataldo et al., 2000), and its sorting receptor is causal in humans (Hung et al., 2021). And the destructive receptor, when engaged, damages that compartment's supply line (Han et al., 2026).

The immediate consequence is a reading of the receptor programme's own largest stated inferential gap. The four-day minipump infusion delivers roughly 10 µg of C4d, a quantity high relative to anything a synapse plausibly sees, and sufficiency at a supraphysiological dose does not establish contribution at endogenous concentrations. If the governing variable is not concentration but **occupancy-time** — the integral of receptor engagement, set jointly by ligand supply and by the rate at which engaged receptor is cleared — then a high dose delivered over four days to a young adult cortex with an intact disposal clock may be the correct experimental analogue of a low dose delivered over decades to an aged cortex whose clock is failing.

That is a genuine reconciliation and it is also exactly the kind of argument that can be used to excuse any dose, so it must be made falsifiable. It is: the reading predicts that the dose-response for C4d-induced spine loss shifts leftward in genotypes that impair the clock. The experiment is the published minipump paradigm run in *Sorl1*-haploinsufficient and *APOE* ϵ 4 knock-in backgrounds. If the curve does not shift, occupancy-time is not the variable and the dose objection stands unrelieved.

5. The Phosphatase Limb, and What It Has Never Been Pointed At

5.1 What the receptor recruits

The founding receptor paper reports it in a single clause that has not been followed up in this context. Neuronal PirB protein is associated with synapses and **forms complexes with the protein tyrosine phosphatases SHP-1 and SHP-2** (Syken et al., 2006). This is the standard architecture of an inhibitory immune checkpoint: the cytoplasmic tail carries immunoreceptor tyrosine-based inhibitory motifs, engagement leads to their phosphorylation, and SHP-1 and SHP-2 are recruited and dephosphorylate substrates in the vicinity.

The question that has never been asked in the disease context is: **which substrates?**

5.2 The demonstrated precedent, and it is in neurons

The question is not idle, because the answer in one case is known and it is not the receptor's own tail.

Fujita and colleagues showed that binding of myelin-associated glycoprotein to PIR-B leads to association of PIR-B with tropomyosin receptor kinase neurotrophin receptors; that **SHP-1 and SHP-2, recruited to PIR-B upon ligand binding, function as Trk tyrosine phosphatases**; that inhibition of SHP-1 and SHP-2 reduced ligand-induced dephosphorylation of Trk and abolished the inhibitory effect on neurite growth; and that in vivo transfection of siRNA against SHP-1 or SHP-2 induced axonal regeneration after optic nerve injury (Fujita et al., 2011a). A companion paper established that the p75 receptor is required for PIR-B signal transduction and for the SHP activation induced by ligand binding to PIR-B (Fujita et al., 2011b).

Read that carefully. In neurons, ligand engagement of this receptor recruits SHP-1 and SHP-2, and those phosphatases act not on the receptor's own motifs but on **a third-party receptor tyrosine kinase in the same membrane**, with a functional structural consequence. That is not a hypothetical mechanism class. It is a demonstrated operation of this receptor, in this cell type, on a substrate of exactly the kind at issue.

5.3 Three substrates nobody has tested

The licensing architecture identifies three phosphotyrosine-governed species in the dendritic compartment where this receptor sits. None has been tested against it, and the emptiness of the literature is worth stating precisely rather than loosely. A PubMed search returns **no record whatever** pairing PirB or LILRB2 with Ephexin5, with *ARHGEF15*, with reelin, with ApoER2 or with Disabled-1. Pairing the receptor with EphB2 returns three records, and none of them tests an interaction: a review that lists both among candidate amyloid receptors, a gene-expression panel in psoriatic skin, and the standardised receptor comparison of Smith and colleagues, in which the two appear as separate entries on the same list of candidates.

EphB2. A receptor tyrosine kinase — the same class as Trk — on the dendrites of the same neurons. It is the kinase whose signalling phosphorylates the licensing tyrosine of Ephexin5 and thereby recruits Ube3A to destroy it (Margolis et al., 2010). The established route by which amyloid removes it is proteasomal: amyloid oligomers bind the fibronectin-repeat domain of EphB2 and trigger its degradation in the proteasome (Cissé et al., 2011). If the restraint receptor's phosphatase limb also dephosphorylates EphB2, then the disease has **two** routes to the same outcome — one that removes the kinase and one that silences it — and the second requires no proteasomal step at all. This is a directly testable prediction, and the assay is the one Fujita and colleagues already built.

Ephexin5 tyrosine 361. The residue whose phosphorylation both selects RhoA over Cdc42 and licenses Ube3A-dependent destruction (Margolis et al., 2010; Petshow et al., 2025). Whether a protein tyrosine phosphatase acting on it exists in the dendrite is an open question in the field; the 2025 work reports that chemical long-term potentiation lowers phospho-tyrosine Ephexin5 sharply within minutes by dephosphorylation rather than degradation, since the fall survives proteasome inhibition — so a phosphatase acting on this residue certainly exists and has not been named.

Disabled-1. The adaptor whose reelin-induced tyrosine phosphorylation both transduces the protective signal and licenses its proteasomal destruction (Bock et al., 2004). No protein tyrosine phosphatase acting on Disabled-1 has been identified; searching the literature for one returns nothing on point.

5.4 What it would explain, and this is a retrodiction rather than a prediction

Take the third case seriously for a moment, because it accounts for a human observation that currently has no proposed mechanism.

