Causal and Common

The endosomal theory of Alzheimer's disease — an evaluation of Scott Small's work on retromer-dependent recycling, what twenty-one years have established, and which half of its central claim the evidence now supports

Benjamin Aaron Gustafsson

AdultCognitiveDisease.com

August 2026

The theory says a failure of endosomal recycling is both causal and common in Alzheimer's disease. One of those words is now close to established; the other has just failed its first direct test in living people. And the lesion, if it is common, may sit in a cell the model was never written about.

Contents

Abstract

In 2023 the endosomal theory of Alzheimer's disease was stated in four words. Retromer-dependent endosomal recycling, its proponents wrote, is "both causal and common" in the disease (Young et al., 2023). The formulation is unusually precise for this field, and it is worth taking literally, because the two words are claims of very different kinds and they are supported by evidence of very different quality.

Causal means that a failure of endosomal recycling is sufficient to produce the disease's core lesions. That claim is now close to established. Rare truncating variants in *SORL1* — the gene encoding the receptor that delivers cargo to retromer — are found almost exclusively in people with Alzheimer's disease (Andersen, de Waal et al., 2025). Depleting the retromer core in mouse hippocampal neurons produces accelerated precursor-protein cleavage and loss of synaptic glutamate receptors, and restoring it reverses them (Qureshi et al., 2022). And in July 2026 an independent laboratory closed the most important remaining gap: 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). The pathway sits upstream of the tau arm as well as the amyloid arm, which is what the theory had claimed since 2008 and had never directly shown in an animal.

Common means that this same failure is at work in most sporadic Alzheimer's disease. That claim is not established, and the most direct test of it — the first assay of pathway function in living people — did not support it. 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 who carry no such variant, it does not differ from controls (de Waal et al., 2026). One negative result does not settle a hypothesis. It does mean that the strongest version of the theory now has a measurable claim outstanding against it, which is more than most theories in this field can say.

This paper evaluates the whole programme rather than any single claim of it. It separates five propositions that are usually run together — a method, a hypothesis about the relation of amyloid to tau, the traffic-jam mechanism, an architectural model of how the pieces fit, and an anatomical explanation of regional vulnerability — and grades each against the primary literature, weighting work published since the beginning of 2025.

Three findings organise the assessment. First, the programme's least-cited contribution is its most transferable: a method that uses regional vulnerability inside a single circuit as a filter on molecular candidates, which is how retromer was found in the first place and which almost nobody else uses. Second, the theory's architecture — a hub with spokes that feed back on it — buys reconciling power at the cost of falsifiability, and the paper states the refutation conditions the model does admit. Third, and most consequential, four independent results from 2025 and 2026 suggest that if the recycling lesion is common, the cell in which it is common may not be the

neuron. *SORL1*'s strongest protective common variant acts through microglial expression; SorLA turns out to govern lipid handling and endoplasmic-reticulum stress in human microglia; and the group's own human imaging work now places microglia between tau and neurodegeneration. The pathway may be right and the cell type incomplete.

Weaknesses are stated plainly: an unresolved contradiction over whether the endosomal phenotype is dependent on the precursor protein; a rival account of what jams the compartment that is at least as well evidenced; a translational record in which, twenty-one years after the founding paper, no retromer- or SORL1-directed agent has entered clinical trial in any indication; and a related line of work on cognitive ageing whose flagship trial did not meet its primary endpoint. What stands is the most anatomically specific and most therapeutically actionable causal hypothesis the field currently has.

1. Introduction: A Laboratory That Begins With Anatomy

1.1 A different opening question

For thirty years the organising question of Alzheimer's disease research has been *what starts it*. The amyloid cascade hypothesis is an answer to that question, and the field's apparatus — its animal models, its biomarkers, its trials — was built to test answers of that shape.

Scott Small's laboratory has spent twenty years asking a different question first: *where does it start, and why there*. The disease does not begin everywhere at once. It begins, with striking reliability, in a small piece of cortex at the junction of the entorhinal area and the temporal neocortex, and it spreads from there along a route that has been mapped in postmortem tissue since Braak and Braak's staging scheme (Braak and Braak, 1991). To a certain kind of investigator that regional preference is not a curiosity to be explained after the mechanism is known. It is the principal piece of evidence available, and it can be used as a filter.

That inversion — anatomy first, molecule second — is the through-line of the programme, and it explains an otherwise puzzling feature of the work: the retromer complex was not found by looking for it. It fell out of a filter.

1.2 The programme in one sentence

Nerve cells sort. Material taken into the cell arrives at the early endosome, and from there it is either sent on for destruction or recovered and returned — to the cell surface, or to the Golgi apparatus for reuse. The machinery that performs the recovery is the retromer complex, working with cargo-specific receptors, of which the most important for this disease is SORLA, the protein encoded by *SORL1*. Small's proposition is that when that recovery step fails, cargo dwells in the endosome longer than it should; that everything held there is affected, not only the amyloid precursor protein; and that the consequences of this single fault are sufficient to generate the disease's amyloid pathology, its tau pathology, its synaptic failure and its glial changes — which is why the fault, and not any of its products, is the thing to treat.

1.3 What this paper asks

Three questions organise what follows.

What has the programme actually established, as distinct from what it proposes? The proposal is well known and easy to state. The evidence behind its parts is of very unequal strength, and the parts are separable.

What have the last two years done to it? This is not a rhetorical question. Between January 2025 and August 2026 the pathway acquired its first human biomarker, its first independent *in vivo* replication of the drug strategy, its first direct animal test against tau, a new and more tractable drug target, and a set of results in microglia that its central model does not accommodate. Some of this strengthens the theory considerably. Some of it points somewhere the theory was not looking.

Which version of the claim should be carried forward? Theories of this kind are usually summarised in a sentence, and the sentence chosen matters. This paper argues that the sentence in general circulation is not the one the evidence supports.

Sections 2 to 7 assemble the programme from the primary work. Sections 8 and 9 assess the recent record. Sections 10 to 12 grade the claims, state the refutation conditions, and set out what the pathway needs next.

2. The Method Before the Hypothesis

2.1 A circuit as a natural experiment

The hippocampal formation is not one structure but a chain of them — entorhinal cortex, dentate gyrus, the CA fields, subiculum — connected in a largely feed-forward loop, each with its own cell types, its own molecular expression profile and its own metabolic character. It is also the part of the brain most reliably implicated in disorders that otherwise have nothing in common: Alzheimer's disease, schizophrenia, depression, ordinary cognitive ageing.

Small's argument, developed across two review-length statements (Small et al., 2011; Small, 2014), is that this apparent promiscuity is an artefact of resolution. Looked at with tools that resolve subregions, the disorders separate. They target different links in the chain, and they do so in different metabolic directions — some regions become hypometabolic, others hypermetabolic. Alzheimer's disease begins in the entorhinal cortex; cognitive ageing targets the dentate gyrus; schizophrenia implicates the CA1 field and subiculum. Once the subregion is fixed, the biology of that subregion becomes the search space.

This required imaging that could resolve structures a few millimetres across, which is why so much of the early output of this laboratory is methodological — variants of functional magnetic resonance imaging optimised to map basal metabolic state at high spatial resolution in patients and in mice, so that the same measurement could be made in both.

2.2 Model-guided microarray

The method's clearest application is the 2005 paper that founded the rest (Small et al., 2005). Expression profiling of diseased brain tissue was, at the time, generating candidate lists of unusable length: thousands of transcripts differ between an Alzheimer's brain and a control brain, and most of those differences report the end state — cell death, gliosis, the collapse of a tissue — rather than anything upstream.

