The Long Way Back

Endosomal recycling failure in Alzheimer's disease: retromer, SORL1 and why the lesion sits on the return leg

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November 2026

The fourth of the short papers, and the only one that is not about a phase. A cell sorts what it takes in, and either destroys it or sends it back; the sending-back is separate machinery, and it is the part that fails. It fails in three places, and the three places are the three phases — so this is not a fourth step but the axis the other three stand on.

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Abstract

The three papers before this one describe three steps of the disease, each with its own decade and its own cast of cells. This paper describes something that runs beside all three.

Every cell in the body takes material in from its own surface, sorts it in a compartment called the early endosome, and then either destroys it or sends it back out. The sending-back is a separate piece of machinery from the taking-in, and it is the piece that fails in this disease. A cargo receptor called SORLA, made by the gene *SORL1*, recognises what is to be saved. A three-protein complex called retromer collects it. A mechanical step then pulls the membrane into a tube and pinches the tube free. If that last step does not happen, the compartment does not empty, and everything waiting in it waits longer — not only the one protein that was being returned.

That single mechanical fact has consequences in three places, and the three places are the three phases. In the brainstem and basal forebrain neurons of Phase I, the endosome is not merely a sorting station but the vehicle that carries a survival signal up a very long axon. In the disposal machinery of Phase II, the same compartment matures into the lysosome, and both the neuron and the microglion depend on it finishing the job. At the synapse of Phase III, the receptors that make a connection work are held at the membrane by a balance between the rate at which they are removed and the rate at which they are returned.

So this is not a fourth step. It is the axis the other three stand on, and it is the only element of the model with a station in all three.

One further finding organises the paper, and it is the corpus's own. Nine long-running research programmes have each spent two or three decades asking what goes wrong at the synapse in this disease, and arrived at nine apparently different answers. Set along the itinerary of one neuron, each occupies a station on a single circuit, and at every station there is a forward leg and a return leg. In eight of the nine, the reported lesion is on the return leg, and the forward leg is frequently not merely intact but increased. That asymmetry is this paper's spine, and it is graded as an inference drawn from other people's published work, not as a finding of our own.

The paper closes with what has been given to people, with the measurement problem that stands in the way of giving them more, a graded ledger, and the results that would undo the account.

How to read this paper

This is the fourth of four short papers and the only one that is not about a phase. The first three can be read in any order; this one is best read after them, because it keeps pointing back at their cells.

Claims are graded where they are made, using the four grades the corpus uses throughout. **Established** means replicated in human material by more than one group. **Probable** means good evidence with a gap, such as a single cohort, or an animal result not yet confirmed in people. **Inference** means a conclusion drawn here, or elsewhere in the corpus, from evidence gathered for another purpose. **Speculative** means coherent and untested.

Two pieces of vocabulary are fixed at the start, because the whole paper turns on them.

A **cycle** is any step a cell performs in two directions: a forward leg that makes, delivers, cuts, engages or instructs, and a **return leg** that recovers, releases, clears, disposes, resolves or restabilises. The distinction is not decorative. A drug that slows a forward leg and a drug that restores a return leg are different kinds of object, they are tested differently, and almost everything tried in this disease so far has been the first kind.

Recycling, in this paper, always means the return leg of membrane traffic specifically: a protein taken into a cell being brought back out to where it was, rather than being destroyed. It is the ordinary word for an ordinary cellular operation, and it is not a metaphor.

1. Why This Is Not a Fourth Step

The three papers before this one are built on a clock. Phase I begins in the third decade of life, in a handful of small nuclei at the base of the brain. Phase II begins in the sixth, when the brain's immune cells lose the restraints that had held them at rest. Phase III begins in the eighth, when the protective matrix around inhibitory neurons is digested and the cortex loses its timing.

The steps are stacked rather than sequential: none ends when the next begins, and a person of seventy-five is carrying all three.

The obvious thing to do with a fourth mechanism is to look for a fourth decade and give it a step of its own. That does not work here, and the reason it does not work is the most useful thing about it.

The endosomal machinery has no decade of its own because it has a station in every one of them. In Phase I it is a transport problem: the signal that keeps a brainstem neuron alive travels to the cell body on an endosome, and if the endosome is deranged the signal does not arrive. In Phase II it is a disposal problem: the same compartment matures into the lysosome, and two different cell types depend on it to finish digesting what they have taken in. In Phase III it is a supply problem: the receptors that make a synapse work are held at the membrane only as long as they are returned there faster than they are removed.

Drawn on the stacked diagram, the three phases are steps and this is a vertical axis cutting through all three. That is not a rhetorical convenience. It is the testable claim of this paper, and Section 3 states what each phase's station is and how old the person is when it is reached.

An omission to declare. The three papers of this series between them run to some twenty-three thousand words and mention this machinery barely at all: no sustained treatment of retromer, of *SORL1*, or of the return leg appears in any of them. That is a real gap and this paper exists to close it. The gap was not deliberate, and it is worth naming because it shows how easily an axis that runs through everything can be left out of an account organised by steps. Each of the three papers now carries one forward-pointing sentence at the place where its own station on this axis belongs.

2. The Machine, in Plain Words

This section is self-contained. A reader who already knows what retromer is can skip to Section 3; nothing later in the paper assumes more than is set out here.

2.1 One counter, two trays

A neuron is continually pulling material in from its own surface — receptors, lipids, whatever has bound to them, and some of its own membrane along with them. All of it arrives at a single compartment, the **early endosome**. That compartment is the cell's sorting counter, and everything that arrives there has one of two fates. It goes onward, to the late endosome and then the lysosome, where it is broken up. Or it is recovered and sent back: to the cell surface, or backwards to the Golgi apparatus for re-use.