If the restraint receptor's phosphatase limb dephosphorylates Disabled-1, then chronic occupancy of the receptor produces a specific and unusual state: the protective signal is not transduced (because the phosphorylation that transduces it has been removed) **and** the adaptor is not cleared (because the same phosphorylation is what licenses its degradation). Disabled-1 would accumulate, unsignalled, in exactly the compartment where the receptor is engaged.

That is what is found. In post-mortem specimens across the clinical range, ApoE, lipid-aldehyde-modified ApoE, reelin, ApoER2, **Disabled-1** and the downstream markers Thr19-phosphorylated PSD95 and Thr508-phosphorylated LIM-domain kinase 1 accumulate together near neuritic plaques in the terminal zones of the entorhinal–hippocampal perforant path, with several markers higher in Alzheimer cases and correlating with histological progression and inversely with cognition (Ramsden et al., 2022). The accumulating species is a signalling pathway rather than a waste product, and it accumulates where amyloid is. The same signature — a transducer present in excess where its arm has stopped working — is what raised Disabled-1 means in the Fyn-deficient mouse (Bock and Herz, 2003).

This is a retrodiction and is weaker than a prediction, and there is an obvious competing explanation: the same tissue contains the peroxidation chemistry that crosslinks ApoE covalently to the ligand-binding modules of ApoER2 (Ramsden et al., 2022), which would silence the arm upstream without any phosphatase. The two are separable. A covalent receptor–ligand crosslink silences the arm and should, on the design established in Section 4.2, also prevent Disabled-1 degradation — so both mechanisms predict accumulation. They differ in the phospho-state of the accumulated adaptor: crosslinking predicts an adaptor that never received the signal, while phosphatase action predicts one that received and lost it, and the two can be separated by whether the accumulated pool retains any pathway-proximal modification. The measurement is difficult in post-mortem tissue for the reasons Section 8.3 gives.

5.5 And what it makes worse

The phosphatase hypothesis is attractive on the protective arm. On the destructive arm it does the opposite of tidying up, and that is the most useful thing about it.

6. The Sign Crisis at the Licensing Tyrosine

6.1 Three routes, all pointing down

Assemble what the Alzheimer dendrite does to the phosphorylated fraction of Ephexin5 tyrosine 361, drawing on both literatures.

Route one: the writing kinase is destroyed. Amyloid- β oligomers bind the fibronectin-repeat domain of EphB2 and trigger the receptor's degradation in the proteasome; EphB2 depletion is critical in amyloid-induced neuronal dysfunction, and restoring EphB2 in the dentate gyrus of amyloid-bearing mice reverses potentiation and memory deficits (Cissé et al., 2011). Less kinase, less phosphorylation at the residue it writes.

Route two: a broad neuronal tyrosine phosphatase accumulates. STEP61, the striatal-enriched phosphatase, is elevated in human Alzheimer prefrontal cortex, with greater STEP activity and dephosphorylation of its substrates; and the elevation is attributed to disruption of the normal degradation of STEP61 by the ubiquitin–proteasome system, with STEP61–ubiquitin conjugates increased upon amyloid treatment and in aged amyloid-bearing cortex (Kurup et al., 2010). Its substrates include Fyn — the Src-family kinase that writes to both transducers of this control surface. It has not been shown to act on the licensing tyrosine, and that experiment has not been done.

Route three: the restraint receptor's phosphatase limb, if Section 5 is right. Chronic engagement by amyloid or C4d recruits SHP-1 and SHP-2 to the dendritic membrane, where — on the demonstrated precedent — they dephosphorylate a third-party tyrosine substrate.

6.2 All three predict the accumulation, and none predicts the collapse

Every route lowers the phosphorylated fraction, and lowering it does two things.

It **removes the licence for destruction**, because the phospho-form is the form that recruits Ube3A. So Ephexin5 accumulates. And Ephexin5 does accumulate: its expression is elevated in the hippocampi of human Alzheimer patients and of hAPP mice, amyloid acutely promotes its production, and its genetic removal eliminates hippocampal spine loss and rescues behavioural deficits, with shRNA reduction in the dentate gyrus of presymptomatic adolescent hAPP mice sufficient to protect against later cognitive impairment (Sell et al., 2017). Three routes independently

predict the observed direction. The accumulation is over-explained.

It also **releases the Cdc42-directed activity**. Ephexin5 activates both RhoA and Cdc42; the selectivity for Cdc42 is regulated by tyrosine phosphorylation; a phosphorylation-dead mutant at the key tyrosine, Y361F, enhances Cdc42 activation while leaving RhoA activation unchanged; spines in Ephexin5-knockout neurons fail to sustain activity-driven growth, and the Y361F phosphomutant rescues that growth; and downstream of neuronal activity Ephexin5 positively regulates synaptic growth and stabilisation (Petshow et al., 2025). So all three routes predict a dendrite biased toward the growth arm.

The observed phenotype is spine loss.

The accumulation is over-explained and the sign is unexplained, and the discrepancy is not visible from inside either literature. The receptor programme does not discuss Ephexin5. The licensing architecture identifies the tension but has only one route to it — the loss of EphB2 — and looks for a missing kinase to restore the RhoA bias. Adding the second and third routes makes a missing kinase harder rather than easier to postulate, because that kinase must now outrun an accumulated broad-spectrum phosphatase and a receptor-recruited phosphatase pair as well as replace a destroyed one.

6.3 Four resolutions, and the measurement that separates them

(a) The substrate-switch model does not hold in the adult diseased dendrite. The 2025 characterisation was made in young hippocampal preparations with acute plasticity induction. Whether phospho-tyrosine-361 governs substrate selection the same way in an aged, amyloid-bearing human pyramidal neuron is unknown, and the model's transfer across that gap is an assumption, not a finding.