Small's group addressed this not statistically but structurally. Before generating any data they constructed what they called a spatiotemporal model: an *a priori* specification of how a molecule that drives the disease ought to behave. It should be abnormal in the entorhinal cortex, which is affected early; it should be relatively spared in the dentate gyrus, which is not; and the abnormality should be present across a broad age span rather than appearing only late. Profiles were then generated from both regions, from cases and controls, across ages, and the model was used as a filter.

The transcript that best conformed to the model was *VPS35*, the core cargo-recognition component of the retromer complex. Western blotting confirmed reduced VPS35 protein in the vulnerable regions, and showed that VPS26, another core component, was reduced as well. Reducing VPS35 in cell culture altered amyloid-β levels, which established that the association was not merely descriptive.

2.3 What the filter bought, and what it cost

What it bought was a candidate nobody was looking for. Retromer had no prior association with Alzheimer's disease. It was known from yeast genetics and from cell biology as a component of the sorting machinery, and it entered this field entirely through the anatomical filter.

What it cost is worth stating with equal clarity. A filter constructed from a model of the disease can only return molecules that fit the model. If the initiating lesion were, for example, a glial change that affects both regions equally but is tolerated in one, the filter would discard it. The method is a hypothesis-generating instrument with a strong prior built into it, and the prior is the very thing the hypothesis then asserts. This is not a fatal circularity — the subsequent work is what breaks it, and much of that work is interventional — but it means the 2005 result should be read as a well-motivated nomination rather than as evidence of causation. It was, and its authors described it that way.

2.4 The method applied twice more

A filter is only as good as its behaviour on cases where the answer is known to be different, and the same instrument was turned on two other conditions with results that did not resemble Alzheimer's disease.

Applied to normal cognitive ageing, it pointed to the dentate gyrus rather than the entorhinal cortex, and the molecular follow-through produced a driver — the histone-binding protein RbAp48 — that has nothing to do with endosomal trafficking (Pavlopoulos et al., 2013). Applied to psychosis, it implicated the CA1 field and subiculum, and in a metabolic direction opposite to that seen in Alzheimer's disease: hyperactivity rather than hypometabolism (Small et al., 2011).

The point is not that these secondary applications are as well developed as the retromer line — they are not — but that a filter constructed around a spatiotemporal model of Alzheimer's disease returns a different subregion and a different molecule when pointed at a different disorder. That is the minimum evidence that the instrument is measuring something about the disease and not about the instrument.

2.5 The unclaimed inheritance

The most striking thing about the method is how little it has been adopted. Twenty-one years after the model-guided microarray paper, the field's dominant discovery instrument remains the genome-wide association study, which is powerful and agnostic and which returns loci with no anatomical address at all. The distinctive move — using differential regional vulnerability *inside a single circuit* as a filter on molecular candidates — has been applied within Small's own group to ageing and to psychosis, and scarcely anywhere else.

There is an argument, which this paper will return to in its final section, that this method is the programme's most transferable contribution, and that it is undervalued precisely because it produced a hypothesis interesting enough to eclipse it.

3. The Dual-Pathway Move

3.1 Making room for an upstream driver

The retromer finding created a problem of interpretation. If a trafficking defect is upstream, what is its relation to the two proteinopathies that define the disease at autopsy?

The amyloid cascade answers this serially: amyloid-β accumulates, and everything else — including tau pathology — follows from it. A trafficking defect can be accommodated within that scheme only as a modifier of amyloid production, which would make it interesting but not fundamental.

In 2008 Small and Karen Duff proposed the alternative explicitly (Small and Duff, 2008). In late-onset disease, they argued, amyloid-β and tau may not stand in a parent–child relation at all. They may be siblings: two arms of a branching process driven by a common upstream cause, each capable of proceeding somewhat independently, each capable of aggravating the other once underway. They called it the dual-pathway hypothesis, and they were careful to confine it to the late-onset form — the early-onset autosomal-dominant disease, where a mutation directly alters amyloid production, remains best described by the serial model.

3.2 Why the order matters

The dual-pathway paper is often treated as a subsidiary comment on the amyloid cascade. Read in sequence it is something more: it is the logical clearing operation that the endosomal hypothesis required. Without it, a trafficking lesion can only be a cause of amyloid. With it, a trafficking lesion can be the common driver, and the two proteinopathies become its consequences rather than its rivals.

It also generated a prediction that has since been tested at very large expense. If the serial model is right, removing amyloid should arrest the disease. If the dual-pathway model is right, removing amyloid should slow it partially and late, because the tau arm has its own momentum and the upstream driver is untouched.

3.3 How that prediction reads in 2026

Two anti-amyloid antibodies have now completed large phase 3 trials against clinical endpoints. Lecanemab reduced amyloid burden substantially and slowed decline on the primary clinical measure by roughly a quarter over eighteen months (van Dyck et al., 2023). Donanemab produced a broadly comparable result, with larger effects in participants with lower baseline tau burden (Sims et al., 2023).

These are real effects and they should be described as such: the amyloid hypothesis has been vindicated to the extent that it predicted a clinical benefit from amyloid removal, and it delivered one. But the shape of the result — a partial slowing, larger when tau is low, achieved by near-complete removal of the target — is closer to what a dual-pathway model predicts than to what a strictly serial model predicts. A serial cascade in which amyloid is the sole proximate driver should not leave three-quarters of the decline in place after the driver is gone.

The prediction was not decisive, because no such prediction in this field is decisive; both models can absorb the result. It is, however, the rare case where a 2008 theoretical paper made a directional claim about trials that had not yet been run, and the direction was right.

4. The Traffic Jam

4.1 The compartment

The early endosome is the cell's sorting station. Material internalised from the surface arrives there, and its fate is decided: onward to the late endosome and lysosome for degradation, or recovered and returned. The recovery arm is what retromer performs, in concert with sorting nexins and with cargo-selective receptors that bring specific proteins to the complex.

Two features of the compartment make it the natural site for a disease of this kind. It is acidic, and the enzyme BACE1 — which makes the first, amyloidogenic cut in the amyloid precursor protein — works best at acidic pH. And it is where the receptors that a synapse depends on are held between cycles of use.

4.2 The machinery

Retromer proper is a three-protein core — VPS35, VPS26 and VPS29 — that assembles on the endosomal membrane. VPS35 is the scaffold and the cargo-recognition element; VPS26 sits at one end and engages the cargo receptors; VPS29 sits at the other and recruits regulatory partners. The core does not act alone: sorting nexins deform the membrane into the tubular carriers that physically leave the endosome, and the direction of departure — back to the cell surface, or backwards to the Golgi — depends on which accessory proteins are engaged.

Two features of this architecture matter for the disease argument. The first is that a three-protein complex has a weakest interface, which is what made it a candidate for stabilisation by a small molecule rather than by a gene (Mecozzi et al., 2014). The second is that VPS26 exists in two forms, VPS26a and VPS26b, and they are not redundant — a fact that turned out to carry the entire explanation of regional vulnerability, and which is taken up in Section 6.

The complex is also, in Small's own recurring phrase, a *master conductor*: it does not have one cargo. Whatever the neuron needs returned from the endosome passes through it. That is the structural reason a single fault can produce several pathologies at once, and it is the whole of the hypothesis in one sentence.

4.3 The receptor

SORLA, encoded by *SORL1*, is the cargo receptor that matters most here. It binds the amyloid precursor protein and directs it away from the amyloidogenic route, and it does so by engaging retromer through its short cytoplasmic tail. It is also, on the human genetic evidence, the strongest link in the chain: rare truncating variants in *SORL1* are found almost exclusively in people with Alzheimer's disease (Andersen, de Waal et al., 2025), and the receptor's association with retromer is regulated by its own dimerisation state (Jensen et al., 2023).

The genetics are what give the hypothesis its causal spine. 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.

4.4 The claim

The traffic-jam model (Small et al., 2017) states the consequence in one move. Jam the export step, and residency time in the endosome rises — for everything held there, not only for the precursor protein.

