The Bond Not Made

Cysteine, lipid peroxidation, and the chemistry of the ApoE receptor — Christopher Ramsden's account of sporadic Alzheimer's disease, six years on

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Two bonds define this theory: the disulfide bridge that ApoE4 has no cysteine to make, and the aldehyde crosslink that forms in its place, fixing the lipoprotein to the receptor it was supposed to release. The neurons that tangle first are the neurons that carry that receptor. Whether the missing bond is where Alzheimer's disease begins is now a chemical question, asked of human tissue, and answerable.

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Abstract

The strongest genetic risk factor for Alzheimer's disease has been known for thirty-three years, and nobody agrees what it does. The three common APOE alleles encode proteins that differ from one another only in the number of cysteine residues they carry — two in ApoE2, one in ApoE3, none in ApoE4 — and that difference alters lifetime risk of dementia by more than an order of magnitude. Explanations of why have multiplied without converging: structural instability, aggregation propensity, impaired lipidation, altered receptor affinity, differential clearance of amyloid. A 2022 review by a group of ApoE specialists listed the candidate properties and declined to name one as primary.

Christopher Ramsden named one. On his account the cysteine count matters because cysteine forms disulfide bridges, disulfide bridges link ApoE molecules into dimers and multimers, and those linked particles conceal the polyunsaturated lipid they carry from oxygen. ApoE4, having no cysteine, cannot make that bond. Its cargo is exposed. The lipid peroxidises, generating reactive aldehydes that attack the lysine- and histidine-rich motifs at the exact point where ApoE meets its receptor — and the ligand becomes covalently fixed to the receptor it was supposed to release. What follows, on this model, is not one disease process but four at once: lipid delivery fails, the Reelin–ApoER2–Dab1 signalling cascade that suppresses tau phosphorylation fails, the actin and microtubule cytoskeletons destabilise, and the trapped lipoprotein sits outside the neuron as a nidus for amyloid. Two bonds define the disease — the disulfide that ApoE4 cannot form, and the aldehyde crosslink that forms in its place.

This paper assesses that account against what has been published since it was first set out, and against what the rest of the field has done in the same period. Four conclusions follow.

First, the programme is unusual in its evidential base. Almost all of it is human brain — 64 rapidly autopsied cases across three brain banks in the central study, 32 more in the amygdala study, postmortem intervals averaging three hours, fixation held to forty-eight hours. Where most theories of Alzheimer's onset are built in transgenic mice and validated afterwards in tissue, this one was built in tissue and has never been tested in an animal. That is simultaneously its greatest strength and the reason its central causal claim remains unproven.

Second, its most consequential result is anatomical rather than chemical. ApoER2 expression in the human brain is not uniform: it is concentrated in entorhinal layer II stellate neurons, the prosubiculum–CA1 border, scattered layer 5 and layer 3 neocortical pyramids, and the locus coeruleus and raphe — which is, region for region and layer for layer, the map of where neurofibrillary pathology begins. That map was drawn from receptor expression, not from tau, and it matches. Its sister receptor VLDLR, expressed everywhere including in the layer 4 stellate cells that never tangle, does not match. This is the single most striking observation in the programme.

Third, and most importantly for the present moment: in the last eighteen months three independent laboratories, none of them his, have converged on the premise he staked out — that the pathogenic entity in APOE-driven Alzheimer's disease is the peroxidisable polyunsaturated lipid the particle carries, and that the protective alleles are protective because of how they handle oxidised lipid. They disagree with him, and with each other, about the direction of the traffic. One holds that protection comes from *not delivering* the lipid into the lysosome; one that it comes from *extracting* oxidised lipid back out through ABCA7; Ramsden that it comes from *concealing* the lipid in transit. A fourth group, publishing four months ago, independently identified the same molecular feature Ramsden identified — the cysteine count and the capacity to dimerise — and assigned it a different job. The convergence on substrate is now strong enough to be called a consensus in formation. The disagreement about direction is sharp, specific, and decidable.

Fourth, the theory has begun to produce things theories of Alzheimer's disease rarely produce. In April 2026 the group reported a phosphoprotein, MECP2-pS423, that rises across the clinicopathological spectrum, colocalises with tau in granulovacuolar bodies, and is measurable in cerebrospinal fluid and in serum. A mechanism-derived blood measurement is a rare output. It is also the point at which the programme's characteristic weakness becomes visible: nearly the entire human evidence base consists of phospho-specific antibodies applied to fixed tissue, and the compartment where most of the signal lands — the granulovacuolar body — is a structure known to accumulate many phosphoproteins for reasons that have nothing to do with this pathway.