Think of a post room with one counter and two trays: one to the incinerator, one return-to-sender. The incinerator tray is the easy operation, because gravity is on its side — a compartment left alone matures towards the lysosome. The return tray needs work, and three separate things have to go right.

2.2 Three things that have to go right

Something has to recognise what is worth saving. That is the job of a cargo receptor. The one that matters most in this disease is **SORLA**, the protein made by the gene *SORL1*. It binds the amyloid precursor protein and directs it away from the route that produces amyloid, and it does so by gripping the recovery machinery with its own short tail inside the cell.

Something has to collect it. That is **retromer**: a complex of three proteins — VPS35, VPS26 and VPS29 — that assembles on the surface of the endosome. VPS35 is the scaffold and does the cargo recognition; VPS26 sits at one end and engages the cargo receptors; VPS29 sits at the other and recruits regulatory partners. Retromer does not have one cargo. In Scott Small's recurring phrase it is a *master conductor*: whatever the neuron needs returned passes through it. That is the structural reason one fault can produce several pathologies at once.

Something has to physically get the parcel off the counter. The membrane has to be deformed into a narrow tube, and the tube has to be pinched free so that it can travel. Proteins called sorting nexins do the deforming; the pinching — the **fission** step — is performed by scission machinery of the dynamin class, and it is regulated. This is the step that is easiest to overlook and the most recently identified as a drug target, which Section 9 returns to.

A parcel that is recognised, collected and tubulated but never cut loose has not been returned. The counter is still occupied.

2.3 Why a jam is worse than a blockage

Here is the move that makes this a disease mechanism rather than a piece of cell biology (Small et al., 2017). Stall the exit, and **residency time** in the endosome rises — for everything held there, not only for the protein whose return was being attempted.

Two properties of that compartment turn raised residency into pathology.

It is **acidic**. BACE1, the enzyme that makes the first, amyloid-producing cut in the amyloid precursor protein, works best at acidic pH. So substrate and enzyme held together for longer in an acidic space makes more amyloid, and more of the C-terminal fragments that precede it.

It is **where synaptic receptors wait**. The glutamate receptors that make a dendritic spine responsive are not permanent fixtures. They are removed and returned continuously, and between cycles they sit in this compartment. Receptors held there are receptors not at the synapse.

From that one mechanical fact, four pathologies follow in parallel rather than in series:

- **Amyloid.** Precursor protein and BACE1 spend longer together in an acidic compartment; the amyloidogenic cut is favoured.
- **Synaptic failure.** Glutamate receptors that should go back to the postsynaptic membrane are retained and diverted towards degradation. The synapse weakens without any cell dying.
- **Tau release.** A congested endosome matures into a multivesicular body; cytosolic contents, tau included, are packaged into internal vesicles and released when that body fuses with the surface — a route out of the cell.
- **Glial change.** Microglia use the same recovery machinery to return their own phagocytic receptors to their surface, so the same lesion blunts clearance.

That parallelism is the claim. It is why this is an axis and not a step: four effects, one cause, no ordering required among them.

2.4 What the evidence for it actually is

It is worth arranging the support by what each kind of study can establish, because the summaries in circulation do not.

Association in human tissue, which is where most readers meet this account, is the weakest of the four tiers. VPS35 and VPS26 are reduced in vulnerable regions (Small et al., 2005); VPS26b and SORLA are reduced in human trans-entorhinal cortex in disease (Simoes et al., 2021). Both are post-mortem, and therefore from the end of the process. **Established** as association; silent on direction.

Perturbation in models is stronger. Retromer-deficient mice develop memory and synaptic dysfunction with raised endogenous amyloid-β, and retromer-deficient flies carrying human precursor protein and BACE develop neuronal loss and amyloid aggregates (Muhammad et al., 2008). Phosphatidylinositol-3-phosphate, which organises endosomal traffic, is depleted in Alzheimer tissue, and reducing the kinase that makes it enlarges neuronal endosomes and enhances amyloidogenic processing (Morel et al., 2013).

Depletion and repletion is the strongest design available in an animal, and it is the one that matters. VPS35 was depleted in mouse hippocampal neurons and then restored with an optimised viral vector; accelerated precursor-protein cleavage and loss of synaptic glutamate receptors both followed the manipulation in **both** directions. The same study found that a deficit in the *neuron's* retromer was by itself sufficient to induce the dystrophic microglial morphology characteristic of the disease, independently of tau (Qureshi et al., 2022).

Human genetics is the only part of the case that carries the direction of causation without a model organism, and Section 8 takes it up.

So the account does not mainly rest on having seen jams in human brains. It rests on the fact that inducing the lesion produces the phenotype, that reversing it removes the phenotype, and on a gene.

3. The Two Clocks

Jim's question when this paper was commissioned was a question about time: when does each of these failures become important? The honest answer has two parts, because the pathway has two clocks and they are not the same clock.

3.1 Clock one: the machine gets slower

The capacity of this machinery declines with age in everybody, disease or no disease. The clearest demonstration is also the one that runs the right way round. In cultured mouse neurons aged *in vitro*, internalisation of the amyloid precursor protein **rises** with neuronal age, and that rise is what drives the age-related synapse loss: blocking amyloid production reversed the synaptic decline of the aged neurons, and driving internalisation upward in young neurons reproduced it (Burrinha et al., 2021). Taking-in goes up; the return leg does not keep pace.