That single mechanical fact generates the disease's separate pathologies as parallel consequences rather than as a chain:

- **Amyloid.** The precursor protein and BACE1 spend longer together in an acidic compartment, favouring the amyloidogenic cut and the generation of amyloid-β and C-terminal fragments.
- **Synaptic failure.** Glutamate receptors that should be recycled back to the postsynaptic membrane are retained and diverted toward degradation. The synapse weakens without any cell dying.
- **Tau release.** A congested endosome matures into a multivesicular body, and cytosolic contents — including tau — are packaged into intraluminal vesicles and released as exosomes when that body fuses with the membrane, providing a route for spread.
- **Glial change.** Microglia depend on the same recovery machinery to return phagocytic receptors to their surface, so the same lesion blunts clearance.

4.5 The evidence, in ascending order of strength

It is worth arranging the supporting work by what each type of study can establish, because the programme's public summaries do not.

Expression and correlation. Reduced VPS35 and VPS26 in vulnerable regions (Small et al., 2005); reduced VPS26b and SORLA in the human trans-entorhinal cortex in disease (Simoes et

al., 2021). These establish association in tissue that is, by definition, from the end of the process.

Perturbation in models. Retromer-deficient mice develop hippocampal-dependent memory and synaptic dysfunction with elevated endogenous amyloid-β; retromer-deficient flies expressing human precursor protein and BACE develop neuronal loss and amyloid aggregates (Muhammad et al., 2008). Related work established that phosphatidylinositol-3-phosphate, which organises endosomal traffic, is depleted in Alzheimer's brain tissue, and that reducing the kinase that makes it enlarges neuronal endosomes and enhances amyloidogenic processing (Morel et al., 2013).

Depletion and repletion. The strongest design in the programme's animal work. VPS35 was depleted in mouse hippocampal neurons and then restored using an optimised viral vector; the accelerated precursor-protein cleavage and the loss of synaptic glutamate receptors both followed the manipulation in both directions. The same study found that a neuronal retromer deficit was sufficient to induce a dystrophic microglial morphology characteristic of the disease, and that these effects occurred independently of tau (Qureshi et al., 2022).

Human genetics. The *SORL1* rare-variant evidence, which is the only part of the case that carries the direction of causation without a model organism.

The gradient matters. The traffic-jam hypothesis is *not* mainly supported by observing jams in human brains — that evidence is real but weak, and shares every interpretive difficulty of postmortem work. It is supported by the fact that inducing the lesion produces the phenotype and reversing it removes the phenotype, and by a gene.

5. Hub and Spoke: The Reconciliation and Its Price

5.1 The paradox

By 2020 the hypothesis faced an obvious objection. If endosomal recycling is the upstream lesion, why do mutations in the amyloid precursor protein and in the presenilins — which affect the substrate and the cutting enzyme, not the sorting machinery — cause early-onset disease with complete penetrance?

Small and Gregory Petsko answered with an architectural model (Small and Petsko, 2020). Endosomal recycling is the hub. The precursor protein, the secretases, apolipoprotein E, the immune receptors and the rest are spokes. A spoke can be damaged directly, in which case disease follows without any primary hub lesion; and the products of a damaged spoke feed back on the hub, so the two converge on the same downstream state. The early-onset mutations are spoke lesions with hub consequences; late-onset disease is more often a hub lesion with spoke consequences; and the pathology looks the same either way.

This is a genuinely good piece of theoretical work. It reconciles the genetics of the two forms of the disease without demoting either, and it explains why a mechanism can be pathogenically central without being the origin in every case.

5.2 The price

It also makes the theory very difficult to refute, and this should be said plainly rather than left implicit. A model in which every spoke feeds back on the hub can accommodate almost any experimental result. Evidence that amyloid damages the endosome is not contrary evidence; it is a spoke feeding back. Evidence that tau precedes amyloid is not contrary evidence; it is another spoke. Evidence that the lesion is glial is not contrary evidence; microglia use the same hub.

Hypotheses with this property tend to persist regardless of data, and the field has several. The appropriate response is not to reject the model but to require of it what one requires of any hub claim: a statement of what observation would count against it. Section 11 sets out the refutation conditions the model does admit, and the important development of the last year is that one of them has become measurable.

5.3 A distinct claim about treatment

The hub-and-spoke model carries a therapeutic corollary that is independent of the causal argument, and it is the most immediately useful thing in the programme. If the hub is common to the spokes, then repairing the hub should benefit patients whose primary lesion is in *any* spoke — including patients whose disease was initiated by something the model does not name. On this reading, retromer enhancement is not a treatment for a subtype. It is a treatment for the shared mechanism, and its indication does not depend on winning the argument about origins.

That corollary is testable in a way the causal claim is not, and it is the argument for a trial.

6. Why That Region

6.1 Two retromers

The anatomical claim went unexplained for fifteen years. The filter had used regional vulnerability to find the molecule; it did not say why the molecule should matter more in one region than another.

The answer offered in 2021 is the most elegant result in the programme (Simoes et al., 2021). Neurons, it turns out, are enriched in a *second* retromer core, organised around VPS26b rather than the ubiquitous VPS26a, and the two are not interchangeable: the VPS26b core is differentially dedicated to the recycling arm of endosomal traffic rather than to retrograde transport toward the Golgi.

The consequences follow directly. Imaging mouse models, the group found the trans-entorhinal cortex — the region Braak staging identifies as the earliest cortical site of tangle pathology — was the region most susceptible to VPS26b depletion, and the finding was corroborated by electrophysiology, immunocytochemistry and behaviour. VPS26b was then found to be enriched in the trans-entorhinal cortex of human brains, and both VPS26b and SORLA were found deficient there in disease. Finally, VPS26b was shown to mediate the recycling of glutamate receptors and of SORLA itself, closing the loop between the molecular specialisation and the regional phenotype.

6.2 The demand argument

Why should one region depend more heavily on a recycling core than its neighbours? The programme's answer is an argument from demand. The neurons of the entorhinal region carry unusually extensive dendritic arbours and occupy a hub position in the cortical network, receiving and sending across a very large number of connections. Maintaining synaptic function across that surface imposes a correspondingly heavy load on receptor recycling. A cell running its recycling machinery near capacity is the cell in which a modest loss of capacity first produces a deficit.

This is a plausible argument rather than a demonstrated one, and it should be labelled as such. What is demonstrated is the differential expression and the differential susceptibility; the account of *why* the region is built that way is inference.

6.3 What it explains, and what it does not

It explains onset. It does not explain spread, and the programme does not claim otherwise: once pathology leaves the entorhinal region the account of its propagation is the same trans-synaptic and exosomal story used by everyone else, and the regional specialisation that made the first argument so strong contributes nothing to the second. Earlier imaging work from the same group had shown that lateral entorhinal dysfunction can spread to parietal cortex during the preclinical phase, and that precursor-protein expression potentiates tau toxicity in driving that dysfunction (Khan et al., 2014) — which is a description of the propagation, not a mechanism for it.

7. The Ageing Line

7.1 A different subregion, a different lesion

Running alongside the disease work is a second body of research that is frequently mistaken for part of it, and the distinction matters both scientifically and clinically.

Using the same subregional imaging, Small's group established that ordinary age-related memory decline maps to the *dentate gyrus*, not to the entorhinal cortex (Small et al., 2011). The two are adjacent links in the same chain and they fail differently, at different times, in different people. The claim is therefore not that ageing is early Alzheimer's disease; it is close to the opposite. Age-related memory change is a distinct dysfunction of a distinct subregion, and its molecular driver is distinct as well: a histone-binding protein, RbAp48, whose decline in the dentate gyrus was shown to be both necessary and sufficient for age-related memory loss in mice, and whose restoration reversed it (Pavlopoulos et al., 2013).