The assessment states what is established, what is inferred, and what is assumed, grades each, sets out seven objections, tracks three predictions the author has put on the record against the trials now testing them, and names six experiments that would decide the matter. What survives is a serious, unusually specific, and unusually human theory of the first chemical event in Alzheimer's disease — one that has been proved chemically possible, shown to be anatomically apt, and never yet shown to occur.

1. Introduction: The First Chemical Event

1.1 Two programmes, one chemistry

Christopher Ramsden is a physician who came to Alzheimer's disease from an unusual direction, and the direction shows in the theory.

His first body of work has nothing to do with dementia. Beginning in the late 2000s he became one of the more disruptive figures in nutritional epidemiology, on a single question: what happens when a population eats large quantities of linoleic acid, the polyunsaturated fat that rose from a trace component of the American diet to its dominant fat over the twentieth century (Blasbalg et al., 2011). The orthodox answer was that it lowers cholesterol and therefore prevents heart disease. Ramsden's answer was that linoleic acid is a peroxidisable molecule, that the products of its peroxidation are biologically active, and that the trials which had supposedly established the benefit had never been fully reported.

He then did something rare: he went and found the data. With colleagues he recovered and re-analysed the unpublished records of the Sydney Diet Heart Study (Ramsden et al., 2013) and the Minnesota Coronary Experiment (Ramsden et al., 2016), two large randomised trials from the 1960s and 1970s in which saturated fat had been replaced with linoleic acid. In both, the intervention lowered serum cholesterol as designed. In both, mortality went the wrong way. The Minnesota re-analysis, published in the *BMJ* in 2016, remains one of the more uncomfortable documents in the field.

From there the programme moved to mechanism and then to intervention. His group characterised the oxidised linoleic acid metabolites — the OXLAMs — as endogenous mediators of nociception (Ramsden et al., 2012; Ramsden et al., 2017), and then ran a series of randomised controlled feeding trials in which dietary linoleic acid was lowered and long-chain omega-3 raised, testing whether changing the substrate changes the disease. The headline trial, in chronic migraine, was published in the *BMJ* in 2021 and reduced headache days. A second, in persistent post-traumatic headache among service members, reported in 2025 (Zamora et al., 2025).

The second programme is the one assessed here. It concerns Alzheimer's disease, it began publicly in 2020, and it is recognisably the same chemistry pointed at a different organ. The brain is the most polyunsaturated tissue in the body. Its lipids are carried by apolipoprotein E. Its dominant genetic risk factor is a variant of apolipoprotein E. A researcher whose working assumption is that peroxidisable lipid is the thing that goes wrong will look at that arrangement and ask a question

most of the field does not ask: not what ApoE4 does to amyloid, but what happens to the *cargo*.

1.2 What kind of claim this is

It is worth being precise about the type of theory under assessment, because the standards of judgment differ.

Most theories in this field are theories of *causation at scale*: they propose an agent — amyloid, tau, inflammation, vascular insufficiency — and argue that its accumulation drives the disease. They are adjudicated by intervention. Remove the agent, see whether the disease slows.

Ramsden's is a theory of the *first chemical event*. Its content is that a specific covalent modification, occurring at a specific molecular interface, at a specific anatomical location, initiates a cascade whose later stages are the pathologies everyone already agrees about. It is a claim about a reaction, not about an accumulation. Claims of that shape have three properties worth noting in advance.

They are hard to prove and easy to make plausible. Demonstrating that a reaction *can* occur is a bench exercise; demonstrating that it *does* occur, at pathogenic stoichiometry, in a living human brain, is enormously harder, and in this case has not been done.

They are unusually specific about anatomy. If the lesion is at an interface, then the tissue that fails should be the tissue that expresses the interface. This produces a falsifiable prediction of a kind that broader theories cannot make, and the programme's best result comes from testing exactly that.

And they generate biomarkers rather than drugs. A theory of the first chemical event tells you what to measure long before it tells you what to give. The trajectory of this programme — from hypothesis, through neuropathology, to a serum assay in 2026, with no candidate compound at any point — is what that kind of theory looks like when it works.