That finding needs a discipline set beside it. The dentate gyrus — the one part of the hippocampal circuit this disease spares — has its own age-related decline, traceable to a different molecular lesion entirely (Pavlopoulos et al., 2013). Ordinary age-related memory loss and this disease are separable, they have different molecular signatures in different subregions, and an account of the disease that explains ordinary ageing equally well has explained neither.

Clock one is slow, general and present in everyone. By itself it produces forgetting, not dementia.

3.2 Clock two: the load arrives

What makes this a disease is that the load on a declining machine rises at particular ages, and each rise belongs to one of the three phases. Table 1 states what is known about when.

Table 1 — What is known about when, on this axis.

Approximate age	What is reported	Where	Grade
Before birth, and through childhood	Enlarged early endosomes in neurons in Down syndrome, in some neurons before birth	Human tissue (Cataldo et al., 2000)	Established
Third to fifth decade	No direct human measurement of this machinery exists in this window	—	Gap
Before amyloid deposition, sporadic disease	Markedly enlarged early endosomes with increased delivery of digestive enzymes to them, at early neuropathological stages	Human neocortex (Cataldo et al., 1997, 2000)	Established
Mild cognitive impairment, before dementia	Rab GTPases up-regulated in individually captured cholinergic basal forebrain neurons	Human tissue, single-cell expression (Ginsberg et al., 2011)	Established
Across the clinical transition	Endosomal regulatory genes up-regulated in individually captured CA1 pyramidal neurons, from normal ageing through mild cognitive impairment to disease	Human tissue, single-cell expression (Ginsberg et al., 2010)	Established
Throughout, independent of disease	Precursor-protein internalisation rises with neuronal age and drives synapse loss	Cultured mouse neurons (Burrinha et al., 2021)	Probable in people
Any age, modifier	*APOE* ε4 accentuates the endosomal enlargement	Human tissue (Cataldo et al., 2000); neuronal models	Probable

Four things in that table deserve emphasis.

The abnormality is **early**. Among the structural abnormalities of this disease, enlargement of the early endosome has the best claim to be the first thing that happens. In Down syndrome it is present decades before dementia and, in some neurons, before birth.

It is early **relative to amyloid**, which is the claim that costs something. The 1997 and 2000 reports found it at early neuropathological stages and before deposition. That is a statement about order in human tissue, and it is the reason this machinery is treated as upstream rather than consequential.

The **third to fifth decade is empty**. There is no human measurement of this machinery in the window during which Phase I is, on the model's own account, already under way. This is the largest single hole in the paper and it is stated as a hole, not smoothed over. The corpus's Phase I evidence for those decades is tau in the locus coeruleus, not endosomes.

And the up-regulations are **up**, not down. In both Ginsberg studies what rises is the machinery, in the cells that are about to fail. Section 7 argues that this is the signature of a return leg that is not keeping up, rather than of a forward leg that has gone wrong — and that the distinction is the single most useful thing the corpus has to offer about this literature.

4. The First Address: The Long Axon

4.1 A cell with a distance problem

The neurons of Phase I have a problem that no other cell in this story has, and it is purely geometric. A cholinergic neuron of the nucleus basalis sits at the base of the brain and sends a single thin axon to the cortex — a journey of several centimetres, which for a cell is an enormous distance. The survival signal it depends on, nerve growth factor, is not made at the cell body. It is picked up at the far end, by the axon terminal, and it has to be carried all the way home.

It is carried on an endosome. For this cell, the compartment described in Section 2 is not only a sorting counter; it is the vehicle. A sorting fault in any other cell makes a mess locally. In this cell it cuts the line between the terminal and the nucleus.

4.2 What the evidence shows

The evidence here is unusually direct, and it comes almost entirely from Ralph Nixon's laboratory.

Trophic signalling from Rab5 endosomes declines early in both Alzheimer's disease and Down syndrome. In human tissue, the Rab GTPases are transcriptionally up-regulated in individually captured cholinergic basal forebrain neurons in mild cognitive impairment — that is, before dementia is diagnosed (Ginsberg et al., 2011). **Established** in human material.

In animals, the lesion is sufficient on its own. Directly over-activating Rab5 — with no amyloid mutation, no tau, nothing else — recapitulates prodromal and neurodegenerative features of the disease, including cholinergic degeneration (Pensalfini et al., 2020). So does over-expressing APPL1, a Rab5 effector on the early endosome, which reproduces the endosomal and synaptic dysfunction together with cholinergic neurodegeneration (Jiang et al., 2025). An earlier study established the link in the other direction, showing that APPL1 mediates the endosome dysfunction induced by the precursor protein's β-cleaved fragment in Down syndrome and Alzheimer's disease (Kim et al., 2016). **Established** in the animals.

And it is reversible in the animals by three independent routes: raising nerve growth factor, lowering the β-cleaved fragment, or reversing Rab5 activation pharmacologically. Three routes to the same rescue is a strong argument that the pathway, and not some incidental consequence of the manipulation, is what is doing the damage.

4.3 What Nixon says the tributaries are

Asked directly, in correspondence in November 2026, what tips the endosome off balance in the sporadic disease, Nixon answered that the C-terminal fragment, cholesterol and *APOE* ε4 are all tributaries to the river of Rab5 activation, and that over-activation blocks the transport of both nerve growth factor and brain-derived neurotrophic factor. His group has extended the same account to frontotemporal dementia and is preparing a review of these early tributaries across Alzheimer's and Parkinson's disease.

