
The Terminating Service

A control surface at the dendritic spine is switched off by destruction rather than by dephosphorylation — and two endosomal programmes describe the machinery that performs the destruction

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September 2026

Both transducers above cofilin serine 3 are condemned by the same phosphorylation that activates them. A surface built that way has no off switch that is not a protease — so its temporal control is vested in the disposal machinery, and the condition of that machinery in Alzheimer's disease is not a matter for speculation. Two laboratory programmes have described it for four decades, and neither has been read as an account of a switch.

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Abstract

The balance between severing and stabilisation of the actin filaments in a dendritic spine is set at one residue of one protein: serine 3 of cofilin-1. Two antagonistic Rho-family arms write that same mark, so the residue cannot report which arm produced it, and the sign of the change in Alzheimer's disease has been disputed in human tissue for a decade without resolution. The sign is set one layer above, at the transducers — and both of the relevant transducers are built to an unusual design. Phosphorylation of Ephexin5 at tyrosine 361 biases the enzyme toward RhoA and simultaneously recruits the ubiquitin ligase Ube3A that consigns it to the proteasome. Reelin-induced tyrosine phosphorylation of Disabled-1 transduces the protective signal and simultaneously targets the adaptor for ubiquitin–proteasome degradation. *The phosphorylation that activates is the phosphorylation that condemns.*

A control surface of that construction has a property that is easy to state and consequential to follow: **it has no off switch that is not a protease.** A phosphatase resets a mark; it cannot remove a transducer. Transience at this surface is therefore not a chemical reaction that proceeds at a fixed rate. It is a *service*, provided by the ubiquitin–proteasome system at the cytosolic transducers and by endosomal sorting, the multivesicular body and the lysosome at the receptors. Anything that degrades the service degrades the neuron's capacity to issue a brief structural instruction — without touching a single kinase, receptor or ligand.

This paper argues that the two laboratory programmes which have characterised that service in Alzheimer's disease — Scott Small's twenty-year account of retromer-dependent endosomal recycling, and Gunnar Gouras's twenty-eight-year account of intraneuronal amyloid retention at the synaptic endosome — are not adjacent literatures to the switch. They are the account of why the switch cannot be thrown, and they have never been read that way, in either direction.

Three joins are made at named objects rather than at shared vocabulary. **At the ubiquitin–proteasome system:** retained intraneuronal amyloid was shown in 2006 to impair multivesicular-body sorting by inhibiting the proteasome and the deubiquitinating enzymes, which predicts that *both* self-terminating transducers should accumulate in a loaded neuron. Ephexin5 protein is in fact elevated in human Alzheimer hippocampus. Disabled-1 has never been measured alongside it, and the paired measurement discriminates between three otherwise indistinguishable explanations of that elevation. **At the multivesicular body:** the compartment through which a spent receptor must pass to be destroyed is the compartment in which amyloid- β 42 accumulates postsynaptically, before plaques, and which distends and mis-sorts when loaded. **At the early endosome:** retromer-dependent retrieval decides whether a receptor is recovered or condemned, and therefore decides whether it can transduce a *second* signal — which is the quantity the switch account requires and which no study of this pathway has measured.

The three programmes also genuinely disagree, and the disagreement is stated rather than smoothed. Small's traffic jam and Gouras's loaded compartment are both **capacity** lesions — one scalar variable, all cargo affected. The switch account requires a **specificity** lesion, because amyloid drives EphB2 into an intact proteasome while the effector that receptor licenses for destruction accumulates: one arm over-runs while the other under-runs, which no scalar variable predicts. The reconciliation offered here is that these are lesions of different services at different times — a capacity failure in the endosomal–lysosomal arm, present before any deposit and carrying the human genetic anchors, and a specificity failure in the ubiquitin–proteasome arm, gated on soluble amyloid and therefore late. That produces an ordering claim which is falsifiable in one experiment, and Section 8 states it.

Five predictions and their refutation conditions follow, together with what the join forbids. The largest of the forbidden moves is the one the deficit framing makes most natural: raising degradative flux across the board in a neuron whose lesion is misdirection rather than shortage is predicted to accelerate the loss it is meant to prevent.

i. Introduction

1.1 The problem

Synapse loss is the strongest structural correlate of cognitive impairment in Alzheimer's disease. In the study that established this, neocortical synapse density carried a multivariate correlation of 0.96 with the Dementia Rating Scale, while plaque density contributed 26 per cent of that model's strength (Terry et al., 1991). Whatever begins this disease, the step that produces the symptom is the loss of dendritic spines, and a spine is an actin structure.

The mechanics of that structure are unusually well understood. A spine's volume is the running balance of filament nucleation and elongation against filament severing and turnover. Severing is performed by cofilin-1, the major actin-depolymerising factor of mammalian neurons, and cofilin is switched by phosphorylation at serine 3: phosphorylated cofilin cannot bind filamentous actin and the network is stable; dephosphorylated cofilin binds and severs. LIM-domain kinases add the phosphate; the slingshot phosphatases and chronophin remove it (Bamburg et al., 2021; Kang and Woo, 2019).

The residue is directly implicated in human disease. Inclusions containing cofilin and actin are prominent in hippocampal and cortical neurites of post-mortem Alzheimer brain, most prominent in neurites contacting amyloid deposits, and present in Alzheimer brain and not in normal brain (Minamide et al., 2000; Bamburg and Bernstein, 2016).

And yet the direction of change at serine 3 in Alzheimer's disease is disputed, in human tissue, by careful laboratories, and the dispute has not moved. Amyloid- β acting through the immune receptor LirB2 produces enhanced cofilin signalling — dephosphorylation — reported in mouse and detected in human Alzheimer brain (Kim et al., 2013), a direction independently reproduced with a natural receptor antagonist (Kawaguchi et al., 2022). Amyloid- β acting through Rho-associated kinase *increases* serine-3 phosphorylation in the post-synaptic fraction of human Alzheimer cortex, where that phosphorylation is reported necessary and sufficient for synaptic impairment (Rush et al., 2018).

The reason the dispute does not move is structural. Two antagonistic arms write the same mark. RhoA acting through Rho-associated kinase phosphorylates LIM-domain kinase on its activation-loop threonine; Rac1 and Cdc42 acting through p21-activated kinase phosphorylate the *same* LIM-domain kinase on the *same* threonine. Both raise phospho-serine-3. The first collapses a spine and the second grows one. A measurement of that phosphosite cannot distinguish them, and

the degeneracy is in the variable, not in the sampling: a perfectly compartment-resolved measurement at a single synapse would still not say which arm produced it.

The information is not lost. It lives one layer up, at the transducers that decide which GTPase is loaded. This paper is about what happens to those transducers, and about who removes them.

1.2 The design that makes this a paper about proteolysis

The two transducers that set the sign are each governed by tyrosine phosphorylation, and each is built to the same unusual design.

Phosphorylation of Ephexin5 at tyrosine 361 biases the exchange factor toward RhoA and simultaneously recruits the ubiquitin ligase Ube3A, which consigns it to the proteasome (Margolis et al., 2010). The 2025 revision of that architecture showed that the residue is a substrate switch rather than a simple brake — the dephosphorylated form directs the enzyme toward Cdc42, and the Cdc42 arm is *required* for activity-driven spine growth (Petshow et al., 2025). Abundance and activity are therefore two readings of one covalent mark.

On the opposing arm, reelin binding to ApoER2 and VLDLR induces Fyn-dependent tyrosine phosphorylation of the adaptor Disabled-1, which transduces the protective signal (Hiesberger et al., 1999; Bock and Herz, 2003) and simultaneously targets Disabled-1 for degradation by the ubiquitin–proteasome pathway; the same kinase is required for both, and in its absence the adaptor is not degraded (Arnaud et al., 2003; Bock et al., 2004). Reelin's structural output at the residue below is stabilising: it induces n-cofilin phosphorylation at serine 3 (Chai et al., 2009).

Two opposed arms, converging on one residue, each self-terminating by licensed proteolysis, with a single Src-family kinase writing to both.

The consequence is the premise of everything that follows. **Transience at this control surface is not achieved by dephosphorylation. It is achieved by destruction.** A phosphatase resets a mark and leaves the transducer in place; it cannot end a structural instruction carried by a molecule that is still there and still active. The phosphatases of this system are in any case non-specific and disease-engaged: cofilin is dephosphorylated by the slingshot phosphatases and by chronophin, amyloid- β signalling converges on slingshot-mediated cofilin activation through the scaffold RanBP9 (Woo et al., 2015), and the wider regulation implicates LIM-domain kinase 1, slingshot homolog 1, β -arrestin, chronophin, phospholipase D1 and 14-3-3 (Kang and Woo, 2019).

So the spine's control surface has no off switch that is not a protease. Three proteolytic systems supply it: the canonical ubiquitin–proteasome system, which handles both transducers and is also the route by which amyloid disposes of EphB2 (Cissé et al., 2011); a dendritic, activity-regulated membrane proteasome that degrades intracellular protein into peptides released extracellularly, where they act as selective activators of NMDA receptors (Türker et al., 2024), and whose properties

coincide with a reported activity-dependent, proteasome-dependent fall in dendritic Ephexin5 (Hamilton et al., 2017); and the endosomal–lysosomal system, which handles the receptor limb and decides whether an internalised receptor is retrieved for a second signal or delivered through the multivesicular body to the lysosome.

That third service, and the state of the first, are what this paper is about — because they are exactly what two long-running laboratory programmes have spent four decades between them characterising in this disease.