1.3 What this assessment asks

Three questions organise what follows.

What does the theory now rest on that it did not rest on six years ago? The 2020 formulation was a hypothesis with preliminary staining. Five subsequent studies have added biochemistry, an anatomical map, a genetic mechanism, an extension into behavioural symptoms, and a fluid measurement. The additions are not decoration; they change what the theory is.

Has the field come to it, or gone past it? Between November 2024 and March 2026, four papers appeared from laboratories with no connection to his, all landing on the same substrate — oxidised polyunsaturated lipid carried by ApoE — and all disagreeing with him about what the protective alleles actually do. This is the most important development of the period and the reason the theory is worth revisiting now rather than in five years.

What would have to be true for this to be right, and can it be shown? Section 14 names six experiments. Two of them are, as far as the published record shows, straightforward.

Sections 2 to 8 assemble the theory and its evidence from the primary work in the order it was built. Section 9 returns to the dietary programme, which matters here more than it appears to. Section 10 sets the theory against the independent literature. Sections 11 to 14 test it, grade it, and say what would settle it. Section 15 offers a reading of the programme that differs from the one it gives of itself.

2. The Theory as First Stated

2.1 The 2020 formulation

The theory entered the record in 2020 as a hypothesis document submitted to the Oskar Fischer Prize, a competition that invited non-amyloid accounts of Alzheimer's disease. The submission is worth reading as a primary source because it states the argument in its rawest form, before the evidence that now supports it existed.

Its claim was that "peroxidation of ApoE and ApoE receptors, and the formation of crosslinked ApoE–ApoE receptor complexes, are the fundamental molecular events underlying the pathogenesis of sporadic Alzheimer's disease." Three consequences were said to follow: impaired receptor-dependent delivery of lipid cargo; disruption of the Reelin–ApoE-receptor signalling cascades that shape and protect synapses; and the trapping of peroxidised ApoE particles outside the neuron, where they serve as a nidus for amyloid-β oligomerisation.

The submission also made a claim about amyloid that was heterodox then and remains the least supported part of the framework: that plaques, astrogliosis and microgliosis "initially reflect protective responses aimed at neutralising and clearing toxic peroxidised ApoE," and become damaging only with chronic exposure. Amyloid-β is, at physiological concentration, a lipid-soluble antioxidant and metal chelator enriched in lipoproteins; BACE1, the enzyme that produces it, is a stress-response protein. From these two facts the submission proposed that a specific physiological role of amyloid secretion is to bind and neutralise peroxidised ApoE particles and hand them to glia.

2.2 The four load-bearing claims

Stripped of the surrounding argument, the theory as stated in 2020 rests on four claims, each independently testable, and it is useful to separate them because they have fared very differently.

Claim 1 — the structural claim. ApoE4, lacking cysteine at residues 112 and 158, cannot form disulfide-linked dimers; ApoE3 and ApoE2 can. The consequence is that ApoE4's lipid cargo and its receptor-binding domain are left exposed.

Claim 2 — the chemical claim. Reactive lipid aldehydes generated by peroxidation of that cargo attack the lysine- and histidine-rich motifs in ApoE and in the ligand-binding domains of its receptors, forming adducts and stable ligand–receptor crosslinks.

Claim 3 — the signalling claim. Because ApoER2 and VLDLR are shared receptors for both ApoE and Reelin, and because Reelin signalling through these receptors suppresses tau

phosphorylation via Dab1 and PI3K, chemical damage at that interface disables a cascade whose failure produces hyperphosphorylated tau, actin destabilisation and synapse loss.

Claim 4 — the anatomical claim. The convergence of these molecules at the synapse — specifically at the ApoE–receptor interface — creates a site-specific vulnerability that explains why particular regions and neurons degenerate and others do not.

Claim 2 was demonstrated at the bench in 2022. Claim 4 was tested against human tissue and largely held in 2023. Claim 1 received its first direct experimental support in 2025, thirty months after Claim 2. Claim 3 remains an inference from rodent and cellular models, and is the load-bearing joint of the whole structure.