This is recorded here as his framing, given to us directly, and it is **not yet a published claim in that form**. It is included because it is the clearest available statement of how several apparently separate risk factors could act on one step, and because it is falsifiable: it predicts that each tributary, applied alone, raises Rab5 activity in the same cells.

4.4 What this contributes to the first paper

What the Brainstem Stops Sending makes an argument from a control case. The pedunculopontine nucleus is a cholinergic group in the brainstem that accumulates tangles and nonetheless keeps its neurons, and the reason it offers is that this nucleus does not depend on the growth factor the disease cuts off. What dies is not the cholinergic cell but the dependent one.

Read alongside this section, that control case becomes a prediction about traffic. If the lesion is a failure to deliver a trophic signal up a long axon on an endosome, then the cell that does not need that delivery should survive, whatever else accumulates in it — which is what is observed. The two arguments are the same argument approached from opposite ends.

This is an **inference**, and the gap in it should be named: nobody has measured endosomal transport in the pedunculopontine nucleus. The nucleus is rarely studied at all, because it requires dedicated dissection.

5. The Second Address: The Disposer

5.1 Downhill is not automatic

The second address is the far end of the same compartment. An endosome that is not emptied matures: late endosome, then lysosome, where the contents are digested. That maturation needs acid. The lysosome runs at a pH around 4.5, maintained by a pump in its membrane, and its digestive enzymes do not work without it.

Two different cells in this story depend on that step, and both acquire the same lesion.

5.2 The neuron

If acidification fails, nothing downstream digests, and the consequence in the neuron is not a quiet accumulation. In mouse models, faulty autolysosome acidification induces an autophagic build-up of amyloid-β inside neurons, and those neurons die in place in a characteristic morphology, the cell body itself becoming a senile plaque (Lee et al., 2022). **Established** in the models; the corresponding human study is now accepted for publication.

What jams the pump. For years the acidification failure was a described fact without a named cause. Nixon's laboratory supplied one. The β-cleaved fragment of the amyloid precursor protein — the uncut stub usually written C99 — when phosphorylated on a single tyrosine, binds into a pocket on the V0a1 subunit of the pump and competitively blocks the rest of the pump from assembling, lowering its activity. Reducing that phosphorylation restores the pump and lysosomal function in Down syndrome fibroblasts and in the brains of Down syndrome model mice; reducing it *below* normal constitutive levels raises pump assembly above baseline, which suggests the fragment tunes the pump in health as well as disabling it in disease (Im et al., 2023). **Established** in human fibroblasts and mouse brain.

The detail worth holding on to is which part of the fragment does it. The sequence that binds the pump is the YENPTY motif — the tag whose ordinary job is to signal that the protein should be pulled in from the cell surface. The same few residues that drive a protein into the endosome, once phosphorylated, disable the pump at the far end of the same pathway. This paper's axis and this section's disposal step turn out to be two functions of one molecule, which is the subject of a companion paper, *The Same Defendant*.

Two consequences deserve drawing out.

On mitochondria. Damaged mitochondria can only pile up if the disposal system has already failed: the recycling machinery still wraps them but cannot digest them. The tagging is competent; the failure is in degradation. On this account "mitophagy" is not an independent event, and a bioenergetic story in which mitochondrial failure is the first domino has the order the wrong way round. This is Nixon's position, stated plainly, and it is a live disagreement rather than a settled matter.

On where the plaque comes from, a dispute this paper does not resolve. On the account just given, the plaque arises from the cell body of a neuron

that ruptures where it stands. On Gunnar Gouras's account, the accumulated peptide relocalises to the axon terminals and deposits far from the soma — and there is a measurement: somatic amyloid in CA1 fell by roughly forty per cent as plaques appeared at the corresponding terminals (Roos et al., 2021). As descriptions of how a raised internal pool damages a synapse the two compose. As accounts of the plaque's origin they do not, and both cannot be right.

5.3 The microglion

The second cell is the one charged with clearing up, and what happens to it is worse than a simple loss of capacity.

In human induced-pluripotent-stem-cell microglia, loss of SORLA decreased lysosomal degradation and lysosomal enzyme activity through altered trafficking of the enzymes themselves. Phagocytic uptake of fibrillar amyloid-β **and of synaptosomes** was *increased* while degradation was *reduced*, so both substrates accumulated aberrantly inside lysosomes, and lysosomal exocytosis — the route by which a cell gets rid of indigestible material — was impaired (Mishra et al., 2025). **Supported**: one group, one system, human cells.

The direction is the important part. The cell responsible for removing synaptic material takes in more of it and digests less. That is not a brake failing off; it is a swallow with no stomach behind it.

And there is a route from the neuron to the microglion that needs no amyloid at all. In the depletion-and-repletion study already cited, a deficit in the *neuron's* retromer was by itself sufficient to induce the dystrophic microglial morphology characteristic of the disease, independently of tau (Qureshi et al., 2022). **Established** in mouse.

5.4 What this contributes to the second paper

The Hands That Let Go is built around nine brakes — the restraints that make a microglion different from an ordinary macrophage, and that are released one by one across the sixth and seventh decades. This section does not add a tenth brake, and it would be a mistake to file it as one.

The brakes decide **whether** the microglion acts. This decides whether the action **finishes**. A microglion with every brake intact and a failed lysosome still accumulates what it has swallowed; a microglion with every brake

released and an intact lysosome does damage of an entirely different kind. The two failures are independent, they are measured differently, and the second paper's account of amyloid clearance — three removal routes, four mechanisms of loss — is incomplete without the digestion step underneath all of them.

This is an **inference** from the two bodies of work set side by side. No study has manipulated a brake and the lysosome in the same microglion.