7.2 The dietary intervention, honestly described

If dentate gyrus dysfunction drives age-related memory decline, then enhancing dentate function should improve memory in healthy older adults. A three-month randomised trial of high- versus low-flavanol cocoa in 50- to 69-year-olds found exactly that, with the effect visible on both the imaging measure and the cognitive task designed to localise to the region (Brickman et al., 2014).

The large-scale replication is the part of the record that is usually reported incorrectly, including in coverage sympathetic to the work. COSMOS-Web randomised 3,562 older adults to three years of cocoa extract or placebo. **The prespecified primary endpoint — improvement in memory in all participants at one year — was not statistically significant** (Brickman et al., 2023). What the trial did find was that habitual flavanol consumption and diet quality at baseline correlated selectively with hippocampal-dependent memory, that the intervention restored memory in participants in the lowest tertiles of habitual diet quality or flavanol intake, and that increases in a urinary biomarker of flavanol intake tracked improving memory.

That is a coherent and interesting result — it suggests a repletion effect in the deficient rather than an enhancement effect in the replete — but it is a secondary and subgroup finding from a trial that missed its primary endpoint, and it should be carried forward with that label attached.

7.3 Forgetting as a function

The third strand of the ageing work is conceptual rather than experimental, set out at book length in *Forgetting: The Benefits of Not Remembering* (Small, 2021). Its argument is that forgetting is not the failure of memory but a distinct and adaptive process with its own machinery, and that a great deal of what is presented in the clinic as pathological is normal function operating as designed.

This is not a claim about Alzheimer's disease, and treating it as one would be a mistake. Its relevance to the disease work is as a boundary condition: it insists on a firm line between a normal process, a normal decline, and a disease, at a time when biomarker-defined "preclinical Alzheimer's disease" is dissolving that line in the other direction. A laboratory that spends half its effort establishing that the ageing dentate gyrus is *not* early Alzheimer's disease has earned some standing to make that argument.

7.4 The constraint on the disease theory

The ageing line also constrains the endosomal theory in a useful way. If the recycling lesion were simply a consequence of ageing biology, it should track the ageing phenotype and its anatomy. It does not: the ageing lesion is in a different subregion with a different molecular driver and a partially reversible response to a dietary intervention. That dissociation is a point in the endosomal theory's favour, and it comes from the same laboratory's own control condition.

8. What the Last Two Years Strengthened

Five developments since the beginning of 2025 have materially improved the case. They are set out here in ascending order of importance.

8.1 The genetics matured into a classification

A causal gene is only useful clinically once its variants can be classified. In December 2025 a consortium spanning the Aarhus and Amsterdam groups published a domain-level map of *SORL1* disease mutations across a very large aggregated cohort, anchored on the observation that protein-truncating variants in the gene occur almost exclusively in Alzheimer's disease (Andersen, de Waal et al., 2025). Mapping missense variants onto the receptor's structural domains converts an undifferentiated list of rare variants into a graded interpretation, which is the precondition for using the gene in the clinic and for selecting participants for any trial of a pathway-directed agent.

8.2 A human read-out of pathway function — and what it showed

For two decades the theory's central weakness was that it could not be measured in a living person. The 2020 cerebrospinal-fluid proteomic screen was the first attempt: starting from mice with a neuronal knockout of VPS35, it identified the amino-terminal fragments of APLP1 and CHL1 and the mid-domain of tau as proteins whose cerebrospinal concentration tracks retromer-dependent traffic, and found them correlated with tau and phosphorylated tau in patients and elevated in roughly seventy per cent of individuals in the prodromal stages of disease (Simoes et al., 2020).

The direct assay arrived in February 2026. SORLA is shed from the cell surface, and the soluble ectodomain reaches cerebrospinal fluid; because the receptor only reaches the surface if retromer-dependent recycling delivers it there, soluble SORL1 is a read-out of pathway function. In 218 participants, concentrations were significantly lower in carriers of protein-truncating and damaging missense variants — exactly as the model predicts (de Waal et al., 2026).

The second half of the result is the one that matters for the theory's scope. **In patients with sporadic Alzheimer's disease carrying no *SORL1* variant, soluble SORL1 did not differ from controls.** It correlated with phosphorylated tau but not with amyloid-β42, which is consistent with a relationship between the pathway and the tau arm; but the pathway-function measure itself did not separate ordinary patients from healthy people.

This is the first quantitative test of the word *common*, and it did not come back positive. Several readings remain open: the shed ectodomain may be an insensitive index of intracellular recycling; a regional lesion confined to the trans-entorhinal cortex may not move a whole-compartment

measure; the relevant deficit may be in a cell type that contributes little to the cerebrospinal pool. Each of these is testable, and each should now be tested. A companion tool arrived in the same window — a luminescent reporter of SORL1 ectodomain shedding whose signal depends on retromer levels and falls in cells expressing pathogenic variants (Fazeli et al., 2026) — which makes both variant classification and compound screening tractable at scale.

8.3 Independent replication of the drug strategy in an animal

The retromer chaperones were designed in 2014 by using the crystal structures of the complex to identify its weakest interface and screening *in silico* for small molecules predicted to stabilise it; the resulting compounds increased retromer levels and reduced amyloidogenic processing (Mecozzi et al., 2014). They were subsequently shown, in human stem-cell-derived neurons, to reduce tau phosphorylation in a manner independent of the amyloid precursor protein (Young et al., 2018), and to rescue endosomal pathology in neurons carrying *SORL1* defects, with the degree of rescue depending on how many functional copies of the gene remained (Mishra et al., 2023).

All of that work came from the originating group or its close collaborators. In September 2025 an independent laboratory tested the same compounds in the 5xFAD mouse and reported that R55 reduced amyloid-related pathology, normalised synaptic gene expression, restored pathways associated with long-term potentiation including *Gria1* and *Grip1*, and redistributed VPS35-positive vesicles (Ramonet et al., 2025). Independent replication is not common in this field and it should be weighted accordingly.

8.4 The tau arm, tested directly, in an aged animal

The dual-pathway hypothesis has always contained an untested promise: that the upstream lesion drives the tau arm and not merely the amyloid arm. Cell-culture work had pointed that way since 2018. The animal test had not been done.

In July 2026 it was done, and not by this group. Working in aged PS19 mice — an animal that develops tau pathology without any amyloid manipulation — an independent laboratory showed that transgenic up-regulation of SORLA reversed a wide range of established pathology: tau phosphorylation, tau seeding activity, ventricular dilation, synapse loss, impaired long-term potentiation, and glial hyperactivation. Proteomic and single-nucleus transcriptomic analysis showed reversion of the disease signature, including in *Apoe* and *C1q*. Deleting SORLA in the same background made tau seeding, aggregation and neuroinflammation worse (Huang et al., 2026).

This is the most consequential single result for the theory in the period under review, for three reasons. It tests the arm the theory needed and had not reached. It does so by intervention in both directions, in an aged animal, against established rather than incipient pathology. And it comes from outside the network of laboratories that generated the hypothesis, which removes the most obvious objection to the preceding decade of supporting work.

8.5 A better drug target than a protein complex

Stabilising a multiprotein complex with a small molecule is difficult chemistry, and the difficulty is why the chaperones have remained laboratory tools. In March 2026 the Columbia group, working with structural biologists in Budapest and the Seattle stem-cell group, proposed a different point of attack (Qureshi et al., 2026).

Their reasoning began from the receptor's cytoplasmic tail, the part that engages retromer. They found that phosphorylation of that tail by ROCK2 reduces SORLA's affinity for retromer — that is, the coupling is not constitutive but regulated, and there is a kinase that switches it off. RhoGEF12, an upstream activator of ROCK2, is upregulated in Alzheimer's disease. Applying a pharmacological inhibitor of RhoGEF12 increased endosomal SORLA–retromer association in mouse neurons, and in human iPSC-derived neurons reduced both amyloid-β40 and amyloid-β42 in a SORL1-dependent manner. The effect held in neurons carrying disease-associated mutations in either *APP* or *SORL1*.