1.3 The two programmes, and why they have not met the switch

Scott Small's programme begins with anatomy rather than with a molecule. The disease begins with striking reliability at the junction of the entorhinal area and the temporal neocortex and spreads along a mapped route (Braak and Braak, 1991), and that regional preference can be used as a filter on candidates rather than explained after the fact (Small, 2014). The founding paper is the clearest application: a spatiotemporal model was constructed *before* the data — a driver should be abnormal in the entorhinal cortex, relatively spared in the dentate gyrus, and abnormal across a broad age span — and the transcript that best conformed was *VPS35*, the cargo-recognition core of the retromer complex, a molecule with no prior association with the disease (Small et al., 2005). The proposition that followed is that when retromer-dependent recovery of cargo from the early endosome fails, everything held there dwells longer than it should, and the disease's separate pathologies are parallel consequences of that single mechanical fault (Small et al., 2017).

Gunnar Gouras's programme rests on a structural fact assembled piece by piece since 1998: a nerve cell manufactures amyloid- β on the same organelles it uses to run its synapses. Different compartments generate distinct peptide populations (Greenfield et al., 1999); the enzymes making the first cut in the precursor protein are localised to synaptic vesicles (Lundgren et al., 2015); and the compartments that hold the peptide are the compartments that recycle glutamate receptors and return worn cargo for disposal. Amyloid- β 42 accumulates within neurons in vulnerable regions in human brain (Gouras et al., 2000), localises by electron microscopy to multivesicular bodies inside synaptic terminals in association with abnormal synaptic structure before plaque pathology (Takahashi et al., 2002), and oligomerises there (Takahashi et al., 2004).

Both programmes are usually read as candidate *origin* stories, and both are weaker read that way than read as accounts of a mechanism. Neither has been read as a description of the machinery on which a proteolytic switch depends, because the switch had not been described as proteolytic. That description is recent, and the joins it makes possible are the subject of this paper.

1.4 What is claimed, and what is not

Claimed. That the control surface above cofilin serine 3 is terminated by proteolysis rather than by dephosphorylation; that the two programmes named above supply the state of two of the three proteolytic services that surface depends on; that three specific joins can be made at named molecules and compartments; that those joins generate discriminating experiments nobody has run; and that the joins imply an ordering among the three lesions which is falsifiable.

Not claimed. Nothing here addresses what initiates the disease, why particular neurons fail first, the substantial fraction of dementia not attributable to the pathologies conventionally measured, or the substantial fraction of people meeting neuropathological criteria who are not demented. The account concerns the *execution* of synaptic loss in the excitatory pyramidal neuron of neocortex and hippocampus, at its dendritic spines. The parvalbumin-positive interneuron is characteristically aspiny and does not fail by the mechanics described here.

1.5 Grades

Claims are graded on a five-point maturity scale, applied to the evidence rather than to the plausibility of the claim. **M1** — human, population-scale or replicated across independent cohorts. **M2** — human, single cohort or tissue series. **M3** — animal, replicated. **M4** — animal, single laboratory. **M5** — in vitro, or inference from adjacent findings. A separate column records whether an intervention was performed in both directions, which is the design that carries direction of causation.

Two rules govern the joins, and they are stated here so the reader can audit them.

No join without a shared object. Two programmes are joined only if they name the same molecule, the same residue, the same compartment or the same measurement. "Both concern the endosome" is not a join. "Both concern the ubiquitin-dependent destruction of a transducer in the dendrite of a pyramidal neuron" is.

No join that resolves a live dispute by paraphrase. Where the joined literatures disagree — and Section 7 shows they do, sharply — the disagreement is stated and an experiment is offered, not a synthesis.

2. The Demand Side: What Has to Be Destroyed

This section states, as a list of requirements, what the switch needs from the proteolytic machinery. Sections 3 and 4 then ask what the two programmes say about the machinery's condition.

2.1 Requirement one: the RhoA transducer must be removed on schedule

In the original description, Ephexin5 restrains excitatory synapse formation through RhoA; EphB receptor activation triggers Ephexin5 tyrosine phosphorylation, which recruits Ube3A and consigns the exchange factor to the proteasome; and the restraint is released (Margolis et al., 2010). The 2025 revision preserves the proteolytic architecture and inverts the interpretation of the protein's role: phospho-Y361 directs the enzyme toward RhoA, the dephosphorylated form toward Cdc42, and the Cdc42 arm is required for activity-driven spine growth and stabilisation (Petshow et al., 2025). The enzyme is a switch, not a brake.

What the switch account requires is therefore narrower and sharper than "less Ephexin5." It requires that the *phosphorylated* species be cleared, on the timescale of a plasticity event, by a Ube3A-dependent proteasomal route. If it is not cleared, the RhoA bias persists after the stimulus that produced it has ended, and a transient instruction becomes a standing one.

There is a second, independent route on the same protein: dendritic Ephexin5 falls by activity-dependent proteasomal degradation (Hamilton et al., 2017), whose properties — dendritic, activity-regulated, proteasome-dependent — coincide with those of the neuronal membrane proteasome (Türker et al., 2024). Whether the second machine performs the first degradation has not been tested and is stated here as a hypothesis. A dendrite contains both machines, and a protein may have more than one disposal route with different kinetics.

2.2 Requirement two: the protective adaptor must be removed on schedule

Reelin binds ApoER2 and VLDLR; the receptors' cytoplasmic tails are bound by Disabled-1; Fyn phosphorylates the adaptor on tyrosine; the signal proceeds through PI3-kinase and Akt to inhibit GSK-3 β and, through LIM-kinase, to stabilise the actin network by phosphorylating cofilin at serine 3 (Hiesberger et al., 1999; Bock and Herz, 2003; Chai et al., 2009).

The same phosphorylation targets Disabled-1 for ubiquitin–proteasome degradation, and apolipoprotein E receptors are required for it: in the absence of receptor engagement, or of Fyn, the adaptor is not degraded (Arnaud et al., 2003; Bock et al., 2004). The protective arm is therefore

self-limiting by the same design as the destructive one. A neuron that cannot degrade Disabled-1 does not thereby acquire more protection; it acquires an adaptor pool whose phosphorylation state no longer tracks current ligand.

2.3 Requirement three: the receptors must be recoverable

Both arms are receptor-gated, and a receptor that has signalled once must be recovered from the endosome to signal again. This is the requirement that makes the switch account depend on sorting, and it is the least examined of the three.

Two lesions on the protective receptor are documented. Apolipoprotein E4 selectively impairs ApoE receptor recycling, sequestering ApoER2 intracellularly, reducing its surface expression and reducing glutamate receptor function and synaptic plasticity (Chen et al., 2010). That block is reversible by a trafficking manipulation: pharmacological and genetic inhibition of NHE6, the principal proton-leak channel of the early endosome, completely reverses the ApoE4-induced recycling block of ApoER2 and of the glutamate receptors co-endocytosed with it, and restores reelin-mediated modulation of excitatory synapses (Xian et al., 2018). Nothing was added to the signalling pathway and nothing was blocked in it; the compartment was repaired and the signalling returned.

A second lesion lies outside the reach of any sorting step. Peroxidation of the lipid cargo generates reactive aldehydes that crosslink apolipoprotein E covalently to the ligand-binding modules of ApoER2 (Ramsden et al., 2022). A receptor sequestered in an endosome can be returned to the surface by fixing the pH; a receptor covalently joined to its ligand cannot be separated by sorting, because ligand and receptor have become one molecule. This chemistry has been demonstrated with purified peptides and recombinant protein at aldehyde concentrations chosen to drive the reaction; the human evidence is immunohistochemical, and it is graded accordingly.

2.4 The demand list, stated compactly

Table 1 — What the switch requires of the proteolytic services

Service	What it must remove	Consequence of failure	Established by
Ubiquitin–proteasome (canonical)	Phospho-Y361 Ephexin5, via Ubc3A	RhoA bias outlives its stimulus; a transient instruction becomes standing	Margolis et al., 2010; Petshow et al., 2025
Ubiquitin–proteasome (canonical)	Phospho-tyrosine Disabled-1, receptor- and Fyn-dependent	Protective adaptor pool decouples from current ligand	Arnaud et al., 2003; Bock et al., 2004
Dendritic membrane proteasome	Dendritic Ephexin5, activity-regulated	Local, use-dependent reset of the switch is lost	Hamilton et al., 2017; Türker et al., 2024
Endosomal retrieval	Nothing — it <i>rescues</i> rather than destroys	Receptor cannot transduce a second signal	Chen et al., 2010; Xian et al., 2018
Multivesicular body / lysosome	Spent receptors condemned for destruction	Condemned receptor is retained; compartment loads	Section 4

The last two rows are the reason this paper exists. Nothing in the switch literature says what state those compartments are in, in this disease. Two other literatures say a great deal.

3. The Retrieval Arm: What the Retromer Programme Supplies

3.1 The governing variable is residency time

The mechanism is mechanical and can be stated without reference to any pathology. Material taken into a neuron arrives at the early endosome and is either sent on for destruction or recovered — to the cell surface, or to the Golgi for reuse. The recovery is performed by the retromer complex working with cargo-specific receptors, of which the most important here is SORLA, encoded by *SORL1*. Jam the export step and residency time rises, for everything held there (Small et al., 2017).

For the switch account, that single sentence is the join, and it is worth stating what it means at the level of a residue rather than a compartment. Residency time in the early endosome is precisely the variable that determines whether an internalised ApoER2 returns to the surface in time to receive the next reelin pulse, or is carried onward to the multivesicular body. The switch account requires *cycling*; the retromer account describes the step at which cycling is decided.

The Alzheimer-vulnerable region relies on a distinct retromer core dedicated to endosomal recycling, built around VPS26b rather than VPS26a (Simoes et al., 2021) — which is the strongest available answer to why a ubiquitous housekeeping machine should produce a regionally specific disease, and it is an answer the switch account does not have and does not need to invent.