6. The Third Address: The Synapse

6.1 A synapse is a balance, not a stock

The third address is the one that matters most for cognition, because synapse loss remains the strongest structural correlate of cognitive decline in this disease — better than plaque burden, better than tangle burden, established for three decades and now measurable in living people (DeKosky and Scheff, 1990; Terry et al., 1991; Mecca et al., 2020).

A dendritic spine is, functionally, a set of receptors held at a membrane: glutamate receptors that make it responsive, neurotrophin receptors that make it maintainable, and a precursor protein whose own function remains contested but whose residence in the endosome is the measured variable. Each of those is removed from the surface by endocytosis and returned, or not, by retrieval.

So the quantity that sets a synapse's strength is not a stock but a **balance** — the rate at which receptors leave against the rate at which they come back. That is the sentence this whole paper exists to establish, and it changes what a therapy would have to do.

6.2 Three cargoes, one receptor, one step

The result that establishes it is four years old and has not entered the summaries.

Working in isogenic human induced-pluripotent-stem-cell neurons engineered to have *SORL1* either depleted or over-expressed, Mishra and

colleagues tracked three transmembrane proteins through the endosomal network and tested the functional consequence with surface-recycling and lysosomal-degradation assays. The three were the amyloid precursor protein; TRKB, the receptor for brain-derived neurotrophic factor; and GLUA1, the subunit that carries most fast excitatory transmission in the forebrain (Mishra et al., 2022).

Trafficking of **all three** cargoes was altered by manipulating SORLA. Depletion significantly impaired the recycling pathway for the precursor protein **and** for the glutamate receptor, at the level of the recycling endosome and of delivery to the cell surface. Raising SORLA **enhanced** recycling for both. And the glutamate-receptor effect was not merely morphological: it registered as a change in network activity on a multi-electrode array. **Established** in human neurons, by bidirectional manipulation — the strongest design available short of a person.

The therapeutic reading changes accordingly. On the amyloid reading, restoring SORLA lowers a toxic product. On the supply reading, restoring SORLA returns a glutamate receptor to a membrane and makes a neuron answerable to brain-derived neurotrophic factor again. These are not the same benefit, they would be measured differently, and only the first has ever been used as the end-point of a preclinical study of this pathway.

6.3 Why the disease starts where it starts

The model's account of place belongs here, because it is an account about recycling capacity specifically.

Neurons carry a second retromer core, built around VPS26b rather than VPS26a, and dedicated to the recycling arm. The two forms are not redundant. The trans-entorhinal cortex — the small piece of cortex where this disease reliably begins — depends on that recycling-dedicated core most heavily, and in the diseased human brain both VPS26b and SORLA are depleted there (Simoes et al., 2021). **Probable**: one group, human tissue, end-stage.

The region the disease starts in is the region that was already running closest to its recycling capacity. That is an explanation of selective vulnerability that does not invoke amyloid at any point, and it is the single most attractive feature of this account.

6.4 What this contributes to the third paper

The Cage and the Clock devotes a section to four receptors and one instruction: amyloid acting at the NMDA receptor, PirB and LilrB2 with C4d as a ligand, EphB2 with Ephexin5, and reelin with ApoER2. Each of those is a surface receptor on a dendrite, and Section 6.1 says what a surface receptor is: a balance between removal and return.

So the endosomal axis is the supply side of every one of them. That is the natural reading, and it has to be marked clearly as an **inference**, because the supporting work does not exist. Nobody has measured PirB, LilrB2, EphB2 or ApoER2 recycling through SORLA or through retromer. The three cargoes that have been measured are the three named above. Extending the finding to the receptors of the third paper is a prediction this paper makes, not a result it reports, and Section 10 lists it among the things that would change the account if tested and found false.

7. The Finding: Eight of Nine on the Return Leg

7.1 Nine answers to one question

Nine long-running research programmes have each spent two to three decades asking what happens, mechanically, at the synapse in this disease. They arrived at nine apparently different answers: a sterol, an aldehyde, a proteolytic fragment, a sorting complex, a retained peptide, a scaffolding protein, a surface protease, an inhibitory receptor, a competition signal. Read one at a time they look like rival origin stories, and the field has largely read them that way.

Set them instead along the itinerary of a lipid and a membrane protein through the compartments of one neuron, and each occupies a distinct station on a single circuit. At every station there is a cycle. **In eight of the nine, the reported lesion is on the return leg.**

Table 2 — The nine programmes, by leg.

Programme	Forward leg — intact or increased	Return leg — the reported lesion
Astrocytic cholesterol supply (Rappoport)	Candidate generation runs on	Resolution never begins
Peroxidation at the receptor (Ramsden)	Ligand binds; is internalised	Acid release fails; ApoER2 not recovered
The uncleared lipid signal (Area-Gómez)	C99 made; the correction runs	Clearance of C99 fails; signal stays on
Retromer-dependent sorting (Small)	Endocytosis normal or accelerated	Retrieval jams; residency time rises
Intraneuronal retention (Gouras)	Production up in loaded cells	Secretion falls; surface neprilysin lost
The membrane platform (Head)	Ligand present; receptors made	Platform unmaintained; receptors delocalise
Surface proteolysis (Margolis)	Activity-driven synthesis runs on	Surface proteasome falls; trimming fails
The system of restraint (Shatz, Brott)	Ligand engagement rises	Restraint not lifted; cofilin stays active
Competitive plasticity (Huang)	Axons compete; signal secreted	Monomer lost to aggregate; no resolution

Five of the nine state this in their own summary vocabulary, without using the word: *retention rather than overproduction*, *the traffic jam*, *a homeostatic correction left switched on*, *chronic candidate generation*, *failure of local disposal*.