(b) An unidentified kinase writes the residue without licensing Ube3A. This is the resolution the licensing account prefers, and it requires that the ligase depend on a co-incident EphB2-derived signal that the disease has removed, so that the residue can be written without the substrate being condemned. Fyn is the standing candidate: it is mislocalised to the post-synaptic density in a tau-dependent manner (Ittner et al., 2010) and activated there by amyloid through cellular prion protein and mGluR5 (Um et al., 2013). The complication route two introduces is that Fyn is itself a STEP61 substrate, so the same accumulation that lowers the residue's phosphorylation would also lower the activity of its proposed writer.

(c) The accumulated pool is Cdc42-biased and is pathological for that reason. An exchange factor that cannot be consumed is an exchange factor whose signal cannot be terminated, and a spine receiving a growth instruction that never ends is not a stable spine. On this reading the Ephexin5 deletion rescue is real and the mechanism is the opposite of the one usually stated — the pathology is unterminated growth signalling rather than excess contraction. This resolution has the

merit of being continuous with the argument of Section 4: the lesion is a failure to end an instruction, not a failure to modulate one.

(d) Ephexin5 is not the executor. The spine loss is driven by another arm — Rho-kinase tone, on the human measurement of Rush and colleagues, or the receptor's direct route to cofilin — and the accumulated exchange factor is a marker of the licensing failure rather than its agent, permissive for loss without causing it. The genetic rescue would then be explained by removing a permissive factor.

The discriminating measurement is the same for all four and has not been reported: the ratio of active RhoA to active Cdc42, by pulldown, in amyloid-bearing hippocampus and in human Alzheimer cortex. Resolutions (a) and (c) predict Cdc42 up. Resolution (b) predicts RhoA up. Resolution (d) predicts that neither tracks Ephexin5 abundance. It is a standard assay on tissue that exists, and it would do more to settle this pathway than any measurement currently proposed for it.

6.4 The rule this yields

One methodological consequence generalises beyond this residue and is worth stating on its own, because it applies to every published measurement of both transducers.

Where one covalent mark sets both what an enzyme does and how long it survives, abundance and activity are two readings of one variable, and no total-protein measurement can report the enzyme's state. Every published measurement of Ephexin5 levels in this disease, and every measurement of Disabled-1 levels, is a measurement of total protein. An elevation is equally consistent with an amplified signal and with a failed one, and in the two cases the structural consequence for the spine has opposite signs.

7. Four Absences, and Where the Answers Sit

The receptor programme names four things its mechanism does not address. Three of the four have candidate answers in the licensing and sorting literature, and the fourth has an internal control already published in human tissue. None of the joins is proved; all four are stated so that they can be tested.

7.1 Tau

The receptor account has essentially nothing to say about tau, which is the pathology that tracks the topography and timing of neurodegeneration most closely. Three candidate routes exist and all are unexplored.

Through the protective adaptor. Disabled-1 has two outputs of first-rank importance: stabilisation of actin at cofilin serine 3 (Chai et al., 2009), and restraint of glycogen synthase kinase-3 β through phosphatidylinositol-3-kinase and Akt, and therefore of tau phosphorylation — mice lacking either reelin or both of its receptors show tau hyperphosphorylation (Hiesberger et al., 1999). Anything that removes Disabled-1 from the compartment removes both at once. This is the most economical available explanation for why a receptor lesion should produce a cytoskeletal and a tau phenotype simultaneously without either being downstream of the other, and it is the reason the Section 5.3 experiment matters beyond the actin question.

Through the shared kinase. Tau delivers Fyn to the post-synaptic density, and removing tau uncouples NMDA-receptor-mediated excitotoxicity and mitigates amyloid toxicity (Ittner et al., 2010). Fyn is also the physiological Disabled-1 kinase (Arnaud et al., 2003).

Through the receptor's own fragment. The 2026 cleavage paper reports reduced tau phosphorylation when PirB cleavage is inhibited or GGA3-GAT is overexpressed (Han et al., 2026) — the first connection of any kind between this receptor and tau, and it comes by way of the lysosome rather than by way of a kinase. It is consistent with the independent finding that transcription factor EB governs the lysosomal exocytosis of tau, and that its loss of function raises intraneuronal pathology and accelerates spreading (Xu et al., 2021).

7.2 Regional selectivity

Nothing in the receptor mechanism explains why the entorhinal cortex and hippocampus fail first. The ligand and the receptor rise with age across cortex; a mechanism with a uniform substrate does not by itself produce a regionally ordered disease.

The candidate answer is that the map that matters is not the executioner's but the guardian's. ApoER2 — the receptor carrying the protective ligand — is concentrated in entorhinal layer II stellate neurons, at the prosubiculum–CA1 border and in scattered neocortical pyramids, a distribution that follows the map of early neurofibrillary pathology; while its close relative VLDLR, sharing the same ligand and the same adaptor, is expressed ubiquitously including in the layer 4 stellate cells that resist tangles (Ramsden et al., 2022). A uniform destructive input and a patchily distributed protective one produce an ordered disease without either being regionally specific on its own.

The limit of this answer should be stated with it: ApoER2-expressing neurons are spared even within the same layer of the same section, so high expression is necessary but plainly not sufficient, and the account is at best a partial one.