3.2 The evidence, in ascending order of what each design can establish

Expression and correlation in vulnerable human regions establishes association in end-stage tissue (Small et al., 2005; Simoes et al., 2021). *M2*.

Perturbation in animals establishes sufficiency in a model: retromer-deficient mice and flies show hippocampal dysfunction, neurodegeneration and amyloid accumulation (Muhammad et al., 2008). *M3*.

Depletion and repletion is the strongest design available in a model, and it was performed. VPS35 was depleted in mouse hippocampal neurons and restored with an optimised vector; accelerated precursor-protein cleavage and loss of synaptic glutamate receptors followed the manipulation in **both** directions. The same study found a neuronal retromer deficit sufficient to induce dystrophic microglial morphology, independently of tau (Qureshi et al., 2022). *M3*, *bidirectional*. Independent replication of the stabilisation strategy followed in an Alzheimer model,

rescuing synaptic dysfunction and endosomal trafficking deficits (Ramonet et al., 2025).

Human genetics carries the direction of causation without a model organism. Rare truncating variants in *SORL1* occur almost exclusively in people with the disease, now mapped to specific receptor domains across large aggregated cohorts (Andersen, de Waal et al., 2025). *M1*. In human neurons, a *SORL1* truncating mutation produces haploinsufficiency and enlarged endosomes; isogenic comparison shows haploinsufficiency alone produces endosome dysfunction while complete loss adds defects in lysosomal function and autophagy (Hung et al., 2021). *M2*.

And the abnormality this pathway produces is the earliest disease-specific structural change known in sporadic Alzheimer's disease. Enlarged rab5-positive early endosomes are 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 28 weeks of gestation; accentuated by *APOE* ϵ 4; minimally influenced by normal ageing; and — the control that makes the timing argument work — **absent at advanced stages of familial disease caused by presenilin mutation**, establishing that the abnormality is not a consequence of amyloid deposition (Cataldo et al., 2000). *M2*.

That last result deserves the emphasis it rarely receives. In the form of the disease with the highest lifetime amyloid burden, the endosomal abnormality is absent. Whatever produces it in sporadic disease, it is not the peptide.

3.3 What the last two years did

Two results from 2026 pull in opposite directions and both matter to the join.

The pathway was placed upstream of tau in an animal, for the first time. Raising SORLA in aged tauopathy mice reversed tau phosphorylation, tau seeding, synapse loss, impaired potentiation and glial activation, while deleting SORLA made all of them worse (Huang et al., 2026). This is a bidirectional intervention against the tau arm in an aged animal, and it is what the theory had claimed since 2008 (Small and Duff, 2008) and had never directly shown. It also converges with an earlier human stem-cell result in which retromer stabilisation reduced tau phosphorylation independently of the precursor protein (Young et al., 2018). *M3*, *bidirectional*.

The first assay of pathway function in living people did not support the claim that the lesion is common. Soluble SORL1 in cerebrospinal fluid is reduced in carriers of damaging *SORL1* variants, as the model predicts; but in patients with ordinary sporadic Alzheimer's disease carrying no such variant, it does not differ from controls (de Waal et al., 2026). *M2*. One negative result does not settle a hypothesis, and a shed ectodomain is an imperfect proxy for intracellular recycling activity. It does mean that the strongest version of the theory now has a measurable claim outstanding against it.

For the present paper the consequence is specific and should not be softened. If retromer failure is *causal* but not *common*, then the retrieval arm of the switch account is compromised in a defined minority — *SORL1* variant carriers, and, by a different route, *APOE* $\epsilon 4$ carriers — rather than in sporadic disease generally, and the convergence claim narrows accordingly. Section 9 records this as the largest live threat to the argument.

3.4 An unresolved contradiction, and a change of cell

Two further items must be carried rather than resolved.

The first is internal to the programme. Depletion of *SORL1* in human neurons has been reported to impair endosomal traffic *independent* of amyloidogenic precursor processing (Knupp et al., 2020), while the isogenic human-neuron study found the endolysosomal dysfunction of *SORLA* loss was relieved by antisense reduction of the precursor protein, placing presenilin-1, the precursor and *SORLA* in a common pathway (Hung et al., 2021). Whether the endosomal phenotype is precursor-dependent is unsettled. The switch account is compatible with either — a receptor that cannot be retrieved is not retrieved whatever jammed the compartment — but the two readings imply different drugs.

The second is a change of cell type, and it is the most interesting development in this literature. *SORL1*'s strongest protective common variant acts through microglial expression (Gorniak-Walas et al., 2026); *SorLA* governs endoplasmic-reticulum homeostasis and lipid metabolism in human microglia, with effects conserved in neurons (Haq et al., 2026); loss of *SORLA* in human induced-pluripotent-stem-cell-derived microglia decreases lysosomal degradation and enzyme activity, so that phagocytic uptake of fibrillar amyloid- β **and of synaptosomes** is increased while degradation is reduced and both substrates accumulate aberrantly (Mishra et al., 2025); and human imaging now places inflammatory alteration between tau and neurodegeneration (Lao et al., 2026).

The synaptosome result belongs in this paper rather than in a footnote. A microglion that takes up synaptic material faster than it can degrade it is a cell whose pruning has become uncoupled from its disposal capacity. The clearing cell has acquired the same class of lesion as the losing cell, in the same compartment, from the same gene. Whether that changes the switch account is treated in Section 9; it certainly changes the claim that the neuron is where the recycling lesion matters.

4. The Terminal Arm: What the Retention Programme Supplies

4.1 One machine, two jobs

The programme's founding structural observation is that the neuron's amyloid-producing machinery and its synaptic machinery are the same machinery. The endoplasmic reticulum and the trans-Golgi network generate distinct populations of the peptide, so the compartment determines the product (Greenfield et al., 1999); ADAM10 and BACE1 are localised to synaptic vesicles (Lundgren et al., 2015); and the compartment in which the longer, aggregation-prone species is retained is a compartment of the synapse.

The consequence, which the programme's own framing has tended to obscure by presenting the work as an origin story, is that a fault in that machinery is necessarily both an amyloid event and a plasticity event — whatever caused the fault.

4.2 The pathology is retention, not overproduction

This is the most under-cited finding in that programme, and it matters here.

Cultured neurons from Alzheimer-model mice were compared with normal neurons over time. In the diseased neurons the amount of amyloid *secreted* fell with time; it did not rise. The ability of synaptic activity to increase secretion while reducing the intracellular pool became impaired in diseased and not in normal neurons. A mechanism was identified: synaptic activity normally increases surface neprilysin — the enzyme that degrades the peptide — and its co-localisation with A β 42, and in the diseased neurons neprilysin fell with time in culture (Tampellini et al., 2011). *M4; single laboratory, not independently replicated.*

The diseased synapse loses an activity-coupled clearance system. It is not making more; it is disposing of less, and the disposal step that fails has a name.

That is already a statement about a proteolytic service, made in a different vocabulary. It is not the service the switch account needs — neprilysin is an extracellular endopeptidase, not the machine that removes Ephexin5 — but it establishes the programme's central shape: **the lesion is on the disposal side, and it is coupled to activity.**

4.3 The finding that closes the loop

In 2006, using two receptor systems as reporters, the group showed that amyloid accumulation in precursor-mutant neurons impairs multivesicular-body sorting: receptor inactivation, degradation and ubiquitin tagging were all impaired, and the evidence indicated that the accumulating amyloid **inhibits the proteasome and the deubiquitinating enzymes** (Almeida et al., 2006). *M5/M4*.

This is the single most important citation in the present paper, and it has never been read against the switch literature.

Its structure within its own programme is a feedback loop with the wrong sign: the cargo disables the machine that would clear the cargo, so a slow accumulation should accelerate rather than plateau, and it requires no external driver once past threshold. That reading is correct and is not disputed here.

Its structure *across* programmes is different and larger. Both transducers of the switch are terminated by ubiquitin-dependent proteasomal degradation. A neuron in which the proteasome and the deubiquitinating enzymes are inhibited by a retained intraneuronal pool is a neuron in which **both** self-terminating transducers should accumulate. That is a prediction, and half of it has already been observed: Ephexin5 protein is elevated in the hippocampi of human Alzheimer patients and of hAPP mice (Sell et al., 2017). Disabled-1 has never, so far as we can determine, been measured alongside it. Section 6 makes that the paper's primary discriminating experiment.

4.4 The compartment is loaded, distended and mis-sorting

The state of the multivesicular body matters to the switch because it is the route by which a condemned receptor reaches the lysosome. Three observations describe that compartment in this disease.

Amyloid- β 42 localises predominantly to multivesicular bodies of neurons in normal mouse, rat and human brain; in transgenic mice and in human Alzheimer brain, intraneuronal A β 42 increases with age and accumulates in multivesicular bodies within presynaptic and *especially postsynaptic* compartments, associated with abnormal synaptic morphology **before** amyloid-plaque pathology (Takahashi et al., 2002). *M2*. The peptide oligomerises within those processes and synapses (Takahashi et al., 2004), and high-resolution reconstruction finds fibrils inside synapses (Capetillo-Zarate et al., 2011).

The compartment enlarges as a consequence: amyloid accumulation causes multivesicular-body enlargement, and the phenotype is reproduced by dominant-negative VPS4A — that is, by disabling the packaging machinery directly (Willén et al., 2017a). ESCRT function regulates precursor-protein sorting in multivesicular bodies and intracellular amyloid accumulation (Edgar et

al., 2015). *M5*.