A tenth programme — the endosomal–lysosomal–autophagy account that supplies most of Sections 4 and 5 — is absent from the table only because its object is a network rather than the synapse. It makes the point more explicitly than any of the nine.

7.2 Why this is not a tautology

The obvious objection is that "return leg" is elastic enough to accommodate anything, and that any lesion can be described as a failure to undo something. The answer is that the account makes a prediction a tautology could not, and the prediction has been tested.

A disease of over-production predicts products elevated and machinery normal. A disease of **failed return** predicts something stranger: products

elevated, return machinery reduced, *and forward machinery up-regulated in compensation*, because a homeostat that detects a shortage at the surface responds by making more.

The third is documented. Amyloid production is up-regulated in cells carrying an internal load, because the homeostat has detected a low external pool (Roos et al., 2021). Precursor-protein internalisation rises in aged neurons (Burrinha et al., 2021). Across the thirteen stations of the full circuit, forward-leg up-regulation is reported at six.

It also explains the thing a step model explains badly: how a modest deficit becomes a progressive one over twenty years. Because the cycle **stalls** rather than stopping, the cell keeps paying the forward cost for a return that never arrives — small at any instant, compounding over decades. No accelerating insult is required, and none has been found.

7.3 The exception, recorded rather than absorbed

One programme does not fit, and it is recorded here rather than argued away.

C4d is a nanomolar ligand of LilrB2. It rises with age and further in Alzheimer cortex, and delivered to normal adult cortex it strips dendritic spines — a loss abolished in animals lacking PirB (Brott et al., 2025). That is a **forward-leg excess**: a signal is added, and the addition alone produces the lesion. Hence eight of nine, not nine.

That the exception is the newest mechanism in the set, and has the cleanest demonstration in normal tissue, is a caution against over-reading the pattern. A ninth programme breaking the rule in the most rigorous available design is exactly how a real pattern starts to come apart.

7.4 How this claim is graded

The return-leg finding is the corpus's own and is graded **Inference**, at the strength the word implies. It is a structural reading of other people's published work, arrived at by placing nine independent literatures on one itinerary. No experiment has been done to test it as such. It has not been peer-reviewed. Its value is that it is cheap to check — anyone who knows one of these nine literatures can look at one row and say whether it is fairly stated — and that it makes the therapeutic prediction in Section 9.

What would weaken it: a station where the lesion is demonstrably on the forward leg and the return leg is intact, as C4d may already be; or a demonstration that the forward-leg up-regulations are artefacts of post-mortem tissue or of the culture models in which some were measured.

8. The Genetics Agree, With One Complication

Everything to this point is mechanism, and mechanism does not establish direction. Genetics does, and here it does.

8.1 The strongest single link

Rare truncating variants in *SORL1* are found almost exclusively in people who have Alzheimer's disease. In December 2025 these were mapped across the receptor's structure in a very large cohort, assigning pathogenicity by domain rather than treating the gene as a single unit (Andersen, de Waal et al., 2025). **Established**.

A gene whose loss-of-function variants appear almost exclusively in people who develop the disease is not a bystander, and no amount of argument about what is downstream of what can make it one. This is the causal spine of the whole account.

The mechanism of one variant has been resolved to the step this paper is about. The p.Y1816C variant causes autosomal dominant Alzheimer's disease by impairing the receptor's **dimerisation on the endosome** — the molecular event that governs its association with retromer (Jensen et al., 2024; mechanism established in Jensen et al., 2023). A dominant Alzheimer mutation whose demonstrated lesion is a failure to engage the recovery machinery is as direct as this kind of evidence gets.

8.2 The four classes, stated honestly

The convergence argument usually offered alongside this gives endosomal recycling the status of a hub on which the disease's other genetic risk factors act as spokes (Small and Petsko, 2020), and is usually stated as four separate classes of Alzheimer risk gene converging on endosomal function. The classes are real. They do not contribute equally, and the corpus has said so before.

- **Endosomal trafficking genes —** *SORL1*, *BIN1*, *PICALM*, *CD2AP* — act on membrane traffic directly, immediately and mechanistically, and *SORL1* carries the rare-variant evidence above.
- **Precursor-processing genes —** *APP*, *PSEN1*, *PSEN2* — act conditionally. Amyloidogenic cleavage happens mostly in the acidic endosomal lumen, so a jam favours that cut — but this is a consequence of prior endosomal dysfunction, not independent evidence of it, and the temporal primacy is exactly what is in dispute.
- **Lipid handling —** *APOE* — acts indirectly. The ε4 variant interferes with endosomal recycling, but its effects are not confined to this compartment.
- **Innate immunity —** *TREM2* — acts indirectly and in a different cell. Microglial phagocytic receptors need retrieval machinery to get back to the surface, so a recycling failure blunts clearance — a parallel mechanism in a parallel cell type, not the neuronal lesion.

Labelling all four as equally converging obscures a difference in kind. A hub that four gene classes converge on is a strong claim about explanatory reach; a hub that one class acts on directly while three touch it obliquely is a weaker one, and the weaker reading is what the evidence supports.

The broader picture is consistent without being decisive. The largest association study of the disease identified seventy-five loci, and pathway analysis places endocytosis and lysosomal function among the most strongly enriched pathways — alongside immunity and lipid metabolism, not instead of them (Bellenguez et al., 2022).

8.3 The complication: which cell carries the risk

One recent result makes the genetics harder to use, and it should not be buried.