2.3 What counted as evidence in 2020

Almost nothing, and the document says so. Its empirical content was a preliminary application of a multiplex immunohistochemistry platform — co-developed with Dragan Maric at NINDS — capable of labelling dozens of markers in a single human brain section, applied to rapidly autopsied entorhinal cortex and hippocampus. The submission reported that more than sixty markers had been successfully stained and that components of the ApoE/Reelin–ApoE-receptor axis accumulated in the immediate vicinity of neuritic plaques. Findings were described as "pending publication."

Two features of that starting position are worth marking, because they shaped everything after.

The first is the choice of instrument. Multiplex immunohistochemistry with iterative antibody stripping allows dozens of proteins to be localised in the same section, so that the question "do these things accumulate in the same neurons, or merely in the same region?" can actually be answered. That question is unanswerable with serial sections, and it is the question on which most of the programme's argument turns. The instrument determined the shape of the evidence.

The second is the choice of tissue. The specimens are rapidly autopsied — mean postmortem interval of three hours in the principal cohort — and minimally fixed, forty-eight hours in ten per cent neutral buffered formalin. This matters more than it sounds. Highly aggregated proteins such as amyloid and tau survive delayed autopsy and prolonged fixation; phosphoproteins and less aggregated species do not. A programme built on detecting phospho-epitopes in human brain is only possible with tissue handled this way, and the decision to work exclusively with such material is a real methodological commitment with real costs — it restricts the available cohorts, which is why sample sizes throughout are moderate.

3. The Chemistry: Can an Aldehyde Break a Receptor?

3.1 Why lysine, and why this receptor

The chemical claim is not arbitrary. It follows from a coincidence of chemistry and structure that the theory noticed and that, once stated, is difficult to unsee.

Reactive aldehydes generated by lipid peroxidation — 4-hydroxynonenal, malondialdehyde, acrolein, 4-oxo-nonenal — are electrophiles. They attack nucleophilic amino acid side chains, and the two they attack most readily are lysine and histidine (Uchida, 2003). This is not controversial; it is the standard chemistry of carbonyl stress, and 4-HNE adducts have been detected immunohistochemically in Alzheimer's brain since the 1990s, with a reported association with APOE4 inheritance (Montine et al., 1997).

The structural coincidence is this. Lipoprotein receptors of the LDL-receptor family bind their ligands through acidic, calcium-coordinating ligand-binding type-A modules, and the ligands bind through basic, lysine-enriched recognition motifs. Both ApoE and Reelin use cationic, lysine-rich motifs to engage adjacent or overlapping anionic sequences in the ectodomains of ApoER2 and VLDLR. The binding chemistry of this receptor family is, in other words, lysine chemistry — and lysine is precisely the residue that reactive lipid aldehydes destroy. Further, the ligand-binding domains of human ApoER2 and VLDLR are reported to be unusually enriched in lysine relative to their rodent counterparts.

So the argument is: the molecule that carries the peroxidisable lipid binds its receptor using exactly the residues that the products of peroxidising that lipid attack. The aldehyde is generated at the interface, on the cargo, a few ångström from its target. If this reaction happens anywhere in biology, this is where it should happen.

3.2 The 2022 bench result

The reaction was tested directly and reported in the *Journal of Alzheimer's Disease* in 2022 (Ramsden et al., 2022), the paper that converted the 2020 hypothesis into a published framework.

The experiments used ApoE peptides containing the lysine–histidine-enriched receptor-binding sequences, analogues engineered to lack the double-lysine motifs, ApoER2 LA1–2 peptides, the full-length ApoER2 ectodomain, and recombinant ApoE4 monomer. These were exposed to

malondialdehyde, crotonaldehyde, 4-hydroxynonenal, 4-oxo-nonenal, and a mixture of reactive aldehydes. Products were characterised by liquid chromatography–mass spectrometry and time-of-flight mass spectrometry, and by Western blotting.

Three results matter.

Adducts formed, as predicted, on the lysine- and histidine-containing motifs. The analogues lacking double-lysine motifs were resistant, which is the internal control the experiment needed: the modification tracks the residues the model says it should track, not the peptide in general.

Stable pyrrole crosslinks formed. This is the step that distinguishes the model from generic oxidative-stress accounts. An adduct modifies a protein; a crosslink covalently joins two proteins. Pyrrole crosslinking by 4-oxo-alkenals is established chemistry, and Montine and colleagues had shown as early as 1996 that products of lipid peroxidation crosslink apolipoprotein E (Montine et al., 1996). What was new here was the demonstration that ApoE can be crosslinked to *its receptor*.