And the terminal step is under transcriptional control whose failure closes a further loop. Transcription factor EB has an essential role in the lysosomal exocytosis of selected tau species; its loss reduced interstitial-fluid tau and was associated with enhanced intraneuronal pathology and accelerated spreading, establishing the route as clearance rather than release (Xu et al., 2021). Separately, a tauopathy-associated carboxy-terminal fragment of tau blocks autophagic clearance and lysosomal degradative capacity and inhibits nuclear translocation of transcription factor EB (Pollack et al., 2024). Independently again, faulty autolysosome acidification in Alzheimer models induces autophagic build-up of the peptide in neurons (Lee et al., 2022).

Four literatures, one direction: the compartment through which a spent receptor must pass in order to be destroyed is loaded, enlarged, sorting-impaired and, in some models, unable to acidify.

4.5 Activity is the regulator, and the control loop is the lesion

Synaptic activity reduces the intraneuronal pool, promotes transport of the precursor to synapses and protects against amyloid-related synaptic alterations (Tampellini et al., 2009). The programme's most consequential experiment ran the manipulation in the opposite direction: two independent means of chronic synaptic inhibition — surgical deafferentation of barrel cortex, and benzodiazepine administration — both **reduced plaques and made the animals worse**, exacerbating loss of the presynaptic marker synaptophysin in model but not normal mice and worsening memory, in the setting of reduced plaques and elevated intraneuronal amyloid (Tampellini et al., 2010). *M4; a designed dissociation*.

Plaque burden and synaptic-behavioural outcome were driven in opposite directions in the same animals, and outcome followed the intraneuronal pool. Whatever else is true, the extracellular deposit is not the variable that tracks function.

The switch account has a use for this that the original does not state. If the disposal service is activity-regulated — and both the neprilysin coupling (Tampellini et al., 2011) and the dendritic proteasome (Hamilton et al., 2017; Türker et al., 2024) are — then a neuron that is quiet is a neuron whose switch resets slowly. Chronic inhibition is not neutral for a proteolytic clock. It is a way of stopping it.

4.6 What raises the retained pool, and why the list matters

At least eight causally independent conditions raise the retained intraneuronal pool: normal ageing, through up-regulated internalisation of the precursor (Burrinha et al., 2021); apolipoprotein E4 (Konings et al., 2023; Nyberg et al., 2025); precursor-protein mutation (Sahlin et al., 2007); disrupted sorting machinery (Edgar et al., 2015; Willén et al., 2017a); seeded aggregates (Olsson et al., 2018; Roos et al., 2021); loss of the degrading enzyme (Tampellini et al., 2011); reduced synaptic activity (Tampellini et al., 2009, 2010); and a prior intracellular load, in cells that have lost the homeostatic correction (Roos et al., 2021).

Ageing is not apolipoprotein E4; a seed is not a mutation. What they share is where they arrive — and, on the argument of Section 4.3, what they do to the proteasome when they arrive there.

5. Three Joins

Each join below names a shared object, states what each literature contributes to it, and identifies the measurement that would settle it.

5.1 Join one — the ubiquitin–proteasome system

Shared object: ubiquitin-dependent proteasomal degradation of a dendritic protein in a pyramidal neuron.

The switch literature establishes that Ephexin5 is destroyed by a Ube3A-dependent proteasomal route licensed by phospho-Y361 (Margolis et al., 2010), and that Disabled-1 is destroyed by a receptor- and Fyn-dependent ubiquitin–proteasome route licensed by its own activating tyrosine phosphorylation (Arnaud et al., 2003; Bock et al., 2004). The retention literature establishes that a retained intraneuronal amyloid pool inhibits the proteasome and the deubiquitinating enzymes (Almeida et al., 2006).

What the join asserts. In a loaded neuron, both self-terminating transducers should accumulate, and they should accumulate in their *phosphorylated*, licensed-but-unexecuted form.

Why this is not already known. Ephexin5 elevation in human Alzheimer hippocampus is documented (Sell et al., 2017), and it was attributed to a different cause: amyloid depletes EphB2 (Cissé et al., 2011), so the kinase that writes the licensing phosphorylation is lost, and the ligase is never recruited. The two explanations make the same prediction for Ephexin5 and *opposite* predictions for Disabled-1. If the elevation is caused by loss of the licensing kinase, Disabled-1 should be unaffected, since its licence is written by Fyn on a different receptor. If it is caused by general proteasomal inhibition, Disabled-1 should accumulate too. A third possibility — that amyloid acutely promotes Ephexin5 *production*, which the same paper reports — predicts elevated transcript and an unchanged ubiquitination ratio.

The discriminating measurement. In the same human tissue, and in the same model neurons: total and phospho-Y361 Ephexin5; total and phospho-tyrosine Disabled-1; the ubiquitinated fraction of each; and *ARHGEF15* and *DAB1* transcript. Three outcomes, three causes, one experiment.

5.2 Join two — the multivesicular body

Shared object: the multivesicular body of the postsynaptic compartment of a cortical or hippocampal pyramidal neuron.

The switch literature establishes that whether a receptor can transduce a *second* signal is decided by sorting: retrieval and re-use, or delivery through the multivesicular body to the lysosome. The retention literature establishes that this exact compartment, in this exact location, accumulates A β 42 before plaques appear (Takahashi et al., 2002), enlarges as a result (Willén et al., 2017a), and sorts its cargo badly when loaded (Almeida et al., 2006; Edgar et al., 2015).

What the join asserts. The disposal route for a spent receptor and the accumulation site for the toxic species are the same address, and the loading of that address is predicted to prolong the residence of condemned receptors rather than merely to store a peptide.

Why it matters more than it sounds. In the deficit framing, a loaded multivesicular body is a toxic depot. In the switch framing it is a jammed off switch, and the consequence is a *plasticity* consequence that does not require the peptide to be toxic at all. This is the strongest form the retention programme's own thesis can take — one machine, two jobs — and it is available to that programme without any claim about initiation.

The discriminating measurement. Surface half-life and internalisation-to-degradation transit time of ApoER2 and of EphB2, measured in neurons with a defined intraneuronal load and in matched neurons in which production is blocked. The prediction is that transit time rises and that the effect is reversed by blocking production, as the receptor-withdrawal results were (Almeida et al., 2005; Snyder et al., 2005).

5.3 Join three — the early endosome and the second signal

Shared object: retromer-dependent retrieval of a receptor from the early endosome.

The switch literature requires ApoER2 to cycle in order for the protective arm to fire repeatedly, and documents two failures of that cycling — the ApoE4 recycling block, reversible by NHE6 inhibition (Chen et al., 2010; Xian et al., 2018), and covalent ligand–receptor crosslinking, which is not reversible by any sorting step (Ramsden et al., 2022). The retromer literature establishes the machinery that performs the retrieval, the human genetics that makes its failure causal, and a bidirectional animal intervention showing that depleting it strips synaptic glutamate receptors and restoring it returns them (Qureshi et al., 2022; Andersen, de Waal et al., 2025).

What the join asserts. ApoER2 is a retromer cargo problem that nobody has treated as one. The recycling block demonstrated for the ApoE4 route should also be produced by retromer or SORLA deficiency, in the absence of ApoE4 — and if it is, then the commonest genetic risk factor and the strongest rare-variant risk gene converge on the same receptor's re-usability by two independent mechanisms.

The discriminating measurement. ApoER2 surface expression, recycling rate and reelin-induced Disabled-1 phosphorylation, in *SORL1*-haploinsufficient human neurons of the kind

already generated (Hung et al., 2021; Knupp et al., 2020), on an *APOE* $\epsilon 3/\epsilon 3$ background. If reelin responsiveness falls with SORLA dose in the absence of $\epsilon 4$, the join holds and the two risk architectures have a shared readout.

5.4 The joins in one table

Table 2 — Three joins at named objects

Join	Shared object	Switch side	Endosomal side	Settled by
1	Ubiquitin-proteasome degradation of a dendritic transducer	Ephexin5 and Disabled-1 are each condemned by their activating phosphorylation	Retained amyloid inhibits the proteasome and the deubiquitinating enzymes	Paired Ephexin5 / Disabled-1 protein, phospho- and ubiquitin-state, plus transcript
2	Postsynaptic multivesicular body	Receptor re-usability is decided by sorting to the lysosome	A β 42 loads, distends and mis-sorts this compartment before plaques	Transit time and surface half-life of ApoER2 and EphB2 against intraneuronal load
3	Retromer-dependent retrieval from the early endosome	ApoER2 must cycle for the protective arm to fire twice	Retromer/SORLA performs the retrieval; loss is causal in human genetics	Reelin-induced Disabled-1 phosphorylation against SORLA dose, on an $\epsilon 3/\epsilon 3$ background

6. Where the Accounts Disagree: Capacity Against Specificity

This is the section a synthesis is most tempted to skip, and skipping it would make the rest worthless.

6.1 Both endosomal programmes are capacity accounts

The traffic jam is a scalar mechanism: retrieval slows, residency time rises, *everything held there* is affected (Small et al., 2017). The loaded compartment is a scalar mechanism: the pool rises, the proteasome and deubiquitinating enzymes are inhibited, sorting degrades across cargo (Almeida et al., 2006). Both are deficit framings in the strict sense — one variable, one direction, all substrates.

The deficit framing is well supported for bulk cargo and is not disputed here. It is also the dominant framing of proteostasis in this disease, and it predicts that everything degraded by the affected machine should accumulate together.

6.2 The observation that a capacity account does not predict

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 amyloid-bearing mice reversed impaired dentate potentiation and memory deficits (Cissé et al., 2011). *M3, bidirectional.*

Set that against the elevation of Ephexin5 in the same disease and the same cell (Sell et al., 2017), and the two do not sit on one scalar.