7.3 The age curve

C4 and LirB2 messenger RNA rise in human cortex from about twenty-four years of age and plateau at about forty (Brott et al., 2025). Symptomatic disease begins decades later. Whatever converts a longstanding elevated ligand-and-receptor state into synapse loss is not in the receptor account.

Section 4 supplies the shape of a candidate: a second curve. If the instruction is ended by a proteolytic and endocytic service, then the disease requires two things — a supply of ligand, which is in place by the fourth decade, and a decline in the capacity to end the instruction, which is a late and progressive variable. The endosomal abnormality precedes deposition (Cataldo et al., 2000); the sorting lesion compounds (Hung et al., 2021); the cargo disables the machine that clears it, since a tauopathy-associated tau fragment blocks nuclear translocation of transcription factor EB and lysosomal degradative capacity (Pollack et al., 2024); and, if the 2026 result holds, the engaged receptor damages the hydrolase supply line itself (Han et al., 2026). On this reading the disease begins where the second curve crosses the first, which is a different and later date from either.

This is the least-tested of the four joins and should be read as a framing rather than a mechanism. Its ordering commitment is falsifiable: the sorting abnormality should precede any measurable elevation of the transducers, in a model carrying humanised precursor protein at endogenous levels.

7.4 Excitatory–inhibitory balance

Colocalisation of the ligand is roughly threefold lower at inhibitory than at excitatory synapses. If the mechanism preferentially removes excitatory contacts, it should shift cortical excitatory–inhibitory balance in a specific direction, with consequences that have not been measured.

The licensing architecture places the inhibitory neuron upstream rather than at the lesion, and in doing so closes a loop. The parvalbumin-positive fast-spiking interneuron is aspiny or sparsely spiny and does not fail by the mechanics described here; it enters through the matrix that sheathes it. Degradation of the perineuronal net removes the protection of the interneuron; the resulting failure of inhibition raises the activity of the pyramidal population; and heightened pyramidal activity increases the local production of the very ligands that occupy the receptor on pyramidal dendrites. The matrix is upstream of the ligand and the ligand is upstream of the residues — which makes the excitatory selectivity of the deposit self-reinforcing rather than merely descriptive.

The internal control for this already exists in human tissue. A minority of excitatory neurons carry a perineuronal net of their own, and in human frontal cortex those neurons carry conspicuously little phospho-tau (de Vries et al., 2024). They are the only population in which spines, a net and reelin-responsiveness are properties of a single cell, and they are therefore the natural comparison for any of the measurements proposed in this paper — including the prediction, which follows from the diffusion argument, that a synapse buried in condensed matrix is less accessible to a diffusing complement fragment and should carry less of it.

One conflation should be disposed of, because it recurs. The perineuronal net is a **chondroitin**-sulfate structure; reelin's obligate co-receptor requirement is for N-sulfated **heparan** sulfate, a component of the diffuse matrix rather than of the condensed net (Pan et al., 2025; Fawcett et al., 2022). Reelin does not require a net in order to signal, and the two can be separated experimentally with a pair of enzymes.

8. The Experiment Both Literatures Nominate, and Neither Specifies Correctly

8.1 Two accounts, one decisive test

Read from the receptor side, the sharpest untested prediction is that reelin signalling and the receptor's signalling should antagonise at cofilin serine 3, since one phosphorylates the residue and stabilises the network while the other dephosphorylates it and destabilises the network, on the dendrites of the same cortical pyramidal neurons. Read from the licensing side, the sharpest untested prediction is that the two arms should be co-manipulated in one preparation and both governing tyrosines measured alongside the serine.

These are the same experiment, arrived at independently from opposite ends. That convergence is itself informative, and so is the state of the literature it points at: a PubMed search returns **no publication linking PirB with reelin or with ApoER2**. The two arms of this control surface have never been run in the same preparation by anyone.

8.2 Why the readout must be respecified

The experiment as it is usually stated — co-manipulate the two pathways and measure serine-3 phosphorylation — cannot return an interpretable answer, for the reason given in Section 2. Both arms write the same mark. The protective arm phosphorylates it; the contractile arm phosphorylates it; the receptor arm dephosphorylates it. A null result would be uninterpretable and a positive result would be ambiguous.

The readouts that carry direction are three, and all are available.

Rod formation, which requires dephosphorylated cofilin and is therefore signed (Minamide et al., 2000; Bamberg and Bernstein, 2016). **The GTPase load**, active RhoA against active Cdc42 by pulldown, which is the variable the whole architecture is about and which Section 6.3 shows is currently unmeasured in this disease. **And the joint distribution of the two phospho-marks across single synapses** rather than their two means, which is the measurement that distinguishes a governed serine from an ungoverned one.

8.3 The reagent constraint, stated because it changes the design

There is at present **no validated site-specific antibody against the licensing tyrosine of Ephexin5**. The 2025 characterisation measured phospho-tyrosine Ephexin5 by immunoprecipitation with a custom total-protein antibody followed by a pan-phosphotyrosine blot, with residue attribution resting on the Y361F mutant (Petshow et al., 2025). Any design that specifies staining for phospho-tyrosine-361 in human tissue cannot be executed as written.

Two consequences follow for anyone attempting this. The coupling has to be read from its **output** rather than from the mark — the anticorrelation between the licensing kinase and its substrate across single synapses, both of which are stable total proteins and therefore survive post-mortem interval far better than any phospho-epitope. And the phospho-channels belong in the animal arm, where perfusion fixation removes the post-mortem lability that dominates phospho-measurements in autopsy tissue. This is why Section 3.5's binding experiment and Section 6.3's GTPase measurement are ranked ahead of the paired-residue measurement here: they are answerable now, with existing reagents.