High-molecular-weight ApoE–ApoER2 heterodimers and ApoE multimers were detected by Western blot. The ligand and receptor became a single covalent species.

3.3 The acid test

The most consequential experiment in that paper is also the least discussed, and it concerns pH.

The normal life cycle of a lipoprotein receptor requires release. The receptor binds its ligand at the cell surface, internalises it, and the acidifying environment of the early endosome triggers dissociation; the ligand goes to the lysosome, the receptor recycles to the membrane. If the ligand cannot let go, the receptor cannot recycle, and the cell loses surface receptor.

This is not a hypothetical failure mode. It is one of the better-established cellular phenotypes of ApoE4: Chen and colleagues showed in 2010 that ApoE4 selectively impairs ApoER2 recycling, reducing glutamate receptor function and synaptic plasticity (Chen et al., 2010), and Xian and colleagues showed in 2018 that the recycling block is pharmacologically reversible by lowering endosomal pH (Xian et al., 2018). The standard explanation is conformational — ApoE4 adopts a molten-globule state near its isoelectric point at about pH 6.5.

Ramsden proposed a different explanation: that the receptor cannot release the ligand because they are covalently joined, and that the covalent bond does not care about pH. The 2022 paper tested it. Malondialdehyde adducts showed partial but incomplete pH-dependent reversibility, greater at pH 4 than at pH 6 — consistent with Schiff-base chemistry, which is acid-labile. Crosslinks formed with the reactive aldehyde mixture showed minimal reversibility and remained stable at lysosomal pH.

That is a genuinely elegant result, and it makes a discriminating prediction. On the conformational account, the recycling block is a reversible physical property of a protein; on the covalent account, it is a bond. The two accounts differ in what should happen when you acidify. Xian and colleagues acidified, and the block reversed — which favours the conformational account for the phenotype they were measuring. But their system contained ApoE4 in the absence of significant peroxidation. The experiment that distinguishes the two has not been done: take neurons, acidify, and test whether the recycling of receptors blocked by *peroxidised* ApoE recovers. On Ramsden's model it should not.

3.4 What the chemistry settles, and what it leaves open

The 2022 experiments establish chemical possibility with a high degree of confidence. Reactive lipid aldehydes adduct the relevant motifs; they crosslink ApoE to ApoER2; the crosslinks are acid-resistant; the reaction depends on the residues the model nominates. This is real, and it is the kind of positive result that hypothesis papers in this field frequently lack.

What it does not establish is that this happens in a human being.

The experiments were conducted with purified peptides and recombinant protein at aldehyde concentrations chosen to drive the reaction. No published work has isolated a crosslinked ApoE–ApoER2 species from human brain tissue and identified it by mass spectrometry. The only human evidence for peroxidised ApoE is immunohistochemical — antibodies raised against lipid-aldehyde-modified ApoE, which in the 2022 study labelled discrete granular structures near plaque cores and showed partial but incomplete overlap with native ApoE, indicating selective modification within the plaque. That is suggestive. It is not identification.

This gap is the single most important open question in the programme, and Section 14 returns to it as the first of the six decisive experiments. It is also, on the face of it, a tractable one: immunoprecipitate ApoE from frozen human brain under non-reducing conditions and look for the receptor.

3.5 The circuit, before the map

Before the anatomical argument was made at scale, the 2022 paper had already made it once, in a smaller and more specific form that is worth recording because it concerns the circuit rather than the region.

The perforant path is the projection from entorhinal cortex to the hippocampal formation. It is the principal input route to the hippocampus, it carries the traffic on which episodic memory depends, and its degeneration is one of the oldest and best-characterised findings in Alzheimer neuropathology. If the theory is right, its terminal zones — where entorhinal axons meet hippocampal and dentate dendrites, and where the synaptic membranes needing constant lipid

resupply are densest — should be a site of preferential failure.