If proteolysis were simply failing, a receptor targeted for proteasomal degradation would be **spared**. The observed direction is the opposite: amyloid achieves a *gain* of degradation by presenting a substrate to an intact machine. In the same neuron and the same compartment, one arm of ubiquitin-dependent degradation over-runs — removing a receptor the cell needs — while the arm it was supposed to license under-runs, leaving in place an exchange factor the cell was supposed to clear.

Any account with a single variable called "clearance" predicts that the receptor and the transducers move together. They do not. The lesion alters the *specificity* of proteolysis, and a measurement of total proteasome activity, total autophagic flux or total lysosomal enzyme content cannot detect it.

6.3 The reconciliation, and its cost

The two descriptions can both be true if they are lesions of different services with different time signatures, and this is the reading proposed here.

The **endosomal-lysosomal service** sustains a capacity lesion. It is amyloid-independent in origin — enlarged endosomes are absent in advanced presenilin-mutant familial disease (Cataldo et al., 2000), and SORL1 depletion has been reported to impair endosomal traffic independently of amyloidogenic processing (Knupp et al., 2020) — it carries the human genetic anchors (Andersen, de Waal et al., 2025), and it is present decades before deposition. It sets the substrate on which everything downstream runs.

The **ubiquitin-proteasome service** sustains, in addition to whatever capacity loss the retained pool imposes, a *specificity* lesion that is gated on soluble amyloid: EphB2 is fed to an intact proteasome, and the substrate it should have licensed is not.

The cost of this reconciliation is that it is an inference, not a finding, and it is graded as such throughout. Its virtue is that it makes an ordering claim, and an ordering claim can be broken.

7. Two Clocks, and the Order They Imply

The reconciliation of Section 6 yields a testable sequence.

Stage one — traffic-gated, amyloid-independent, decades early. Retrieval capacity falls, by genotype (*SORL1*, *APOE* $\epsilon 4$) or by age. Endosome enlargement appears. Receptor re-usability declines. No deposit is required, and in the one human form with maximal deposit this stage is absent (Cataldo et al., 2000).

Stage two — load-gated. The retained intraneuronal pool rises by any of at least eight independent routes, secretion falls, surface neprilysin is lost, and the proteasome and deubiquitinating enzymes are inhibited (Tampellini et al., 2011; Almeida et al., 2006). Both self-terminating transducers should now begin to accumulate.

Stage three — oligomer-gated, late. Soluble amyloid depletes EphB2 through the proteasome (Cissé et al., 2011), removing the licence for the RhoA transducer's destruction specifically. Ephexin5 rises further and in a form that is not merely un-degraded but *un-licensed*. The specificity lesion is now established, and the mark at serine 3 becomes driven by chronic ligand occupancy rather than gated by the tyrosine above it.

The ordering prediction. In a model carrying humanised precursor protein at endogenous levels rather than an over-expressing transgene: endosomal enlargement and impaired ApoER2 recycling should precede accumulation of ubiquitinated Ephexin5, which should precede EphB2 loss and the rise of *un*-ubiquitinated Ephexin5, which should precede measurable dispersion of phospho-serine-3.

How it fails. If Ephexin5 elevation is found to precede any detectable sorting abnormality, the staging is wrong and the elevation must be explained transcriptionally. If ubiquitinated and un-ubiquitinated Ephexin5 rise together, the two proteolytic lesions are not separable in time and the two-clock reading collapses into a single deficit — in which case the capacity framing of Section 6.1 is sufficient and this paper's central distinction is unnecessary.

The knock-in requirement is not a technicality. Most of the retention programme's cellular mechanism was established in animals engineered to over-produce the precursor protein — the systems in which an accumulation account looks best. Knock-in models at normal expression exist (Saito et al., 2014), the case has not been rebuilt in them, and the one published knock-in test went against a prediction (Andersson et al., 2023). An ordering experiment in an over-expressing line compresses stages one and two and cannot test the claim.

8. Predictions

Table 3 — Predictions and refutation conditions

#	Prediction	If it fails
1	In loaded neurons and in human Alzheimer hippocampus, Disabled-1 accumulates alongside Ephexin5, and both in ubiquitinated form	General proteasomal inhibition is not the operative mechanism; Ephexin5 elevation is kinase-loss or transcriptional, and Join 1 fails
2	Restoring endosomal recycling — by NHE6 inhibition or by retromer stabilisation — restores the <i>excursion</i> of phospho-serine-3 to a plasticity stimulus, without a large change in baseline	Repair of the receptor limb is insufficient; the transducer limb must carry the argument alone, and the therapeutic emphasis of Section 10 is wrong
3	<i>SORL1</i> -haploinsufficient human neurons on an $\epsilon 3/\epsilon 3$ background show reduced ApoER2 surface expression and reduced reelin-induced Disabled-1 phosphorylation	ApoER2 is not a retromer-dependent cargo in the relevant sense, and Join 3 fails
4	Intraneuronal load predicts transit time from internalisation to degradation for ApoER2 and EphB2, and blocking production reverses it	The multivesicular-body join is anatomical coincidence rather than mechanism
5	In a knock-in model at endogenous expression, sorting abnormality precedes ubiquitinated-Ephexin5 accumulation, which precedes EphB2 loss and un-ubiquitinated accumulation, which precedes dispersion of phospho-serine-3	The two-clock reading collapses; a single capacity deficit is sufficient

One methodological obstacle applies to predictions 1 and 5 and should be stated rather than discovered. No validated antibody against phospho-Y361 of Ephexin5 is in general use, and post-mortem tissue is a hostile substrate for phospho-epitopes with short half-lives. The paired measurements above should therefore run first in perfusion-fixed animal tissue and in human neuron models, with human post-mortem cortex as the confirmatory rather than the primary arm — and any null result in post-mortem tissue read as uninformative rather than as refutation, because the confound biases toward the null.

9. What the Join Forbids

It forbids raising degradative flux across the board. This is the therapeutic instruction the deficit framing makes natural, and on the present account it is predicted to harm in a specific case. If the disease's lesion at this control surface is misdirection rather than shortage — an intact proteasome being handed the wrong substrate — then increasing flux increases the rate of the arm that is already over-running. The receptor whose loss the cell cannot afford is degraded faster; the transducer that should be cleared is not, because it is not being presented. Blanket induction is only safe if the specificity claim is false.

It forbids inducing autophagy in a neuron that cannot yet acidify. Faulty autolysosome acidification is documented in Alzheimer models, with autophagic build-up of the peptide in neurons (Lee et al., 2022), and a tau fragment inhibits nuclear translocation of transcription factor EB (Pollack et al., 2024). Driving cargo into a terminal compartment that cannot degrade it adds substrate to a jam. Re-acidify before inducing.

It forbids lowering Ephexin5 as a therapy. Heterozygous loss-of-function mutations in *ARHGEF15* cause autosomal-dominant hereditary cerebral small-vessel disease with osteoporotic fracture, through RhoA/ROCK2 **inactivation**, with complete co-segregation in two families, further variants in two sporadic cases, and a transgenic mouse recapitulating both pathologies (Ding et al., 2023). Cerebral small-vessel disease is itself a leading cause of vascular dementia. The proposed therapy is a phenocopy of a human dementing vasculopathy with skeletal fragility, and the 2025 revision adds that the protein is required for activity-driven spine growth (Petshow et al., 2025), so the neuronal cost is ablation of the growth arm rather than removal of a brake.

It forbids total-protein readouts of either transducer. For a molecule whose abundance and activity are two readings of one covalent mark, a western blot for total protein is not a measurement of the quantity of interest. This applies retrospectively: the elevation reported in human tissue is a total-protein result, and its interpretation is exactly what Join 1 is designed to settle.

It forbids treating a phosphatase intervention as a substitute for a protease. A drug that lowers a phosphorylation level does not remove the protein that the phosphorylation was supposed to remove. Rho-kinase inhibitors exist and one is clinically available (Zheng et al., 2025); on this account they address the mark and not the mechanism that ends the instruction.

10. Scope, Weaknesses, and What Would Sink the Argument

The "common" problem is the largest threat. If retromer-dependent recycling is causal but not common in sporadic disease (de Waal et al., 2026), the retrieval arm of this account applies to a genetically defined minority and the convergence claim shrinks accordingly. The argument survives as a mechanism and weakens as a general account of Alzheimer's synaptic execution. This is not a hedge; it is the specific thing to watch.

The cell type may be wrong for part of the argument. Four independent results now place the *SORL1* recycling lesion substantially in microglia (Gorniak-Walas et al., 2026; Haq et al., 2026; Mishra et al., 2025; Lao et al., 2026), and one of them has microglia taking up synaptosomes faster than they degrade them. A synapse can be lost because its own switch will not reset, or because a phagocyte with a full lysosome keeps eating and cannot finish. These are different lesions with a shared gene, and the present paper describes only the first.

Two load-bearing results are single-laboratory. The impaired-secretion and neprilysin result (Tampellini et al., 2011) and the loss of homeostatic correction in already-loaded cells (Roos et al., 2021) do not appear to have been independently reproduced outside the originating group, and both carry weight in Section 4.

The measurement problem for intraneuronal amyloid is answered but not closed. The standard immunoassay systematically underestimates the peptide once it has assembled, because assembly hides the epitopes (Stenh et al., 2005), and detection difficulties have made the topic controversial, with detergent in tissue processing capable of removing the pool altogether (Gouras et al., 2012). Label-free structural methods agree qualitatively (Klementieva et al., 2017, 2020) but none quantifies the pool absolutely. Any experiment in Table 3 that uses intraneuronal load as an independent variable inherits this.