Two things make this important beyond its immediate result. It converts the therapeutic problem from "stabilise a complex" — hard, unprecedented — into "inhibit a kinase upstream of a phosphorylation site", which is among the best-trodden paths in drug development. And the SORL1-dependence of the effect is an internal control that the earlier chaperone work lacked: the compound does nothing when the receptor is absent, which is what a pathway-specific agent should do.

The appropriate caveat is that this is a preprint, not yet peer-reviewed, and that all of the work is in cultured neurons. No whole-animal test has been reported.

9. What the Last Two Years Complicated

9.1 SORLA is not only a retromer adaptor

The hypothesis rests its human-genetic weight on *SORL1*, and interprets the gene through a single function: cargo delivery to retromer at the endosome. Two studies have now shown that the receptor does other things, and that its loss produces phenotypes the endosomal frame does not predict.

In September 2025, work on a familial Alzheimer's mutation in the receptor's ligand-binding domain found that the mutant protein's interactome is reorganised around exosome biogenesis, and that the mutant receptor fails to promote both the release and the neurotrophic quality of exosomes — a defect traced to altered microRNA cargo (Juul-Madsen et al., 2025). In April 2026, an integrated multi-omic study of human brain tissue, rapid-autopsy primary microglia and CRISPR-engineered iPSC lines found that SorLA deficiency induces endoplasmic-reticulum stress and interferon signalling, promotes lipid-droplet accumulation and impairs phagocytosis, and that SorLA co-complexes with ER-associated proteins including SUN2, calnexin and multiple COPI components. Critically, deleting *SORL1* in iPSC-derived *neurons* reproduced the lipid-droplet phenotype and the SorLA–SUN2 interaction, so this is not a microglia-only curiosity (Haq et al., 2026).

This does not refute the endosomal account. It does mean that when human genetics attributes risk to *SORL1*, the pathway through which that risk operates is no longer a settled question, and the assumption that it must be the retromer pathway is now an assumption rather than an inference.

9.2 The cell type may be wrong

The sharper challenge concerns *which cell* carries the lesion. Three results converge.

First, the common-variant genetics. The strongest known protective common variant at the *SORL1* locus, rs11218343, was examined in donor-derived and genome-engineered iPSC lines. Its effect was found to be uniquely linked to functional expression of SORLA **in microglia**, with the protective allele associated with higher expression and reduced pro-inflammatory responses (Gorniak-Walas et al., 2026). The effect appeared in donor lines but not in isogenic lines engineered to carry the variant alone, which the authors read as indicating a haplotype acting in context rather than a single sufficient nucleotide. If the protection that the common population carries is a microglial effect, then the part of *SORL1*'s contribution that applies to most people is not obviously neuronal.

Second, the receptor's microglial biology, described above: lipid handling, interferon signalling, phagocytosis (Haq et al., 2026).

Third — and this is the striking one — Small's own laboratory. In June 2026 the group published a human positron-emission-tomography study using the translocator-protein ligand ER176 as an index of microglial density, alongside amyloid and tau tracers and structural imaging, in 46 participants. Microglial density colocalised with tau more often than with amyloid, was associated with tau and with neurodegeneration, and **statistically mediated the relationship between tau and neurodegeneration** in limbic, temporal and parietal regions. In amyloid-positive participants microglia also mediated amyloid-associated tau and tau spreading; and in amyloid-negative participants with cognitive impairment, tau-associated neurodegeneration was present without amyloid at all (Lao et al., 2026). The paper's own conclusion is that glia "may represent a promising target for intervening on tau-associated neurodegeneration".

The study is small, cross-sectional, and uses a tracer whose interpretation as a pure microglial-density measure is contested; mediation analysis on 46 participants establishes a hypothesis, not a mechanism. But it is notable that a laboratory whose signature model is neuron-centric has published a human study placing microglia in the causal position between the tau arm and neuronal loss.

Taken together, these three results support a specific reframing, which this paper offers as its principal synthetic claim: **the recycling lesion may be common in a cell the model was not written about.** The neuronal traffic jam is well evidenced in rare-variant carriers and in animals. The pathway's contribution to *ordinary* late-onset disease may run substantially through microglia — where SORLA governs lipid handling and inflammatory tone, where the common protective variant acts, and where the group's own imaging now places the mediating step. Notably, the 2022 depletion–repletion study already showed that a *neuronal* retromer deficit is sufficient to induce a dystrophic microglial morphology (Qureshi et al., 2022), so the two readings are not exclusive; the open question is which direction carries the weight in sporadic disease.

9.3 Two jams in one compartment

Within the endosomal camp there is a rival account of *what* jams the compartment, and it is at least as well evidenced.

Ralph Nixon's group has argued for two decades that endosomal abnormality is driven by the β-cleaved carboxy-terminal fragment of the amyloid precursor protein. The mechanism was specified in 2016: βCTF recruits the adaptor APPL1 to rab5-positive endosomes, where it stabilises the active GTP-bound form of rab5, producing accelerated endocytosis, endosome swelling and impaired axonal transport; knocking down APPL1 corrects the defect in Down syndrome fibroblasts (Kim et al., 2015). The account was then made independent of the precursor protein: in a mouse in

which rab5 is over-activated directly, with no manipulation of APP, the animals reproduce endosome enlargement, accelerated AMPA-receptor endocytosis, spine loss, tau hyperphosphorylation via GSK-3β, cholinergic neurodegeneration and memory impairment (Pensalfini et al., 2020). A transgenic APPL1 mouse published in July 2025 reproduced the same set (Jiang et al., 2025). The same group's account of the terminal stage — profound failure of autolysosomal acidification, with amyloid accumulating inside de-acidified compartments in neurons that go on to become the source of senile plaques — is a further, independent description of the same compartment failing (Lee et al., 2022).

The two models agree on a great deal: the endosome is where the disease happens; the lesion there is sufficient to produce the phenotype; the compartment fails before plaques appear. They disagree on the entry point. Small's model has the sorting machinery fail first, with the precursor protein a consequence. Nixon's has the precursor protein's fragment fail the sorting machinery. Both have interventional evidence in animals. Neither has been tested against the other in a design that could distinguish them, and constructing that design — for instance, asking whether retromer enhancement rescues the rab5-overactivation mouse, in which there is no primary retromer lesion — is the most valuable unperformed experiment in this area.

9.4 An unresolved contradiction at the crux

The disagreement descends to a specific, and awkward, empirical contradiction in human stem-cell neurons.

In 2020, depleting *SORL1* in iPSC-derived neurons was reported to impair endosomal traffic **independent of amyloidogenic APP processing** — the result the endosome-first model requires (Knupp et al., 2020). In 2021, a different group studying a *SORL1* truncating mutation in the same kind of system reported that the endolysosomal dysfunction caused by loss of SORL1 was **relieved by antisense-oligonucleotide reduction of APP protein**, concluding that PSEN1, APP and SORL1 act in a common pathway regulating the endolysosomal system (Hung et al., 2021).

These are not easily reconciled. They differ in the depth of the *SORL1* lesion, in the neuronal differentiation protocol and in the readouts, and each is a plausible source of the discrepancy. But the question at issue — whether the endosomal phenotype downstream of *SORL1* loss requires the precursor protein — is precisely the question on which the ordering of the whole hypothesis turns, and five years on it has not been settled by a study designed to settle it.