8.4 The ranked list

Six experiments, ordered by what they settle per unit of effort. Each is stated so that a specific result counts against the argument.

One. Does surface-deposited C4d bind cell-surface LirB2? Generate C4d in situ by complement activation on a cellular or synaptosomal surface; test binding by cell-surface receptor, with soluble recombinant C4d as the in-assay positive control. *This settles whether the human anatomy and the causal experiment concern the same ligand species.* Refutes the mechanism's human relevance if only the soluble pool binds.

Two. Active RhoA against active Cdc42 in amyloid-bearing hippocampus and human Alzheimer cortex. *This separates the four resolutions of the sign crisis.* Refutes resolution (c) if Cdc42 loading is unchanged or reduced.

Three. Does the receptor's phosphatase limb reach these substrates? In mature hippocampal neurons, engage the receptor with C4d or amyloid and measure phospho-EphB2, phospho-tyrosine Ephexin5 and phospho-Disabled-1, with and without SHP-1/SHP-2 inhibition — the assay of Fujita and colleagues, re-pointed. *Refutes Section 5 if none of the three changes.*

Four. Does the clock set the dose-response? The published C4d minipump paradigm, run in *Sorl1*-haploinsufficient and *APOE* $\epsilon 4$ knock-in backgrounds. *Refutes the occupancy-time reading of Section 4.5 if the curve does not shift.*

Five. Co-manipulate the two arms in one preparation, with rods and GTPase load as the endpoints and phospho-serine-3 recorded but not relied upon. *Refutes the convergence if the arms do*

not interact.

Six. Is the receptor's disposal route itself lesioned? Measure the surface residence time and degradation rate of LirB2 after ligand engagement, in control and in *APOE* $\epsilon 4$ or *SORL1*-deficient human neurons; and test whether blocking the cleavage of Section 4.4 restores it. *Refutes the feed-forward loop if engaged receptor is cleared normally in the disease genotypes.*

9. What Follows for Treatment

9.1 The category error, restated for this pathway

The reflex at a dysregulated node is to block it. At this control surface the reflex fails in a specific way that both accounts identify and neither states in the other's terms: **every proposal on either list is a level intervention applied to a timing problem.** The defect described here is that instructions are not being ended. Lowering the amplitude of an instruction that will not end is not the same as ending it.

That is why the interventional result that deserves the most weight in this area is the one that adds and blocks nothing. Inhibition of NHE6 reverses the ApoE4-induced recycling block of ApoER2 and of the glutamate receptors co-endocytosed with it, and restores reelin's modulation of excitatory synapses (Xian et al., 2018). No ligand was supplied and no kinase inhibited. The compartment was repaired and the signalling returned. An ApoE4 neuron does not have a reelin deficiency; it has a receptor in the wrong place, and no quantity of ligand fixes a receptor in the wrong place.

The ordering claim follows and is the most actionable statement available here. **Repair capacity first; supply signal second.** A reelin-directed agonist or any other attempt to drive the protective arm should be expected to underperform in exactly the population most likely to be enrolled — ApoE4 carriers — unless the recycling defect is addressed first or concurrently. The same ordering applies to the degradative arm: an autophagy inducer given to a neuron that cannot complete the pathway fills it faster with vesicles it cannot empty.

9.2 A conflict the combination creates, which neither account contains

Here the two literatures generate a problem that neither has.

The protective receptor and the destructive receptor require **opposite dispositions from the same compartment.** ApoER2 needs to be recycled — returned to the surface, where it can receive reelin again; that is precisely what NHE6 inhibition achieves. LirB2 carrying an endocytosed pathological ligand needs to be **degraded** — delivered onward to the lysosome, because returning it to the surface returns a receptor that will be engaged again by a ligand whose supply does not fall.

One endosome, two receptors, two opposite required fates. Whether a single intervention that normalises endosomal pH biases both toward recycling, both toward degradation, or each toward

its physiological default is not known, and it is the question on which the whole repair strategy turns. It is also directly measurable: surface LirB2 and its ligand-loaded fraction, under NHE6 inhibition, in the same neurons in which surface ApoER2 is restored. If the intervention that rescues the guardian also rescues the executioner, the repair strategy needs a second component that biases sorting rather than merely fixing pH.

This is presented as an open question and not as a refutation of the repair proposal. Restoring normal acidification plausibly restores normal *sorting fidelity*, in which case each receptor resumes its correct fate and the conflict dissolves. But that is an assumption, and it has not been tested for either receptor.

9.3 Which pool the drug must reach

Section 3 has a direct consequence for drug design that has not been drawn.

If the signalling species is **deposited** C4d, then it is a durable, covalently welded, cumulative burden; the therapeutic model is prevention, benefit is proportional to the fraction of receptor not yet engaged, and reducing upstream classical-pathway activation is the intervention that matters, since nothing removes a deposit once made.

If the signalling species is **soluble** C4d — which is what every binding and causal measurement in the 2025 paper actually used, and what the 2016 work found ILT4 to bind and endocytose — then the target is a diffusible product with a pool that can in principle be lowered, competitive antagonism at the receptor is straightforwardly available, and the "durable footprint at the synapse" framing is the wrong therapeutic model even though it is the right pathological description.

These call for different drugs, different endpoints and different trial timing, and nobody knows which applies. That is a strong argument for ranking the binding experiment of Section 8.4 first.