The over-expression dependence. Stated in Section 7 and repeated here because it governs the ordering experiment, which is the paper's most consequential proposal.

The central positive claim is an inference. That the disease's lesion at this control surface is misdirected rather than merely reduced proteolysis follows from two published findings placed side by side (Cissé et al., 2011; Sell et al., 2017) and has not been tested directly. Join 1 is the test.

And nothing here explains onset. The account is compatible with amyloid-first, tau-first, vascular-first and inflammatory-first origins, which is a weakness as well as a strength: a claim compatible with every upstream story constrains none of them. The one ordering commitment it makes is Section 7's, and it can be broken.

II. Validity Ledger

Claim	Source	Maturity	Bidirectional?	Note
Synapse density is the strongest structural correlate of cognitive impairment	Terry et al., 1991	M2	—	$r = 0.96$ multivariate; plaques 26% of model strength
Phospho-Y361 licenses both RhoA bias and Ube3A-dependent degradation of Ephexin5	Margolis et al., 2010; Petshow et al., 2025	M5	Yes	The 2025 work inverts the functional reading, not the proteolytic architecture
Activating tyrosine phosphorylation of Disabled-1 also targets it for UPS degradation	Arnaud et al., 2003; Bock et al., 2004	M5	Yes	Fyn required for both; receptor engagement required for degradation
Amyloid drives EphB2 into the proteasome; restoring EphB2 rescues potentiation and memory	Cissé et al., 2011	M3	Yes	The observation a capacity account cannot predict
Ephexin5 protein is elevated in human Alzheimer hippocampus	Sell et al., 2017	M2	—	Total-protein readout; cause unresolved between three candidates
Retained intraneuronal amyloid inhibits the proteasome and deubiquitinating enzymes, impairing MVB sorting	Almeida et al., 2006	M5	—	Keystone of Join 1; two reporter receptor systems
Aβ42 accumulates in MVBs, especially postsynaptically, before plaques	Takahashi et al., 2002	M2	—	Human and transgenic; electron microscopy
Amyloid accumulation enlarges MVBs; phenotype reproduced by dominant-negative VPS4A	Willén et al., 2017a	M5	—	Establishes the packaging machinery as sufficient
Secretion falls and surface neprilysin is lost in diseased neurons	Tampellini et al., 2011	M4	—	Single laboratory; not independently replicated

Claim	Source	Maturity	Bidirectional?	Note
Chronic synaptic inhibition lowers plaques and worsens synapses and memory	Tampellini et al., 2010	M4	Yes	Designed dissociation; two independent means of inhibition
Enlarged early endosomes are the earliest disease-specific change; absent in advanced PSEN familial disease	Cataldo et al., 2000	M2	—	The presenilin control establishes independence from deposition
Truncating <i>SORL1</i> variants occur almost exclusively in cases	Andersen, de Waal et al., 2025	M1	—	Domain-mapped across aggregated cohorts
<i>SORL1</i> haploinsufficiency enlarges endosomes in human neurons; full loss adds lysosomal and autophagic failure	Hung et al., 2021	M2	—	Isogenic; relieved by lowering APP
SORL1 depletion impairs endosomal traffic independently of amyloidogenic processing	Knupp et al., 2020	M2	—	In unresolved tension with the row above
VPS35 depletion strips synaptic glutamate receptors; repletion restores them	Qureshi et al., 2022	M3	Yes	Also induces dystrophic microglia independently of tau
Raising SORLA reverses tau pathology, synapse loss and impaired LTP in aged tauopathy mice; deleting it worsens them	Huang et al., 2026	M3	Yes	Independent laboratory; first direct animal test against tau
Soluble SORL1 in CSF is unchanged in sporadic Alzheimer's disease without a <i>SORL1</i> variant	de Waal et al., 2026	M2	—	The "common" claim's first direct human test
SORLA loss in human microglia raises phagocytic uptake of synaptosomes while lowering degradation	Mishra et al., 2025	M2	—	Relocates part of the lesion to the clearing cell

Claim	Source	Maturity	Bidirectional?	Note
ApoE4 blocks ApoER2 recycling; NHE6 inhibition reverses it and restores reelin's synaptic modulation	Chen et al., 2010; Xian et al., 2018	M3	Yes	Compartment repaired, signalling returned
Peroxidation crosslinks ApoE to ApoER2 ligand-binding modules	Ramsden et al., 2022	M5	—	Driven-reaction chemistry; human evidence immunohistochemical
<i>ARHGEF15</i> heterozygous loss of function causes dominant cerebral small-vessel disease with osteoporosis	Ding et al., 2023	M1	—	Two families, two sporadic cases, transgenic mouse
The disease's lesion at this control surface is misdirected rather than reduced proteolysis	This paper, from Cissé 2011 + Sell 2017 + Almeida 2006	Inference	—	Untested; Join 1 is the test
The three lesions are ordered: sorting, then load, then oligomer-gated specificity	This paper	Inference	—	Requires a knock-in model; fails cleanly

12. Conclusion

The dispute over the direction of cofilin phosphorylation in Alzheimer's disease has run for a decade in human tissue and will not be settled at that residue, because two antagonistic pathways write the same mark. One layer above it sits a control surface with an unusual property: both of its opposed transducers are condemned by the phosphorylation that activates them, so the surface is switched off by destruction rather than by dephosphorylation, and its temporal control is vested in the proteolytic machinery rather than in the signalling machinery.

That relocates the question. A signalling system whose off switch is a protease is only as fast as its disposal service, and the condition of that service in this disease is not a matter for speculation. Two laboratory programmes have described it in detail, from two directions, for four decades — one from the retrieval end, with the human genetics that carries direction of causation, and one from the terminal end, with the electron microscopy that puts the peptide in the compartment through which a spent receptor must pass. Neither has been read as an account of a switch, because until recently the switch was not described as proteolytic; and the switch literature, in turn, has assumed the disposal service to be intact.

The most consequential single item in this intersection has been available since 2006, in a paper about receptor sorting: a retained intraneuronal pool inhibits the proteasome and the enzymes that remove ubiquitin tags. If that is true in the dendrite of a pyramidal neuron, then the two transducers that govern spine actin should both be found accumulating there, in licensed but unexecuted form — and one of them already has been, in human tissue, attributed to a different cause. The measurement that distinguishes the causes is a paired blot on tissue that already exists.

What the joined account is not is a theory of how the disease begins. The retrieval lesion arrives decades early and without amyloid; the load arrives by at least eight independent routes; the specificity lesion is gated on soluble oligomer and therefore late. Three different clocks, one control surface, and a symptom that appears when the surface can no longer issue a brief instruction. A reader looking for what starts Alzheimer's disease will not find it here. A reader asking why a synapse that is still fully wired stops being able to change should find the machinery named.

References

- Almeida CG, Tampellini D, Takahashi RH, Greengard P, Lin MT, Snyder EM, Gouras GK. Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. *Neurobiology of Disease*. 2005;20(2):187–198. PMID 16242627.
- Almeida CG, Takahashi RH, Gouras GK. Beta-amyloid accumulation impairs multivesicular body sorting by inhibiting the ubiquitin-proteasome system. *Journal of Neuroscience*. 2006;26(16):4277–4288. PMID 16624948.
- Andersen OM, de Waal MWJ, Monti G, Tesi N, Jensen AMG, de Geus C, van Spaendonk R, Vogel M, van der Lee SJ, Olsen JG, Hulsman M, Holstege H. Domain mapping of disease mutations reveals pathogenic SORL1 variants in Alzheimer's disease. *Molecular Neurodegeneration*. 2025;20(1):122. PMID 41327266.
- Andersson E, Schultz N, Saito T, Saido TC, Blennow K, Gouras GK, Zetterberg H, Hansson O. Cerebral A β deposition precedes reduced cerebrospinal fluid and serum A β 42/A β 40 ratios in the App^{NL-F/NL-F} knock-in mouse model of Alzheimer's disease. *Alzheimer's Research and Therapy*. 2023;15(1):64. PMID 36964585.
- Arnaud L, Ballif BA, Förster E, Cooper JA. Fyn tyrosine kinase is a critical regulator of disabled-1 during brain development. *Current Biology*. 2003;13(1):9–17. PMID 12526739.
- Bamburg JR, Bernstein BW. Actin dynamics and cofilin-actin rods in Alzheimer disease. *Cytoskeleton (Hoboken)*. 2016;73(9):477–497. PMID 26873625.
- Bamburg JR, Minamide LS, Wiggan O, Tahtamouni LH, Kuhn TB. Cofilin and actin dynamics: multiple modes of regulation and their impacts in neuronal development and degeneration. *Cells*. 2021;10(10):2726. PMID 34685706.
- Bock HH, Herz J. Reelin activates SRC family tyrosine kinases in neurons. *Current Biology*. 2003;13(1):18–26. PMID 12526740.
- Bock HH, Jossin Y, May P, Bergner O, Herz J. Apolipoprotein E receptors are required for reelin-induced proteasomal degradation of the neuronal adaptor protein Disabled-1. *Journal of Biological Chemistry*. 2004;279(32):33471–33479. PMID 15175346.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*. 1991;82(4):239–259. PMID 1759558.
- Burrinha T, Martinsson I, Gomes R, Terrasso AP, Gouras GK, Almeida CG. Upregulation of APP endocytosis by neuronal aging drives amyloid-dependent synapse loss. *Journal of Cell Science*. 2021;134(9):jcs255752. PMID 33910234.
- Capetillo-Zarate E, Gracia L, Yu F, Banfelder JR, Lin MT, Tampellini D, Gouras GK. High-resolution 3D reconstruction reveals intra-synaptic amyloid fibrils. *American Journal of Pathology*. 2011;179(5):2551–2558. PMID 21925470.
- Cataldo AM, Peterhoff CM, Troncoso JC, Gomez-Isla T, Hyman BT, Nixon RA. Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. *American Journal of Pathology*. 2000;157(1):277–286. PMID 10880397.
- Chai X, Förster E, Zhao S, Bock HH, Frotscher M. Reelin stabilizes the actin cytoskeleton of neuronal processes by inducing n-cofilin phosphorylation at serine3. *Journal of Neuroscience*. 2009;29(1):288–299. PMID 19129405.