The strongest known protective common variant at the *SORL1* locus was examined in donor-derived and genome-engineered stem-cell lines, and its effect was found to be uniquely linked to functional expression of the receptor **in microglia**, the protective allele associating with higher expression and reduced pro-inflammatory responses. The effect appeared in donor lines but not in isogenic lines carrying the variant alone, which the authors read as a haplotype acting in context rather than a single sufficient nucleotide (Gorniak-Walas et al., 2026). A separate integrated study of human brain tissue, primary microglia and engineered lines found that SorLA deficiency induces endoplasmic-reticulum stress and interferon signalling, promotes lipid-droplet accumulation and impairs phagocytosis, with the lipid-droplet phenotype reproduced in neurons (Haq et al., 2026).

The consequence is uncomfortable and worth stating plainly. When human genetics attributes risk to *SORL1*, the cell type through which that risk operates has become an open question rather than a settled one. The neuron-centred reading developed in Sections 4 and 6 is a reading of what the receptor does **in a neuron**. It is not a demonstration that the neuronal arm is where the population-level risk is carried.

9. Therapy, and the Measurement Problem

9.1 Why this pathway is attractive to a drug developer

The anti-amyloid antibodies now licensed slow decline modestly (van Dyck et al., 2023). This account offers a specific reason the effect might be smaller than the completeness of plaque removal would predict: the internal and external pools are actively coupled, and lowering the external pool in a cell that already carries an internal load may *increase* production rather than reduce it (Roos et al., 2021). That is a forward-leg intervention meeting a return-leg lesion. The alternative is to restore a recovery step, and three classes of agent exist, at very different stages.

9.2 Stabilise the complex

Retromer is a three-protein complex, which means it has a weakest interface, which means it is a candidate for stabilisation by a small molecule rather than by a gene. Pharmacological chaperones were designed to do exactly that and were shown to limit precursor-protein processing (Mecozzi et al., 2014). In a human stem-cell model they reduced tau phosphorylation **independently of the precursor protein —** which is the result that makes the hub claim more than rhetoric (Young et al., 2018). They rescue the endosomal pathology produced by *SORL1* defects in human neurons (Mishra et al., 2023). And in September 2025 an independent laboratory gave a retromer chaperone to amyloid-model mice and reported pathology falling and synaptic gene expression recovering (Ramonet et al., 2025).

Probable. The honest caveat is that the early-generation chaperones have modest potency and short half-lives, and are better described as research tools than as candidate medicines. Independent replication in an animal is nonetheless the most encouraging development in this pathway.

9.3 Raise the receptor

If loss of SORLA function causes disease in people, restoring it should help. A gene-therapy programme exists, and its obstacle is mundane: the human *SORL1* gene is too large for the viral vector, so truncated versions retaining the critical domains have had to be engineered (Andersen et al., 2024, conference abstract only).

The most important recent result tested the arm this programme had claimed since 2008 and never reached in an animal: raising SORLA in **aged** tauopathy mice attenuated tau phosphorylation, seeding, synapse loss and glial activation, and deleting it made all of them worse (Huang et al., 2026).

A correction of ours belongs here. The corpus's August 2026 paper described that study as reversing established pathology. It did not. The receptor was raised from the beginning, not introduced after the damage had accumulated; the authors' own word is *attenuate*. The paper has been corrected. What the result shows is protection across the life of the animal. Reversal from a treatment start — which is what a patient would need — remains untested in this pathway by anyone.

9.4 Target the fission step

The newest line targets the mechanical step from Section 2.2 rather than the complex itself. RhoGEF12 regulates the endosomal SORL1–retromer step, and inhibiting it is reported to be therapeutic in human neuronal models of the disease (Qureshi et al., 2026, preprint). A kinase or an exchange factor is a far more tractable drug target than a three-protein complex, which is the strategic argument for it.

This is **Speculative** as a therapy and is given one paragraph deliberately. It is a 2026 preprint. It sits inside an unresolved dispute about the sign of the relevant signalling — whether the kinase arm should be inhibited or supported depends on measurements that two laboratories report with opposite signs in the same cell type, and the corpus treats that contradiction as unadjudicated. Readers who want that argument should go to *The Three Cargoes*, which sets it out at length. It is mentioned here only so that its absence from the rest of this paper is deliberate rather than an oversight.

9.5 The measurement problem

The obstacle in front of all three classes is not the drug. It is that **there is no accepted way to measure endosomal recycling function in a living person.**

That has four consequences. You cannot tell which patients have the lesion, so you cannot select for a trial. You cannot tell whether a dose engaged the target, so a negative result cannot distinguish a wrong hypothesis from a wrong dose. You cannot tell whether the pathway is still worth repairing at the stage at which patients present. And you cannot establish the thing this paper most needs — whether the lesion precedes the pathology in individual people rather than in autopsy series.

Three candidate read-outs exist, all early. Spinal-fluid proteins have been linked to retromer-mediated traffic in mice and in humans, offering a panel rather than a single marker (Simoes et al., 2020). Soluble SORL1 in cerebrospinal fluid has been proposed as a marker of the functional impact of rare *SORL1* variants (de Waal et al., 2026). And a luminescent reporter assay now quantifies SORL1 ectodomain shedding and retromer-dependent recycling activity, though in cells rather than in people (Fazeli et al., 2026).

The corpus's recommendation is unchanged and is stated here as the paper's main practical conclusion: **measure it in people before treating it.** A pathway this well supported mechanically and this poorly instrumented

clinically is a pathway that will produce an ambiguous trial, and an ambiguous trial in this field sets the question back a decade.