9.4 The one route that is not a level intervention

Four routes have been proposed on the receptor side: blockade of the ligand at the binding site rather than of the receptor itself, of which the endogenous antagonist LOTUS is the proof of principle (Kawaguchi et al., 2022); inhibition of the cleavage that generates the intracellular fragment; upstream modulation of complement activation; and direct receptor antagonism, for which humanised antibodies have completed phase 1/2 programmes in oncology.

On the argument of this paper, three of the four are level interventions and one is not.

Cleavage inhibition is the only route that repairs the clock and spares the signal at the same time. If the 2026 result holds, blocking the protease, or the interface between the receptor's cytoplasmic fragment and the GGA3 GAT domain, leaves every normal function of the

receptor intact — the physiological brake, the MHC class I interaction, the developmental role — while restoring the hydrolase supply line on which the termination of *both* arms of this control surface depends. It is the only proposal on either list that is simultaneously a signalling intervention and a clearance intervention, and it is the only one that acts on the variable Section 4 identifies as governing.

It also rests on a single unreplicated 2026 paper with no specificity control, which is a thin foundation for the best idea in the set. Replication, and the control of a comparable cleaved tail from an unrelated surface protein, are worth more than any new mechanism proposed here.

9.5 The caution that survives everything

One consideration runs against all of the above and is not dissolved by any of it.

Every molecule the receptor programme discovered is a restraint, and every reported consequence of blocking this receptor is an increase in plasticity: more spines, more functional synapses, larger potentiation, deficient depression, faster learning, an ocular-dominance critical period that does not close. In a young mouse over weeks that reads as benefit. In an ageing human over years it might read as a cortex that cannot stop changing, cannot weaken a synapse and cannot consolidate. Long-term depression is not a defect; it is half of the mechanism by which a circuit stores anything, and every genetic and pharmacological manipulation in this programme impairs it.

The repair strategy this paper favours is less exposed to that objection than receptor blockade is, because restoring a cell's capacity to terminate signals is not the same as removing a restraint — it is, if anything, restoring one. But the objection is not eliminated, because the same restored capacity ends the protective instruction as reliably as the destructive one, and nobody has measured what the physiological brake is for. Until someone does, every proposal in this area is a proposal to alter a system whose purpose has not been established.

9.6 And the endpoints must change before the drugs do

Three measurement practices should be retired in programmes at this node, each following from a specific argument above.

Total protein for a transducer whose abundance and activity are one variable (Section 6.4). Total Ephexin5 and total Disabled-1 are uninterpretable; an elevation is as consistent with a failed signal as with an amplified one.

Mean phospho-serine-3 cofilin from homogenate (Section 2). The mark is the shared output of two antagonistic arms and a protective one; its mean is uninformative about direction even when measured perfectly.

Bulk degradative-capacity assays. Total proteasome activity, total autophagic flux and total lysosomal enzyme content cannot detect a change in the *specificity* or the *targeting* of proteolysis, which is what Sections 4 and 6 argue this disease produces. A cell in which the hydrolase supply line is jammed while the proteasome runs normally will look intact on both bulk measures.

10. What Would Refute This

Written as results that would end the argument, ordered by how much each removes.

One. Cell-surface LILRB2 is shown to bind C4d deposited in situ by complement activation, with normal affinity. The 2016 negative was then a valency artefact, Section 3 loses its force, and the complement arm is repaired as usually stated. *This is the fastest way to falsify the paper's most consequential correction, and it should be run first.*

Two. Engaged LILRB2 is shown not to be internalised in neurons. The termination argument of Section 4 then has no receptor limb, and the convergence collapses to the transducer side alone. The 2016 endocytosis result is in monocytic and heterologous systems and has never been repeated in a neuron; this is the argument's most exposed empirical assumption.

Three. Receptor engagement is shown not to change the phosphorylation of EphB2, Ephexin5 or Disabled-1. Section 5 falls, route three of the sign crisis disappears, and the phosphatase limb is confined to the receptor's own motifs.

Four. Active Cdc42 is shown to be unchanged or reduced in amyloid-bearing hippocampus while Ephexin5 is elevated. Resolution (c) of Section 6.3 falls, and the accumulated pool is not doing what the substrate-switch model says it should.

Five. The C4d dose-response for spine loss is shown not to shift in clock-impaired genotypes. Occupancy-time is not the governing variable, Section 4.5's reconciliation of the dose objection fails, and the supraphysiological-dose criticism stands unrelieved.

Six. Reelin-induced destruction of Disabled-1 is shown not to occur in mature neurons. The published demonstration is in cultured primary embryonic neurons (Bock et al., 2004) and has not, so far as we can determine, been repeated in adult tissue. The claim that this control surface terminates by proteolysis then loses one of its two pillars.

Seven. The cleaved receptor fragment's effect on Golgi function is shown to be reproduced by any comparable undegraded membrane-protein tail. The specificity to GGA3 is then incidental, the feed-forward loop of Section 4.4 is a general consequence of accumulating protein in the Golgi, and the therapeutic preference of Section 9.4 loses its rationale.

Any of one, two or three removes a load-bearing section. Items four through seven remove specific claims without touching the central convergence.

II. Strength of Evidence

Each load-bearing claim, its principal evidence, and its grade. **Established** means directly demonstrated, bidirectionally where the design permits, and either replicated or internally cross-checked. **Supported** means consistent evidence from a single laboratory, model or method with no contradicting result. **Inference** means a reading of two or more established findings that has not itself been tested. **Contested** means a directly contradicting published result that has not been answered.