Working in postmortem specimens from twenty-six individuals (eight with Alzheimer's dementia, seven with mild cognitive impairment, six cognitively normal older controls, five young controls), the group reported that ApoER2 is strongly expressed in exactly those terminal zones, and that the components of the axis accumulated there in disease: aggregates of the ApoER2 LA1–2 ligand-binding modules, native ApoE, 4-hydroxynonenal-modified ApoE, Reelin, Dab1, Thr19-phosphorylated PSD95, and the downstream signalling markers Tyr607-phosphorylated P85α and Thr508-phosphorylated LIMK1. Plaque-associated ApoER2 LA1–2 aggregates correlated positively with Braak stage and amyloid plaque load and inversely with Mini-Mental State Examination score, and Reelin, Dab1 and phospho-PSD95 behaved similarly.

Two details of this result deserve emphasis. The aggregating species was the *ligand-binding module itself* — the LA1–2 region, which is the acidic, calcium-coordinating structure that grips the lysine motif of ApoE and Reelin, and the exact structure the aldehyde chemistry is proposed to attack. And 4-HNE-modified ApoE showed only partial overlap with native ApoE within plaques, appearing as discrete granular structures near the core and elongated structures projecting outward — the pattern one would expect if a subset of the ApoE in a plaque had been chemically altered rather than the whole deposit being uniformly modified.

This was the theory's first anatomical prediction and its first anatomical confirmation, and it was made about a circuit rather than a list of regions. The 2023 study generalised it.

4. The Anatomy: A Map Drawn Without Tau

4.1 The claim, and why it is unusual

The best result in this programme is not chemical. It is a map.

Alzheimer's disease is not a global brain disease. Neurofibrillary pathology begins in a small number of places — Braak and Del Tredici's work places the earliest pretangle material in the locus coeruleus, and the first frank tangles in entorhinal layer II — and proceeds through a stereotyped sequence, sparing some populations entirely even in advanced disease. Layer 4 stellate cells of neocortex do not tangle. Neighbouring pyramidal neurons in the same layer, receiving the same inputs, do or do not tangle apparently at random.

Why has never been satisfactorily answered. The dominant explanation for the *sequence* — prion-like propagation of tau along connections — says nothing about the *origin*, and nothing about what molecular property makes the first neurons vulnerable.

Ramsden's theory makes a prediction here that almost no other theory makes, and it is disarmingly simple. If the lesion is at the ApoE receptor, then the neurons that degenerate first should be the neurons that express the receptor. The map of ApoER2 should be the map of early tau.

This is a strong prediction because it is drawn from an independent variable. Receptor expression is measured by *in situ* hybridisation for LRP8 and by immunohistochemistry for ApoER2 protein; the vulnerability map comes from eighty years of neuropathology. The two have nothing to do with each other unless the theory is right.

4.2 The 2023 study

The test was published in *Acta Neuropathologica Communications* in December 2023 (Ramsden et al., 2023). It is the central document of the programme.

Sixty-four rapidly autopsied cases were examined, spanning the clinicopathological spectrum from cognitively normal controls through mild cognitive impairment to advanced dementia, drawn from three brain banks with different autopsy and fixation protocols: the Banner Sun Health Research Institute Brain and Body Donation Program (34 cases; mean postmortem interval three hours), the University of Auckland Neurological Foundation Human Brain Bank (18 cases,

providing the pontine specimens), and the University of Kentucky Alzheimer's Disease Research Center (12 cases, used for validation only).

Five regions were examined, chosen because each is known to develop tau pathology in the earliest stages: entorhinal cortex layer II, the prosubiculum–CA1 border region, temporal neocortex, the locus coeruleus, and the raphe nucleus. Methods included *in situ* hybridisation for LRP8, single-marker immunohistochemistry for quantification, multiplex fluorescence immunohistochemistry with up to six iterative staining rounds for spatial context, and Western blotting against lysates from cells transfected to overexpress the human target proteins. Quantification was automated (HALO image analysis, with a separate object-colocalisation module used to distinguish pathological plaque-associated Dab1 from the Dab1 normally present in healthy neurons). Group differences were tested by Kruskal–Wallis, associations by Spearman correlation, with false-discovery-rate adjustment.

4.3 The result

The map matched.

In entorhinal cortex, ApoER2 and LRP8 signals were strong in the soma of Reelin-expressing layer II stellate neurons and in a subset of layer II pyramids, and in their basal and apical dendrites projecting into the layer I–II border. Expression was higher in layer II than layer III, producing a visible laminar termination threshold at the layer II–III boundary — which is where the vulnerability boundary also sits. Strong expression appeared in a subset of layer 4 pyramids and was minimal or absent in neighbouring layer 4 neurons.