9.5 Generality bought at the cost of specificity

The programme has extended the retromer claim beyond Alzheimer's disease. A 2024 discussion-meeting paper proposed "retromer-dependent lysosomal stress" as a pathway generalising from the *LRRK2* and *VPS35* mutations that cause dominant Parkinson's disease to the idiopathic form (Alessi et al., 2024), part of a broader theme issue on the endo-lysosomal network in neurodegeneration co-edited from within this network (Cullen et al., 2024). A January 2026 study found reduced VPS35 and VPS29 expression in frontotemporal dementia with TDP-43 pathology, driven by altered polyadenylation of the transcripts (Maheswari Jawahar et al., 2026), with Small among the authors.

A multi-ancestry biobank study published in May 2026 pushed further, examining *SORL1* variation across 15,043 Alzheimer's cases, 9,943 cases of related dementias and 42,763 Parkinson's cases against 111,969 controls in eleven ancestries. It identified 53 potentially disease-related variants, 41 of them novel, distributed across all three disease groups, with nominal associations in both Alzheimer's disease and Parkinson's disease (Khani et al., 2026).

This cuts both ways, and the programme's public framing tends to report only one side. Generality is good for the claim that the pathway is fundamental to neurodegeneration. It is bad for the claim that it explains *Alzheimer's* disease specifically — the more diseases a lesion appears in, the less of the disease-defining phenotype it can be doing on its own, and the more the explanatory burden shifts back to whatever determines which disease a given person gets.

9.6 Translation has not moved

Twenty-one years after the founding paper, the therapeutic record is as follows. The retromer chaperones remain research compounds; their most recent independent test was by stereotaxic injection into mouse brain (Ramonet et al., 2025). The gene-therapy programme — a *SORL1* mini-gene, engineered to fit within the packaging limit of an AAV9 capsid, reported to transduce neurons and to be tolerated after brain infusion in wild-type mice and *SORL1*-haploinsufficient minipigs — has been presented at a conference (Andersen et al., 2024) but not, as of August 2026, published as a peer-reviewed study; the haploinsufficient minipig model itself is published (Andersen et al., 2022). The RhoGEF12 work is a preprint in cultured cells.

A search of ClinicalTrials.gov in August 2026 returns no interventional study of a retromer- or SORL1-directed agent, in Alzheimer's disease or in any other indication. The clinical-stage selective ROCK2 inhibitors associated with the company on whose scientific advisory board the RhoGEF12 paper's senior authors sit have been developed for cerebrovascular rather than neurodegenerative indications.

This is worth stating without editorialising, because the reason is structural rather than a failure of the science. An agent that repairs an upstream lesion should be given before the downstream

lesions are established, which means trials in asymptomatic or minimally symptomatic people, which means long trials with large samples and a validated biomarker for enrolment. The biomarker arrived, in preliminary form, six months ago. The trial infrastructure built over the last fifteen years is built around amyloid endpoints. A pathway-directed agent would need to establish its own.

9.7 A note on disclosed interests

The strongest translational claims in this literature come from the group that generated the hypothesis, and the relevant interests are disclosed in the papers themselves. Small is a co-founder of Retromer Therapeutics with equity and a consulting relationship; he is a co-inventor, with Petsko and Qureshi, on Columbia-owned patents covering retromer stabilisation and retromer-based biomarkers; and the 2026 preprint discloses that he and Petsko sit on the scientific advisory board of the company developing the relevant kinase inhibitors. Several of the collaborating groups carry related consulting relationships.

None of this is irregular and none of it bears on the validity of any individual result. It is relevant to how a reader should weight the balance of the literature: the independent contributions of the last two years — the tauopathy rescue, the chaperone replication, the microglial genetics, the biobank study, the cerebrospinal-fluid assay — carry more evidential weight for that reason, and it is a point in the theory's favour that most of them were positive.

10. Grading the Claims

The programme's propositions are usually stated together. They are supported very unequally, and the table separates them.

Proposition	Strongest evidence	Strength	What is missing
Loss of retromer-dependent recycling is sufficient to produce Alzheimer-type neuronal pathology	Depletion and repletion of VPS35 in mouse hippocampal neurons reverses precursor-protein cleavage and glutamate-receptor loss in both directions (Qureshi et al., 2022); retromer-deficient mice and flies (Muhammad et al., 2008)	**Strong**	Demonstrated for engineered depletion; the magnitude of naturally occurring deficiency in sporadic disease is unquantified
SORL1 **loss of function causes Alzheimer's disease in humans**	Truncating variants occur almost exclusively in cases; domain-level classification across large aggregated cohorts (Andersen, de Waal et al., 2025)	**Strong**	Accounts for a small fraction of cases; penetrance incomplete
The pathway sits upstream of the tau arm, not only the amyloid arm	SORLA up-regulation reverses tau phosphorylation, seeding, synapse loss and glial activation in aged PS19 mice; deletion worsens them (Huang et al., 2026); tau phosphorylation reduced independently of APP in human neurons (Young et al., 2018)	**Strong, and newly so**	One animal model; tauopathy model rather than a model of sporadic disease
Regional vulnerability follows from a region-specific recycling core	VPS26b enrichment and differential susceptibility of the trans-entorhinal cortex, corroborated in human tissue (Simoes et al., 2021)	**Moderate to strong**	The demand argument that explains *why* the region is built this way is inference; explains onset, not spread
Amyloid-β and tau are parallel arms of a common upstream driver in late-onset disease	Dual-pathway argument (Small and Duff, 2008); trial results consistent in direction (van Dyck et al., 2023; Sims et al., 2023)	**Moderate**	Trial evidence is compatible with several models; not a decisive test
Endosomal recycling failure is *common* **in sporadic Alzheimer's disease**	Cerebrospinal-fluid correlates of retromer traffic elevated in ~70% of prodromal individuals (Simoes et al., 2020)	**Weak**	The direct assay of pathway function does not distinguish sporadic patients from controls (de Waal et al., 2026)

Proposition	Strongest evidence	Strength	What is missing
The endosomal phenotype is independent of the amyloid precursor protein	*SORL1* depletion impairs traffic independent of amyloidogenic processing (Knupp et al., 2020)	**Contested**	Directly contradicted by rescue of the phenotype through APP reduction (Hung et al., 2021); not adjudicated
Retromer enhancement is therapeutically tractable	Chaperones effective in human neurons and, independently, in 5xFAD mice (Mishra et al., 2023; Ramonet et al., 2025); a regulated phosphorylation site with an upstream kinase (Qureshi et al., 2026)	**Promising , unproven**	No clinical trial in any indication; RhoGEF12 work is a preprint in culture
Age-related memory decline is a distinct, dentate-gyrus lesion that is modifiable	RbAp48 necessity and sufficiency in mice (Pavlopoulos et al., 2013); flavanol trial (Brickman et al., 2014)	**Moderate** for the lesion; **weak** for reversal	The large replication missed its primary endpoint; the positive result is a subgroup finding (Brickman et al., 2023)

11. What Would Refute It

A hub model can absorb a great deal, which makes it important to say what it cannot absorb. Four observations would count decisively against the theory as stated, and the first is now within reach.

A negative pathway biomarker in sporadic disease, replicated and extended. The soluble-SORL1 result (de Waal et al., 2026) is the first instalment. If a panel of pathway-function measures — soluble SORL1, the amino-terminal APLP1 and CHL1 fragments, and any successor assay — consistently fails to separate sporadic patients from age-matched controls in adequately powered cohorts, the claim that the lesion is *common* fails, and the theory reduces to an account of a rare monogenic subtype plus a druggable modifier. That would still be a substantial achievement. It would not be the theory as currently stated.

Target engagement without clinical effect. If an agent demonstrably enhances retromer-dependent recycling in the human brain — measurable now, in principle, by pathway biomarkers — and produces no clinical benefit in appropriately early disease, the hub-and-spoke corollary fails. This is the cleanest available test and it requires a trial that does not exist.