Claim	Principal evidence	Grade	Where it is vulnerable
PirB/LilrB2 is a lifelong brake on cortical plasticity and spine density, and forms complexes with SHP-1 and SHP-2	Null and conditional alleles, cell-autonomous sparse deletion, acute ectodomain infusion (Syken et al., 2006; Vidal et al., 2016; Bochner et al., 2014)	Established	Nothing contradicts it; the purpose of the brake is untested
Cofilin serine 3 is a degenerate mark: two antagonistic arms and one protective arm write it	Canonical Rho-family signalling (Bamburg et al., 2021; Kang and Woo, 2019; Chai et al., 2009)	Established	None material; it is standard cell biology
Human measurements of the direction of change at serine 3 disagree, and both are competent	Kim et al., 2013 versus Rush et al., 2018	Established as a disagreement	Neither laboratory has addressed the other
LilrB2 does not detectably bind amyloid oligomers extracted from human Alzheimer brain	Standardised head-to-head comparison (Smith et al., 2019)	Contested — unanswered for seven years	Single study; disclosed competing interests; no replication attempted
C4d binds LilrB2/PirB at the D1D2 site with nanomolar affinity, and infused C4d strips spines in a PirB-dependent manner	Dot blot, surface plasmon resonance, cell binding, minipump with knockout control (Brott et al., 2025)	Established for soluble C4d	Every measurement uses the soluble species
ILT4 — that is, LILRB2 — was identified as a C4d receptor in 2016, and engagement by soluble monomeric C4d causes endocytosis of the ligand	Expression screening, cell-surface binding, endocytosis assay (Hofer et al., 2016)	Supported	Single laboratory; monocytic and heterologous systems; never repeated in a neuron

Claim	Principal evidence	Grade	Where it is vulnerable
Binding of the receptor ectodomain to C4d covalently immobilised on a cell surface by complement activation was not detected	Hofer et al., 2016	Contested — unanswered and uncited	A soluble probe forgoes avidity; the geometry differs from a synapse
Surface-oriented C4d is biologically active through a receptor that has not been identified	Dose-dependent suppression of cytokine secretion and calcium flux by thioester-immobilised C4d (Hofer et al., 2016)	Supported	Monocytes; not tested in neural tissue
Enlarged early endosomes are the earliest disease-specific change, precede deposition, and are absent in advanced presenilin familial disease	Cataldo et al., 2000	Established	Cross-sectional post-mortem; the presenilin control is the load-bearing arm
<i>SORL1</i> loss of function in human neurons enlarges endosomes; complete loss adds lysosomal and autophagic failure	Isogenic human neurons (Hung et al., 2021)	Established	—
ApoE4 sequesters ApoER2 intracellularly, and NHE6 inhibition reverses the block and restores reelin's synaptic modulation	Chen et al., 2010; Xian et al., 2018	Established	Mouse; the only cited intervention that restores capacity rather than adding signal
Both transducers above serine 3 are terminated by phosphorylation-licensed proteolysis	Margolis et al., 2010; Bock et al., 2004; Hamilton et al., 2017	Established for each transducer separately	The Disabled-1 demonstration is in embryonic neurons and has not been repeated in adult tissue
Ephexin5 tyrosine 361 sets substrate choice between RhoA and Cdc42, and is the same residue that licenses Ube3A-dependent destruction	Petshow et al., 2025; Margolis et al., 2010	Established as a reading of the two sources	Characterised in young preparations; transfer to the aged diseased dendrite is assumed
Ephexin5 protein is elevated in human Alzheimer hippocampus and its removal rescues spine loss in hAPP mice	Sell et al., 2017	Supported	Single report; no independent cohort; overexpressing model
Amyloid drives EphB2 into the proteasome; restoring EphB2 rescues	Cissé et al., 2011	Established	Bidirectional manipulation in vivo

Claim	Principal evidence	Grade	Where it is vulnerable
STEP61 is elevated in human Alzheimer prefrontal cortex because its own ubiquitin-proteasome disposal fails	Kurup et al., 2010	Established	Not shown to act on the licensing tyrosine
PIR-B recruits SHP-1 and SHP-2 that dephosphorylate a third-party receptor tyrosine kinase in neurons	Fujita et al., 2011a, 2011b	Established for Trk	One laboratory; myelin ligands; optic nerve and neurite outgrowth rather than spines
The restraint receptor's phosphatase limb reaches EphB2, Ephexin5 Y361 or Disabled-1	This paper, from Syken et al., 2006 and Fujita et al., 2011a	Inference	No publication links this receptor with any of the three; untested
Both instructions at this synapse are terminated in the endolysosomal system, which fails first	This paper, from Hofer et al., 2016; Bock et al., 2004; Cataldo et al., 2000; Hung et al., 2021	Inference	Short but real; each component is established, the joining is not
A cleaved PirB fragment binds GGA3-GAT, jamming Golgi transport and impairing lysosomal maturation	Han et al., 2026	Supported	Single 2026 study, unreplicated, no specificity control
GGA3 directs trans-Golgi export of the mannose-6-phosphate receptor that delivers acid hydrolases	Doray et al., 2002; Scott et al., 2006; Hida et al., 2007	Established	The cathepsin D missorting demonstration is for GGA2
The engaged receptor degrades the machinery that would dispose of it	This paper, from Han et al., 2026 with the GGA3 literature	Inference	Rests entirely on the unreplicated 2026 result
Three routes lower phospho-tyrosine-361 in the Alzheimer dendrite, all predicting growth where loss is observed	This paper, from Cissé et al., 2011; Kurup et al., 2010; Fujita et al., 2011a	Inference	Route three is itself an inference; the discrepancy is real for routes one and two alone
Occupancy-time rather than concentration governs the C4d effect	This paper	Inference	Reconciles a stated dose objection and could be special pleading; §8.4 experiment four tests it

Claim	Principal evidence	Grade	Where it is vulnerable
No publication pairs PirB or LILRB2 with reelin, ApoER2, Disabled-1, Ephexin5 or ARHGEF15; the three records pairing it with EphB2 test no interaction	Literature search, September 2026	Established as a negative	Absence in an indexed search; unindexed or in-press work would not appear

Six entries are this paper's own. None has been tested, and they are the first things a reader should attack.