In the prosubiculum–CA1 border region — the first part of the hippocampal formation to tangle — expression was moderate to strong in basal pyramids and neurites localised to the basal stripe, and lower in middle and apical layers.

In temporal and frontal neocortex, the strongest expression was in the perikarya of a subset of layer 5 and layer 2/3 pyramids, in their basal dendrites, and in the distal portions of their apical tufts at the layer I–II border. Again a laminar threshold near the layer II–III boundary. And, critically, expression was minimal or absent in a subset of *neighbouring* layer 5 pyramids and in most layer 4 neurons.

In the upper pons, strong LRP8 and ApoER2 signal was found in locus coeruleus and raphe neurons, with high expression in neuritic projections. Within the locus coeruleus, ApoER2 overlapped substantially with MAP2-labelled dendritic arbours and minimally with the axonal marker neurofilament light or the presynaptic marker synaptophysin — that is, the receptor is a dendritic protein in the very neurons where the disease is thought to begin.

4.4 The controls inside the result

What makes this more than a coincidence of two anatomical descriptions is that the study contains its own negative controls, and they behave correctly.

Two other ApoE receptors were examined. LRP1 was expressed by glia and neurons, with prominent signal in glia surrounding plaques — a distribution that does not resemble the tangle map. VLDLR, which shares Reelin as a ligand with ApoER2 and shares the Dab1 adaptor, was strongly and ubiquitously expressed by neurons in all neocortical layers *including the layer 4 stellate neurons that are resistant to tangle formation*.

This is the sharpest observation in the paper. VLDLR and ApoER2 are close relatives with overlapping ligands and an identical downstream adaptor. If the finding were an artefact of receptor family biology, or of some general property of lipoprotein receptors in vulnerable tissue, VLDLR would track vulnerability too. It does not. The correspondence is specific to ApoER2.

And the correspondence extends to the sub-neuronal scale. Tau inclusions are known to originate in distal dendrites before progressing to proximal dendrites and soma. ApoER2, Dab1, P85α, LIMK1 and PSD95 are enriched in distal dendritic tips. The receptor is not merely in the right cells; it is in the right part of the right cells.

Two caveats belong here. Expression mapping is cross-sectional, and it shows where a receptor is, not what is happening to it. And a subset of ApoER2-expressing neurons is spared even in the same layer of the same section — the study notes these explicitly. High expression is therefore necessary but plainly not sufficient, and the theory needs a second variable to explain the sparing. It proposes one — differential demand for pathway activation, with entorhinal and locus coeruleus neurons firing near-continuously across the wake–sleep cycle — but this is offered as a suggestion, not a measurement.

4.5 The locus coeruleus, and a second variable

The locus coeruleus deserves separating out, because it is where the theory's anatomical claim is most exposed and most interesting.

It is the earliest site of pretangle tau in the human brain, appearing in people in their twenties and thirties, decades before any clinical sign. It is a small nucleus of a few tens of thousands of noradrenergic cells with an axonal arbour of extraordinary length and branching complexity — a single locus coeruleus neuron may project to much of the ipsilateral cortex. And it presents the sharpest version of the puzzle the theory exists to solve: why *there*, and why first.

The 2023 study found strong LRP8 and ApoER2 signal in locus coeruleus and raphe neurons, with high expression in neuritic projections and, within the locus coeruleus, substantial overlap with MAP2-labelled dendrites and minimal overlap with axonal and presynaptic markers. Dab1,

phospho-PSD95 and phospho-tau accumulated in both the locus coeruleus–peri-coeruleus complex and the raphe in Alzheimer cases, were less pronounced or absent in neurologically normal controls, and correlated with Braak stage. Extracellular ApoE accumulation was present in many Alzheimer cases; Reelin deposits in only a few.

Two things follow.

The first strengthens the theory. If tau pathology begins in the locus coeruleus and the locus coeruleus strongly expresses the receptor whose disruption the theory holds responsible, then the theory's explanation of *origin* is at least as good as its explanation of *sequence* — and origin is what the propagation models conspicuously do not address.