- Chen Y, Durakoglugil MS, Xian X, Herz J. ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. *Proceedings of the National Academy of Sciences USA*. 2010;107(26):12011–12016. PMID 20547867.
- Cissé M, Halabisky B, Harris J, Devidze N, Dubal DB, Sun B, Orr A, Lotz G, Kim DH, Hamto P, Ho K, Yu GQ, Mucke L. Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature*. 2011;469(7328):47–52. PMID 21113149.
- de Waal MWJ, van der Lee SJ, Lunding M, Boonkamp L, Barrett N, Monti G, Jensen AMG, Vaegter CB, Raska J, Cesnarikova S, Sedmik J, Trieu C, Weiss MM, van Spaendonk R, Vermunt L, Ozhegov G, Tesi N, Hulsman M, Janulien D, Moller A, Bohaciakova D, van der Flier WM, Andersen OM, Teunissen CE, Holstege H. Soluble SORL1 in cerebrospinal fluid as a marker for functional impact of rare SORL1 variants. *Alzheimer's and Dementia*. 2026;22(2):e71042. PMID 41685556.
- Ding X, Chen Y, Guo C, Fu Y, Qin C, Zhu Q, Wang J, Zhang R, Tian H, Feng R, Liu H, Liang D, Wang G, Teng J, Li J, Tang B, Wang X. Mutations in ARHGEF15 cause autosomal dominant hereditary cerebral small vessel disease and osteoporotic fracture. *Acta Neuropathologica*. 2023;145(5):681–705. PMID 36929019.
- Edgar JR, Willén K, Gouras GK, Futter CE. ESCRTs regulate amyloid precursor protein sorting in multivesicular bodies and intracellular amyloid- β accumulation. *Journal of Cell Science*. 2015;128(14):2520–2528. PMID 26002056.
- Gorniak-Walas M, Telugu NS, Rudolph IM, Diecke S, Willnow TE. Alzheimer's disease risk single nucleotide polymorphism rs11218343 is linked to functional expression of SORL1 in microglia. *Alzheimer's and Dementia*. 2026;22(4):e71390. PMID 42002722.
- Gouras GK, Tsai J, Naslund J, Vincent B, Edgar M, Checler F, Greenfield JP, Haroutunian V, Buxbaum JD, Xu H, Greengard P, Relkin NR. Intraneuronal A β 42 accumulation in human brain. *American Journal of Pathology*. 2000;156(1):15–20. PMID 10623648.
- Gouras GK, Willén K, Tampellini D. Critical role of intraneuronal A β in Alzheimer's disease: technical challenges in studying intracellular A β . *Life Sciences*. 2012;91(23–24):1153–1158. PMID 22727791.
- Greenfield JP, Tsai J, Gouras GK, Hai B, Thinakaran G, Checler F, Sisodia SS, Greengard P, Xu H. Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer beta-amyloid peptides. *Proceedings of the National Academy of Sciences USA*. 1999;96(2):742–747. PMID 9892704.
- Hamilton AM, Lambert JT, Parajuli LK, Vivas O, Park DK, Stein IS, Jahncke JN, Greenberg ME, Margolis SS, Zito K. A dual role for the RhoGEF Ephexin5 in regulation of dendritic spine outgrowth. *Molecular and Cellular Neuroscience*. 2017;80:66–74. PMID 28185854.
- Haq I, Ngo JC, Roy N, Lee E, Choudhury MA, Soni RK, Teich AF, Mayeux RP, De Jager PL, He Y, Wu X, Bennett DA, Olah M, Sher F. Alzheimer's disease risk protein SorLA regulates ER homeostasis and lipid metabolism in human microglia, with conserved effects in neurons. *Acta Neuropathologica*. 2026;151(1):37. PMID 41942750.
- Hiesberger T, Trommsdorff M, Howell BW, Goffinet A, Mumby MC, Cooper JA, Herz J. Direct binding of Reelin to VLDL receptor and ApoE receptor 2 induces tyrosine phosphorylation of disabled-1 and modulates tau phosphorylation. *Neuron*. 1999;24(2):481–489. PMID 10571241.
- Huang H, Shi CH, Yang W, Piña-Crespo J, Bhatnagar J, Curatolo J, Murad R, Shah P, Campos A, Houser A, Porritt RA, Zhang T, Xiao Q, Feng S, Yip KY, Huang TY. SORLA up-regulation suppresses pathological effects in aged tauopathy mouse brain. *Science Advances*. 2026;12(29):eade6825.

- Hung C, Tuck E, Stubbs V, van der Lee SJ, Aalfs C, van Spaendonk R, Scheltens P, Hardy J, Holstege H, Livesey FJ. SORL1 deficiency in human excitatory neurons causes APP-dependent defects in the endolysosome-autophagy network. *Cell Reports*. 2021;35(11):109259. PMID 34133918.
- Kang DE, Woo JA. Cofilin, a master node regulating cytoskeletal pathogenesis in Alzheimer's disease. *Journal of Alzheimer's Disease*. 2019;72(s1):S131–S144. PMID 31594228.
- Kawaguchi Y, Matsubayashi J, Kawakami Y, Nishida R, Kurihara Y, Takei K. LOTUS suppresses amyloid β -induced dendritic spine elimination through the blockade of amyloid β binding to PirB. *Molecular Medicine*. 2022;28(1):154. PMID 36510132.
- Kim T, Vidal GS, Djuricic M, William CM, Birnbaum ME, Garcia KC, Hyman BT, Shatz CJ. Human LILRB2 is a β -amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science*. 2013;341(6152):1399–1404. PMID 24052308.
- Klementieva O, Willén K, Martinsson I, Israelsson B, Engdahl A, Cladera J, Uvdal P, Gouras GK. Pre-plaque conformational changes in Alzheimer's disease-linked A β and APP. *Nature Communications*. 2017;8:14726. PMID 28287086.
- Klementieva O, Sandt C, Martinsson I, Kansiz M, Gouras GK, Borondics F. Super-resolution infrared imaging of polymorphic amyloid aggregates directly in neurons. *Advanced Science*. 2020;7(6):1903004. PMID 32195099.
- Knupp A, Mishra S, Martinez R, Braggins JE, Szabo M, Kinoshita C, Hailey DW, Small SA, Jayadev S, Young JE. Depletion of the AD risk gene SORL1 selectively impairs neuronal endosomal traffic independent of amyloidogenic APP processing. *Cell Reports*. 2020;31(9):107719. PMID 32492427.
- Konings SC, Nyberg E, Martinsson I, Torres-Garcia L, Klementieva O, Guimas Almeida C, Gouras GK. Apolipoprotein E intersects with amyloid- β within neurons. *Life Science Alliance*. 2023;6(8):e202201887. PMID 37290814.
- Lao PJ, Lee S, Talmasov D, Dass D, Chikwem N, Johnson A, Smith A, Guzman D, Okafor A, Houlihan H, Heuer L, Sanchez T, Maldonado A, Palacios C, Rossano S, Andrews H, Reitz C, Kreisl WC, Noble JM, Qureshi YH, Small SA. Inflammatory alterations mediate tau-associated neurodegeneration. *Brain Communications*. 2026;8(4):fcag242. PMID 42404434.
- Lee JH, Yang DS, Goulbourne CN, Im E, Stavrides P, Pensalfini A, Chan H, Bouchet-Marquis C, Bleiwas C, Berg MJ, Huo C, Peddy J, Pawlik M, Levy E, Rao M, Staufenbiel M, Nixon RA. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of A β in neurons, yielding senile plaques. *Nature Neuroscience*. 2022;25(6):688–701. PMID 35654956.
- Lundgren JL, Ahmed S, Schedin-Weiss S, Gouras GK, Winblad B, Tjernberg LO, Frykman S. ADAM10 and BACE1 are localized to synaptic vesicles. *Journal of Neurochemistry*. 2015;135(3):606–615. PMID 26296617.
- Margolis SS, Salogiannis J, Lipton DM, Mandel-Brehm C, Wills ZP, Mardinly AR, Hu L, Greer PL, Bikoff JB, Ho HH, Soskis MJ, Sahin M, Greenberg ME. EphB-mediated degradation of the RhoA GEF Ephexin5 relieves a developmental brake on excitatory synapse formation. *Cell*. 2010;143(3):442–455. PMID 21029865.
- Minamide LS, Striegl AM, Boyle JA, Meberg PJ, Bamberg JR. Neurodegenerative stimuli induce persistent ADF/cofilin-actin rods that disrupt distal neurite function. *Nature Cell Biology*. 2000;2(9):628–636. PMID 10980704.
- Mishra S, Morshed N, Sidhu SB, Kinoshita C, Stevens B, Jayadev S, Young JE. The Alzheimer's disease gene SORL1 regulates lysosome function in human microglia. *Glia*. 2025;73(7):1329–1348. PMID 40183375.