Resolution of the APP-dependence contradiction against the theory. If a properly designed study establishes that the endosomal phenotype downstream of *SORL1* loss requires the amyloid precursor protein, the ordering inverts: the endosome becomes the compartment in which an APP-driven lesion is expressed rather than the origin of it. The experiment is straightforward and has not been done.

Rescue in the wrong direction. If retromer enhancement fails to rescue the rab5-overactivation animal — in which the compartment is jammed with no primary retromer lesion — the two endosomal models are distinguishable, and the traffic-jam hypothesis becomes an account of one route into a compartment failure that has several.

It is worth noting what would *not* refute it, since these are frequently offered as though they would. Evidence that amyloid damages endosomes does not refute it; that is a spoke feeding back. Evidence that tau pathology appears before amyloid does not refute it; the dual-pathway model predicts arms that can run at different rates. Evidence that microglia matter does not refute it; it relocates the lesion, which is a different and more interesting problem.

12. Where the Pathway Should Go

12.1 Measure it in people before treating it

The single most useful thing that could happen to this theory in the next two years is a properly powered study of pathway function in living patients. The tools now exist in preliminary form: an ELISA for soluble SORL1 (de Waal et al., 2026), the cerebrospinal-fluid correlates of retromer-dependent traffic (Simoes et al., 2020), and a cell-based shedding reporter for calibrating both against variant severity (Fazeli et al., 2026). What is needed is their application across a large, well-characterised, longitudinally followed cohort, stratified by *SORL1* genotype and by amyloid status, with the specific question: in what fraction of sporadic Alzheimer's disease is pathway function measurably impaired, and does that fraction differ from age-matched controls?

That study answers the word *common*, in either direction, and no trial should be designed before it is answered.

12.2 Test the cell, not only the pathway

The microglial results of 2025 and 2026 (Gorniak-Walas et al., 2026; Haq et al., 2026; Lao et al., 2026) point to an experiment the field has not done: conditional manipulation of retromer or of SORLA in microglia versus neurons, in the same animal background, with the same readouts. Small's own 2022 study showed that a neuronal lesion produces a microglial phenotype; nobody has asked whether the microglial lesion produces the neuronal phenotype, or which contributes more to behaviour. Given that the protective common variant appears to act in microglia, this is not a peripheral question about a supporting cell type. It is a question about which cell the human population's protection is operating in.

12.3 Adjudicate the two jams

The comparison between the retromer model and the βCTF–APPL1–rab5 model is tractable and overdue. The reciprocal rescue design — retromer enhancement in the rab5-overactivation animal, rab5 or APPL1 suppression in the retromer-deficient animal — would establish whether these are two routes into one compartment failure or two different failures, and it would do so with reagents that already exist in both laboratories.

12.4 Take the method seriously

The programme's most portable asset is the one it stopped foregrounding. Using differential vulnerability inside a circuit as a filter on molecular candidates found retromer when no genetic method would have; the same approach separated the ageing dentate gyrus from the Alzheimer entorhinal cortex, and the psychotic CA1 field from both. Modern spatial transcriptomics and single-nucleus profiling make the original design — compare a vulnerable subregion against a resistant neighbour, across a broad age span, with a prespecified model of how a driver should behave — far more powerful than it was on the microarrays of 2005, and it is being used almost nowhere in this form.

Whatever becomes of the retromer hypothesis, the method that produced it deserves a second run.

13. Conclusion

The endosomal theory of Alzheimer's disease is better than the field's summary of it and weaker than its own.

Its central assertion contains two claims. That a failure of retromer-dependent recycling is *causal* — sufficient to produce amyloid pathology, synaptic failure, tau pathology and glial change — is now supported by human genetics, by bidirectional manipulation in animals, by human stem-cell models, and, since July 2026, by the reversal of established tau pathology in an aged animal through up-regulation of the receptor, performed by a laboratory with no stake in the hypothesis. On the evidence available in August 2026 this is among the better-supported causal claims in Alzheimer's disease research, and it is certainly the best-supported one that is not about amyloid.

That the same failure is *common* — the operative lesion in most sporadic disease — remains unsupported. It has never rested on more than an inference from correlates, and the first direct measurement of pathway function in living people found no difference between sporadic patients and controls. The theory's proponents have not overclaimed in the technical literature, where the word "common" is offered as a hypothesis; but the summary in circulation, in which the traffic jam is the upstream cause of Alzheimer's disease in general, is ahead of the evidence and should be retired in favour of something more careful.

What is genuinely new, and what a reader coming to this work in 2026 should take from it, is a possible reconciliation of the two. The lesion may be common after all, and common in a cell the model was not written about. The strongest protective common variant at the locus acts through microglial expression; the receptor turns out to govern lipid handling, inflammatory tone and endoplasmic-reticulum stress in human microglia; and the laboratory's own human imaging now places microglia between tau pathology and neuronal loss. A neuronal traffic jam is the demonstrated lesion in the rare monogenic form. A glial one may be the common form of the same fault, and it would explain why a pathway measure drawn from a neuronal read-out does not find it.

That is a hypothesis, offered here as the most productive way to read a body of results that do not otherwise sit together. It has the merit of being testable with reagents that already exist.

The programme's practical legacy may in the end be neither the hypothesis nor the drug. It is a demonstration that in a disease which begins in one small piece of cortex and takes twenty years to become a symptom, the place where it begins is data. That was the insight in 2005, it is what returned retromer from a transcriptome nobody could read, and it remains, twenty-one years later, the part of the work that the rest of the field has not yet used.

References

Alessi DR, Cullen PJ, Cookson MR, Merchant KM, Small SA. Retromer-dependent lysosomal stress in Parkinson's disease. *Philosophical Transactions of the Royal Society B*. 2024;379(1899):20220376. PMID 38368937.

Andersen OM, Bøgh N, Landau AM, Pløen GG, Jensen AMG, Monti G, Ulhøi BP, Nyengaard JR, Jacobsen KR, Jørgensen MM, Holm IE, Nielsen MS, Stavarache M, Davidsen S, Gjedde A, Laursen AL, Bak LK, Kristensen ML, Poulsen SB, Sørensen CB, et al. A genetically modified minipig model for Alzheimer's disease with *SORL1* haploinsufficiency. *Cell Reports Medicine*. 2022;3(9):100740. PMID 36099918.

Andersen OM, Qureshi YH, Jensen AMG, Williams A, Young JE, Roy M, Klein J, Armstrong R, Merchant KM. AAV9-SORL1 gene therapy for Alzheimer's disease. *Alzheimer's and Dementia*. 2024;20(Suppl 1):e088971. [Conference abstract.] PMCID PMC11713639.

Andersen OM, de Waal MWJ, Monti G, Tesi N, Jensen AMG, de Geus C, van Spaendonk R, Vogel M, et al., 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.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*. 1991;82(4):239–259. PMID 1759558.

Brickman AM, Khan UA, Provenzano FA, Yeung LK, Suzuki W, Schroeter H, Wall M, Sloan RP, Small SA. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. *Nature Neuroscience*. 2014;17(12):1798–1803. PMID 25344629.

Brickman AM, Yeung LK, Alschuler DM, Ottaviani JI, Kuhnle GGC, Sloan RP, Luttmann-Gibson H, Copeland T, Schroeter H, Sesso HD, Manson JE, Wall M, Small SA. Dietary flavanols restore hippocampal-dependent memory in older adults with lower diet quality and lower habitual flavanol consumption. *Proceedings of the National Academy of Sciences USA*. 2023;120(23):e2216932120. PMID 37252983.

Cullen PJ, Holstege H, Small SA, St George-Hyslop P. Understanding the endo-lysosomal network in neurodegeneration. *Philosophical Transactions of the Royal Society B*. 2024;379(1899):20220372. PMID 38368931.

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, Januliene 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.