10. Graded Ledger

#	Claim	Grade	Resting on	What would overturn it
1	Early endosomes are enlarged in Alzheimer neurons before amyloid deposition, and in Down syndrome decades before dementia	Established	Cataldo 1997, 2000; Ginsberg 2010, 2011 (human)	A powered human series finding the change only after deposition
2	Stalling endosomal exit raises residency time for all cargo, not only the precursor protein	Established	Small 2017; Morel 2013	Export blocked with non-APP cargo residency unchanged
3	Inducing retromer deficiency produces the phenotype; restoring retromer removes it	Established (mouse)	Qureshi 2022; Muhammad 2008	Failure of the repletion arm elsewhere
4	SORLA traffics and recycles GLUA1 and TRKB as well as APP	Established (human neurons)	Mishra 2022, bidirectional	A bidirectional human-neuron study showing APP alone
5	Rab5 over-activation alone is sufficient to produce cholinergic degeneration	Established (mouse)	Pensalfini 2020; Jiang 2025; Kim 2016	Failure to replicate outside the originating laboratory
6	Rare truncating *SORL1* variants occur almost exclusively in people with the disease, and one dominant mutation acts by impairing SORLA dimerisation on the endosome	Established	Andersen, de Waal 2025; Jensen 2024, 2023	Comparable variant frequency in controls

#	Claim	Grade	Resting on	What would overturn it
7	The trans-entorhinal cortex depends on a recycling-dedicated retromer core and is depleted of it in disease	Probable	Simoes 2021 (one group, end-stage)	Independent series showing no regional VPS26b difference
8	Precursor-protein internalisation rises with neuronal age and drives synapse loss	Probable in people	Burrinha 2021 (cultured mouse)	Human data showing internalisation flat with age
9	Microglial lysosomal digestion fails while uptake rises, in the same cell	Supported	Mishra 2025 (one group, human iPSC)	Uptake and degradation shown falling together
10	Retromer stabilisation reduces tau phosphorylation independently of APP	Probable	Young 2018; Mishra 2023; Ramonet 2025	The independent animal replication failing to hold
11	In eight of nine synapse-directed programmes, the lesion is on the return leg	**Inference (ours, not peer-reviewed)**	Nine published literatures; forward-leg up-regulation at six of thirteen stations	A station with a forward-leg lesion and intact return; or the up-regulations proving artefactual
12	The endosomal axis is the supply side of the four synaptic receptors in Phase III	**Inference (ours, untested)**	Mishra 2022 for three cargoes; extension by analogy	PirB, EphB2 or ApoER2 recycling shown unaffected
13	The pedunculopontine nucleus survives because it does not require endosomal trophic delivery	**Inference (ours, untested)**	Paper 1's control case read against Section 4	Endosomal transport measured there and found deranged
14	C99, cholesterol and *APOE* ε4 act as tributaries to Rab5 activation	**Probable; Nixon's framing, given in correspondence, not yet published in this form**	Correspondence, Nov 2026; Kim 2016 for the C99 arm	Any one tributary alone failing to raise Rab5 activity

#	Claim	Grade	Resting on	What would overturn it
15	There is no validated human read-out of endosomal recycling function	Established (by absence)	Simoes 2020; de Waal 2026; Fazeli 2026, all early	A validated, replicated human assay

11. What Would Change This Account

Four results would change it, and two of them are cheap.

A human series finding endosomal enlargement only after amyloid deposition. This is the load-bearing claim of the whole axis. The existing evidence is from 1997 and 2000, from one group, in small series. It has never been attempted at modern scale. If the order reversed, the pathway would become a consequence of the disease rather than an upstream driver, and almost everything in Sections 4 to 6 would have to be re-read as sequelae.

A measurement of this machinery in the third to fifth decade. Table 1 has a hole where Phase I is. If the machinery is intact in those decades in people who later develop the disease, then the axis does not run beside Phase I and the paper's central structural claim is wrong for the earliest third of the lifespan.

A forward-leg lesion with an intact return leg. The C4d result may already be this. A second clean example would move the return-leg finding from an organising structure to a tendency with exceptions, which is materially weaker.

A trial. No return-leg agent in this pathway has been given to a person. Until one is, most of Section 10 describes cells and animals. The measurement problem in Section 9.5 is what stands between the pathway and that trial, and it is the thing most worth the field's money.

Where this sits in the series

What the Brainstem Stops Sending describes the base of the stack: the small nuclei that fail from the third decade, and what each withdraws from the forebrain. *The Hands That Let Go* describes the second step: the nine restraints that keep the brain's immune cells at rest, and what happens as they are released. *The Cage and the Clock* describes the third: the digestion of the perineuronal net, the failure of fast-spiking inhibition, and what amyloid does at the synapse.

This paper describes the axis that runs through all three, and it is the only one of the four that can be read as a claim about every phase at once. Its three addresses — the long axon, the disposer, the synapse — correspond to the three steps in order, and the correspondence is the argument.

Corpus papers drawn on

Causal and Common (the endosomal theory, and Small's programme assessed); *The Three Cargoes* (SORL1 as a supply line, and the ROCK2 sign problem); *The Other Half of the Cycle* (thirty-three recovery steps, graded, with the eight drugs already given to people); *The Acid Test* (Nixon's endosomal–lysosomal–autophagy account); *The Same Machine* (Gouras, intraneuronal retention); *No Switch but the Endosome* (restraint and termination); *The Common Shape* (the return-leg finding, stated for a general scientific reader); *The Gate and the Ransom* (the nucleus basalis).

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