- Muhammad A, Flores I, Zhang H, Yu R, Staniszewski A, Planel E, Herman M, Ho L, Kreber R, Honig LS, Ganetzky B, Duff K, Arancio O, Small SA. Retromer deficiency observed in Alzheimer's disease causes hippocampal dysfunction, neurodegeneration, and Abeta accumulation. *Proceedings of the National Academy of Sciences USA*. 2008;105(20):7327–7332. PMID 18480253.
- Nyberg E, Konings SC, Lindblom N, Israelsson B, Klementieva O, Martinsson I, Gouras GK. Neuronal endolysosomal alterations induced by apolipoprotein E4 emerge over time in primary neurons. *Journal of Biological Chemistry*. 2025;301(8):110479. PMID 40675218.
- Olsson TT, Klementieva O, Gouras GK. Prion-like seeding and nucleation of intracellular amyloid- β . *Neurobiology of Disease*. 2018;113:1–10. PMID 29414379.
- Petshow S, Coblentz A, Hamilton AM, Sarkar D, Anisimova M, Flores JC, Zito K. Activity-dependent regulation of Cdc42 by Ephexin5 drives synapse growth and stabilization. *Science Advances*. 2025;11(13):eadp5782. PMID 40138406.
- Pollack SJ, Dakkak D, Guo T, Chennell G, Gomez-Suaga P, Noble W, Jimenez-Sanchez M, Hanger DP. Truncated tau interferes with the autophagy and endolysosomal pathway and results in lipid accumulation. *Cellular and Molecular Life Sciences*. 2024;81(1):304. PMID 39009859.
- Qureshi YH, Berman DE, Marsh SE, Klein RL, Patel VM, Simoes S, Kannan S, Petsko GA, Stevens B, Small SA. The neuronal retromer can regulate both neuronal and microglial phenotypes of Alzheimer's disease. *Cell Reports*. 2022;38(3):110262. PMID 35045281.
- Ramonet D, Daerr A, Hallbeck M. Stabilizing the retromer complex rescues synaptic dysfunction and endosomal trafficking deficits in an Alzheimer's disease mouse model. *Acta Neuropathologica Communications*. 2025;13(1):190. PMID 40931359.
- Ramsden CE, Keyes GS, Calzada E, Horowitz MS, Zamora D, Jahanipour J, Sedlock A, Indig FE, Moaddel R, Kapogiannis D, Maric D. Lipid peroxidation induced ApoE receptor-ligand disruption as a unifying hypothesis underlying sporadic Alzheimer's disease in humans. *Journal of Alzheimer's Disease*. 2022;87(3):1251–1290. PMID 35466940.
- Roos TT, Garcia MG, Martinsson I, Mabrouk R, Israelsson B, Deierborg T, Kobro-Flatmoen A, Tanila H, Gouras GK. Neuronal spreading and plaque induction of intracellular A β and its disruption of A β homeostasis. *Acta Neuropathologica*. 2021;142(4):669–687. PMID 34272583.
- Rush T, Martinez-Hernandez J, Dollmeyer M, Frandemich ML, Borel E, Boisseau S, Jacquier-Sarlin M, Buisson A. Synaptotoxicity in Alzheimer's disease involved a dysregulation of actin cytoskeleton dynamics through cofilin 1 phosphorylation. *Journal of Neuroscience*. 2018;38(48):10349–10361. PMID 30341179.
- Sahlin C, Lord A, Magnusson K, Englund H, Almeida CG, Greengard P, Nyberg F, Gouras GK, Lannfelt L, Nilsson LN. The Arctic Alzheimer mutation favors intracellular amyloid-beta production by making amyloid precursor protein less available to alpha-secretase. *Journal of Neurochemistry*. 2007;101(3):854–862. PMID 17448150.
- Saito T, Matsuba Y, Mihira N, Takano J, Nilsson P, Itohara S, Iwata N, Saido TC. Single App knock-in mouse models of Alzheimer's disease. *Nature Neuroscience*. 2014;17(5):661–663. PMID 24728269.
- Sell GL, Schaffer TB, Margolis SS. Reducing expression of synapse-restricting protein Ephexin5 ameliorates Alzheimer's-like impairment in mice. *Journal of Clinical Investigation*. 2017;127(5):1646–1650. PMID 28346227.
- Simoes S, Guo J, Buitrago L, Qureshi YH, Feng X, Kothiyi M, Cortes E, Patel V, Kannan S, Kim YH, Chang KT, Hussaini SA, Moreno H, Di Paolo G, Andersen OM, Small SA. Alzheimer's vulnerable brain region relies on a distinct retromer core dedicated to endosomal recycling. *Cell Reports*. 2021;37(13):110182. PMID 34965419.

- Small SA, Kent K, Pierce A, Leung C, Kang MS, Okada H, Honig L, Vonsattel JP, Kim TW. Model-guided microarray implicates the retromer complex in Alzheimer's disease. *Annals of Neurology*. 2005;58(6):909–919. PMID 16315276.
- Small SA, Duff K. Linking Abeta and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. *Neuron*. 2008;60(4):534–542. PMID 19038212.
- Small SA. Isolating pathogenic mechanisms embedded within the hippocampal circuit through regional vulnerability. *Neuron*. 2014;84(1):32–39. PMID 25277453.
- Small SA, Simoes-Spassov S, Mayeux R, Petsko GA. Endosomal traffic jams represent a pathogenic hub and therapeutic target in Alzheimer's disease. *Trends in Neurosciences*. 2017;40(10):592–602. PMID 28962801.
- Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P. Regulation of NMDA receptor trafficking by amyloid-beta. *Nature Neuroscience*. 2005;8(8):1051–1058. PMID 16025111.
- Stenh C, Englund H, Lord A, Johansson AS, Almeida CG, Gellerfors P, Greengard P, Gouras GK, Lannfelt L, Nilsson LN. Amyloid-beta oligomers are inefficiently measured by enzyme-linked immunosorbent assay. *Annals of Neurology*. 2005;58(1):147–150. PMID 15984012.
- Takahashi RH, Milner TA, Li F, Nam EE, Edgar MA, Yamaguchi H, Beal MF, Xu H, Greengard P, Gouras GK. Intraneuronal Alzheimer A β 42 accumulates in multivesicular bodies and is associated with synaptic pathology. *American Journal of Pathology*. 2002;161(5):1869–1879. PMID 12414533.
- Takahashi RH, Almeida CG, Kearney PF, Yu F, Lin MT, Milner TA, Gouras GK. Oligomerization of Alzheimer's β -amyloid within processes and synapses of cultured neurons and brain. *Journal of Neuroscience*. 2004;24(14):3592–3599. PMID 15071107.
- Tampellini D, Rahman N, Gallo EF, Huang Z, Dumont M, Capetillo-Zarate E, Ma T, Zheng R, Lu B, Nanus DM, Lin MT, Gouras GK. Synaptic activity reduces intraneuronal Abeta, promotes APP transport to synapses, and protects against Abeta-related synaptic alterations. *Journal of Neuroscience*. 2009;29(31):9704–9713. PMID 19657023.
- Tampellini D, Capetillo-Zarate E, Dumont M, Huang Z, Yu F, Lin MT, Gouras GK. Effects of synaptic modulation on β -amyloid, synaptophysin, and memory performance in Alzheimer's disease transgenic mice. *Journal of Neuroscience*. 2010;30(43):14299–14304. PMID 20980585.
- Tampellini D, Rahman N, Lin MT, Capetillo-Zarate E, Gouras GK. Impaired β -amyloid secretion in Alzheimer's disease pathogenesis. *Journal of Neuroscience*. 2011;31(43):15384–15390. PMID 22031884.
- Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Annals of Neurology*. 1991;30(4):572–580. PMID 1789684.
- Türker F, Brennan A, Margolis SS. Neuronal membrane proteasome-derived peptides modulate NMDAR-dependent neuronal signaling to promote changes in gene expression. *Molecular Biology of the Cell*. 2024;35(1):ar6. PMID 37910253.
- Willén K, Edgar JR, Hasegawa T, Tanaka N, Futter CE, Gouras GK. A β accumulation causes MVB enlargement and is modelled by dominant negative VPS4A. *Molecular Neurodegeneration*. 2017a;12(1):61. PMID 28835279.
- Woo JA, Boggess T, Uhlar C, Wang X, Khan H, Cappos G, Joly-Amado A, De Narvaez E, Majid S, Minamide LS, Bamberg JR, Morgan D, Weeber E, Kang DE. RanBP9 at the intersection between cofilin and A β pathologies: rescue of neurodegenerative changes by RanBP9 reduction. *Cell Death and Disease*. 2015;6(3):e1676. PMID

25741591.

Xian X, Pohlkamp T, Durakoglulil MS, Wong CH, Beck JK, Lane-Donovan C, Plattner F, Herz J. Reversal of ApoE4-induced recycling block as a novel prevention approach for Alzheimer's disease. *eLife*. 2018;7:e40048. PMID 30375977.

Xu Y, Du S, Marsh JA, Horie K, Sato C, Ballabio A, Karch CM, Holtzman DM, Zheng H. TFEB regulates lysosomal exocytosis of tau and its loss of function exacerbates tau pathology and spreading. *Molecular Psychiatry*. 2021;26(10):5925–5939. PMID 32366951.

Young JE, Fong LK, Frankowski H, Petsko GA, Small SA, Goldstein LSB. Stabilizing the retromer complex in a human stem cell model of Alzheimer's disease reduces TAU phosphorylation independently of amyloid precursor protein. *Stem Cell Reports*. 2018;10(3):1046–1058. PMID 29503090.

Zheng C, Xia W, Zhang J. Rock inhibitors in Alzheimer's disease. *Frontiers in Aging*. 2025;6:1547883. PMID 40182055.