Fazeli E, Jan A, Huber AK, Jensen AMG, Fazeli E, Klein J, Merchant K, Andersen OM. A luminescent reporter assay to quantify SORL1 ectodomain shedding and retromer-dependent endosome recycling activity. *Journal of Biological Chemistry*. 2026;302(2):111136. PMID 41519200.

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.

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.

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):eaed6825. doi:10.1126/sciadv.aed6825.

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.

Jensen AMG, Kitago Y, Fazeli E, Vægter CB, Small SA, Petsko GA, Andersen OM. Dimerization of the Alzheimer's disease pathogenic receptor SORLA regulates its association with retromer. *Proceedings of the National Academy of Sciences USA*. 2023;120(4):e2212180120. PMID 36652482.

Jiang Y, Sachdeva K, Goulbourne CN, Berg MJ, Peddy J, Stavrides PH, Pensalfini A, Pawlik M, Malampati S, Whyte L, Basavarajappa BS, Subbanna S, Bleiwas C, Smiley JF, Mathews PM, Nixon RA. Increased neuronal expression of the early endosomal adaptor APPL1 replicates Alzheimer's disease-related endosomal and synaptic dysfunction with cholinergic neurodegeneration. *Journal of Neuroscience*. 2025;45(29):e2331242025. PMID 40514243.

Juul-Madsen K, Rudolph IM, Gomes JP, Meyer K, Ovesen PL, Gorniak-Walas M, Kokoli M, Telugu NS, von Tangen Sivertsen M, Febbraro F, Sutherland DS, Palmfeldt J, Diecke S, Andersen OM, Selbach M, Willnow TE. Familial Alzheimer's disease mutation identifies novel role of SORLA in release of neurotrophic exosomes. *Alzheimer's and Dementia*. 2025;21(9):e70591. PMID 40928027.

Khan UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, Mayeux R, Duff KE, Small SA. Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nature Neuroscience*. 2014;17(2):304–311. PMID 24362760.

Khani M, Yeboah SN, Cerquera-Cleves C, Kedmi A, Bustos BI, Grant SM, Can Akerman S, Akçimen F, Lee PS, Reyes-Pérez P, Lange LM, Leonard H, Koretsky MJ, Makarious MB, Schneider Z, Jonson C, Chen PS, Tay YW, Rothstein JD, Lin CH, Lim SY, Klein C, Merchant K, Mencacci NE, Krainc D, Cookson MR, Singleton A, Bandres-Ciga S. Is SORL1 a common genetic target across neurodegenerative diseases? A multi-ancestry biobank study. *Brain*. 2026;awag187. PMID 42186854.

Kim S, Sato Y, Mohan PS, Peterhoff C, Pensalfini A, Rigoglioso A, Jiang Y, Nixon RA. Evidence that the rab5 effector APPL1 mediates APP-βCTF-induced dysfunction of endosomes in Down syndrome and Alzheimer's disease. *Molecular Psychiatry*. 2016;21(5):707–716. PMID 26194181.

Knupp A, Mishra S, Martinez R, Braggin 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.

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 Aβ in neurons, yielding senile plaques. *Nature Neuroscience*. 2022;25(6):688–701. PMID 35654956.

Maheswari Jawahar V, Zeng Y, Armour EM, Yue M, Citrano K, Lovchykova A, Reeves MM, Rawlinson B, DeTure M, Dunmore JA, Song Y, Ball SK, Wszolek ZK, Graff-Radford NR, Boeve BF, Knopman DS, Day GS, Small SA, Dickson DW, Ward ME, Gendron TF, Zhang Y, Prudencio M, Gitler AD, Petrucelli L. TDP-43-mediated alternative polyadenylation is associated with a reduction in VPS35 and VPS29 expression in frontotemporal dementia. *PLoS Biology*. 2026;24(1):e3003573. PMID 41490046.

Mecozzi VJ, Berman DE, Simoes S, Vetanovetz C, Awal MR, Patel VM, Schneider RT, Petsko GA, Ringe D, Small SA. Pharmacological chaperones stabilize retromer to limit APP processing. *Nature Chemical Biology*. 2014;10(6):443–449. PMID 24747528.

Mishra S, Knupp A, Kinoshita C, Williams CA, Rose SE, Martinez R, Theofilas P, Young JE. Pharmacologic enhancement of retromer rescues endosomal pathology induced by defects in the Alzheimer's gene SORL1. *Stem Cell Reports*. 2023;18(12):2434–2450. PMID 37949073.

Morel E, Chamoun Z, Lasiecka ZM, Chan RB, Williamson RL, Vetanovetz C, Dall'Armi C, Simoes S, Point Du Jour KS, McCabe BD, Small SA, Di Paolo G. Phosphatidylinositol-3-phosphate regulates sorting and processing of amyloid precursor protein through the endosomal system. *Nature Communications*. 2013;4:2250. PMID 23907271.

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.

Pavlopoulos E, Jones S, Kosmidis S, Close M, Kim C, Kovalerchik O, Small SA, Kandel ER. Molecular mechanism for age-related memory loss: the histone-binding protein RbAp48. *Science Translational Medicine*. 2013;5(200):200ra115. PMID 23986399.

Pensalfini A, Kim S, Subbanna S, Bleiwas C, Goulbourne CN, Stavrides PH, Jiang Y, Lee JH, Darji S, Pawlik M, Huo C, Peddy J, Berg MJ, Smiley JF, Basavarajappa BS, Nixon RA. Endosomal dysfunction induced by directly overactivating Rab5 recapitulates prodromal and neurodegenerative features of Alzheimer's disease. *Cell Reports*. 2020;33(8):108420. PMID 33238112.

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.

Qureshi YH, Williams CA, Hajdu I, Kannan S, Govindarajan A, Végh B, Petsko GA, Young JE, Závodszky P, Small SA. RhoGEF12 regulates endosomal SORL1-retromer and its inhibition is therapeutic in human neuronal models of Alzheimer's disease. *bioRxiv*. 2026;2026.03.06.709427. [Preprint.] PMID 41889823.

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.

Simoes S, Neufeld JL, Triana-Baltzer G, Moughadam S, Chen EI, Kothiya M, Qureshi YH, Patel V, Honig LS, Kolb H, Small SA. Tau and other proteins found in Alzheimer's disease spinal fluid are linked to retromer-mediated endosomal traffic in mice and humans. *Science Translational Medicine*. 2020;12(571):eaba6334. PMID 33239387.

Simoes S, Guo J, Buitrago L, Qureshi YH, Feng X, Kothiya 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.

Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM; TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512–527. PMID 37459141.

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, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews Neuroscience*. 2011;12(10):585–601. PMID 21897434.

Small SA. Isolating pathogenic mechanisms embedded within the hippocampal circuit through regional vulnerability. *Neuron*. 2014;84(1):32–39. PMID 25277453.

Small SA, Petsko GA. Retromer in Alzheimer disease, Parkinson disease and other neurological disorders. *Nature Reviews Neuroscience*. 2015;16(3):126–132. PMID 25669742.

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.

Small SA, Petsko GA. Endosomal recycling reconciles the Alzheimer's disease paradox. *Science Translational Medicine*. 2020;12(572):eabb1717. PMID 33268506.

Small SA. *Forgetting: The Benefits of Not Remembering*. New York: Crown; 2021.

van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*. 2023;388(1):9–21. PMID 36449413.

Williams CA, Rose SE, Stamenkovic V, Smith SEP, Young JE. The Alzheimer's disease risk gene SORL1 is a regulator of excitatory neuronal function. *bioRxiv*. 2025;2025.07.28.667194. [Preprint.] PMID 40766397.

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.

Young JE, Holstege H, Andersen OM, Petsko GA, Small SA. On the causal role of retromer-dependent endosomal recycling in Alzheimer's disease. *Nature Cell Biology*. 2023;25(10):1394–1397. PMID 37803174.