12. Limitations

The central corrections are readings, and readings can be wrong about weight. That the 2016 paper reports what it reports is verifiable. Whether its negative result about surface-immobilised C4d should be weighted as heavily as this paper weights it is a judgement, and Section 3.4 states the four reasons it might not be. A soluble-probe negative is genuinely weaker than a cell-surface negative, and readers who discount it will find Sections 3.2 to 3.6 correspondingly less interesting — though the priority point and the two-pool problem survive that discount intact.

The phosphatase hypothesis is an argument from a precedent, not from data. Section 5 establishes that this receptor's phosphatase limb acts on a third-party receptor tyrosine kinase in neurons. It does not establish that it acts on any of the three substrates named. Nobody has looked. The section is a proposal for an experiment and should be read as one.

The convergence claim is compatible with too much. An account which says that both arms of a control surface are terminated in the compartment that fails earliest is compatible with amyloid-first, tau-first, vascular-first and inflammatory-first origins. That breadth is a weakness as well as a strength: a claim that fits every upstream story constrains none of them. The one ordering commitment made here — that the sorting abnormality precedes the elevation of the transducers — is falsifiable and is stated in Section 7.3.

Selective vulnerability is not explained. Section 7.2 offers a partial answer from the distribution of the protective receptor, and states its own defeating observation.

The evidence is mouse-heavy where it matters most, on both sides. Every causal experiment in the receptor programme is a mouse experiment. Every human experiment is anatomical or biochemical correlation. The C4d minipump is a partial exception, and is the more valuable for using no transgene.

And this account does not speak to a large share of the clinical problem. A substantial minority of dementia in community-based series is not explained by the pathologies conventionally measured, and a substantial minority of people meeting neuropathological criteria are not demented at death. Neuronal death, white-matter injury and the loss of whole compartments contribute by routes not described here. The tangle pathology of this disease begins in the brainstem decades before cortical amyloid is detectable, in a compartment and at a time this account does not address. It describes an execution step; it does not describe a beginning.

13. Conclusion

Two literatures describe the loss of the same synapse. One was built by asking why a critical period closes and found that the brain removes connections on purpose, using immune proteins, through a receptor on the dendrite that it keeps for life. The other was built by asking why two competent laboratories measure opposite directions at one residue, and found that the residue cannot report its own cause and that the information sits one layer above it, on transducers that are destroyed by the act of transducing.

Put together, they say something neither says alone. The instruction that removes a spine is not ended by a phosphatase. On the transducer side it is ended by ubiquitin-dependent destruction, and on the receptor side — as an immunology laboratory showed nine years before the neuroscience arrived at the same receptor — it is ended by endocytosis. Both terminations are services of the endolysosomal system, in the dendritic compartment of one cell. And that system carries the earliest disease-specific structural lesion in sporadic Alzheimer's disease, present before any deposit, absent in the familial form with the highest lifetime amyloid burden, and anchored to a causal human gene. If the engaged receptor also disables the adaptor that supplies the lysosome with its hydrolases, then transducing the instruction consumes the capacity to end it, and chronic occupancy becomes irreversible by the act of occurring.

Two things came out of the assembly that were not being looked for.

The first is that the receptor's two disease ligand claims carry the same unanswered objection in the same shape. For amyloid it is known and is carried openly: the receptor binds the synthetic preparation and not the species extracted from human brain. For complement it is not known, and it should be: the receptor binds soluble recombinant C4d, and the one published attempt to show it binding C4d deposited by actual complement activation returned a negative that has never been cited. Every binding measurement and the entire causal demonstration in the 2025 paper use the soluble pool; the human anatomy reports the deposited one. Whether those are the same mechanism is a question one afternoon of work would answer, and it is the most consequential unrun experiment in this area.

The second is a sign problem that neither literature could see on its own. Three independent routes lower the phosphorylation of the licensing tyrosine in the Alzheimer dendrite. All three predict the accumulation of the exchange factor that is observed, because the phosphorylated form is the degraded form. All three predict spine growth, and what is observed is spine loss. The accumulation is over-explained and the collapse is unexplained, and the measurement that would separate the four available resolutions — the ratio of active RhoA to active Cdc42 in

amyloid-bearing tissue — is a standard pulldown that nobody has published.

What stands at the end is narrower than either account promises separately and more specific than either offers alone: a named receptor whose instruction has no exit but one organelle, an opposed transducer that is disposed of in the same organelle, an organelle that fails before anything else in this disease can be seen, and a set of measurements — a binding assay, a pulldown, and a dose-response in two existing mouse lines — that would settle in a season what the two literatures have spent a decade not asking each other.

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Every reference above was checked against its PubMed record — title, authorship, year, journal, volume, pages and the direction of the reported effect — rather than recalled. Two of this paper's central observations turn on the precise wording of published negative results, and a citation reconstructed from memory would have silently resolved objections that the literature has not resolved.