The second is more demanding of it. Expression alone cannot be the whole story, because other populations express ApoER2 and are spared, and because within the locus coeruleus itself the theory offers no account of why the tau appears first in axons rather than in the dendritic compartment where the receptor mostly sits. The programme's proposed second variable — demand, the idea that neurons which fire almost continuously must turn over pathway components incessantly and are therefore more exposed to any failure of resupply — is intuitively attractive, fits the entorhinal and coeruleus cases, and is entirely unquantified. Nothing in the published work measures turnover, activity, or metabolic load in these populations. This is where a theory of a receptor interface has to become a theory of a *rate*, and it has not yet.

There is, however, an unusual development worth recording. In 2025 Ramsden appeared as a co-author on a study using multicomponent magnetic-resonance relaxometry to measure locus coeruleus microstructure *in living people* — 120 cognitively unimpaired individuals aged 22 to 94, in which transverse relaxation rate declined with age, particularly in the rostral-middle segment, and lower values predicted steeper longitudinal memory decline at advanced ages (Bae et al., 2025). This is not a test of the theory. But it places the group in possession of an in-vivo measurement of the structure their postmortem work nominates as the origin, at a moment when they have also acquired a fluid marker. A programme that could correlate a serum phosphoprotein against imaging of the locus coeruleus in the same living cohort, longitudinally, would be doing something none of the postmortem work can do.

5. Four Arms, and the Case Against Spread

5.1 The pathway as a four-armed switch

The theory's account of what goes wrong downstream depends on a specific reading of ApoER2–Dab1 biology, drawn from a substantial preclinical literature. On that reading the pathway is not a single signalling line but a four-armed switch, and disruption at the receptor throws all four arms at once.

Arm one — microtubules. Reelin binding to ApoER2 triggers tyrosine phosphorylation of Dab1, which recruits PI3K through its regulatory subunit P85α, activating Akt and inhibiting GSK3β. GSK3β is a principal tau kinase. Disable the arm and tau is hyperphosphorylated; microtubules destabilise. This is the best-characterised arm, established in Herz's laboratory from 1999 onward (Hiesberger et al., 1999).

Arm two — actin. The same signalling regulates LIM domain kinase 1, which controls cofilin-mediated remodelling of the actin cytoskeleton in dendritic spines. Disable the arm and the actin skeleton of the spine destabilises.

Arm three — the synapse. Activated GSK3β phosphorylates PSD95 at Thr19, which drives disassembly of the postsynaptic density. Disable the arm and synapses come apart.

Arm four — lipid supply. ApoER2 is also an endocytic receptor for ApoE and ApoJ, and therefore the route by which the neuron takes delivery of the cholesterol and specialised phospholipids it needs to rebuild membranes. Disable the arm and the raw material for synaptic remodelling stops arriving; the lipoprotein accumulates outside the cell.

The structural elegance of this is that four of the principal molecular derangements of Alzheimer's disease — hyperphosphorylated tau, cytoskeletal collapse, synapse loss, and extracellular lipoprotein deposition — become four outputs of one failure rather than four separate diseases requiring four separate explanations.

5.2 Co-accumulation

The 2023 study tested this by asking whether markers of all four arms accumulate together, in the same neurons, in the same regions.

They did. Seven components — Dab1, pP85α-Tyr607, pLIMK1-Thr508, pTau-Ser202/Thr205, pPSD95-Thr19, ApoJ and ApoE — accumulated in abnormal neurons and near plaques in entorhinal cortex, were higher in MCI and Alzheimer cases than controls, and correlated with histological progression or antemortem cognitive deficit. In the prosubiculum–CA1 region eight markers did the same, adding phosphorylated Dab1 at Tyr220. Multiplex imaging indicated that Dab1, pP85α, pLIMK1, pPSD95 and pTau accumulated together within many of the same ApoER2-expressing neurons and within MAP2-labelled dystrophic dendrites near ApoE- and ApoJ-enriched plaques.

Two observations within this deserve separating out.

Dab1 accumulation is the pathway's own read-out of failure. Reelin signalling through ApoER2 induces rapid proteasomal degradation of Dab1 (Bock et al., 2004). Dab1 protein is therefore consumed by successful signalling; its accumulation implies a local failure of that signalling. This is a clean inferential move — an increase in a protein taken as evidence that a pathway has stopped running — and it is the single most important inference in the programme. It is also entirely dependent on a rodent and cell-culture result being true of human neurons *in situ*.

Dab1 accumulation ran ahead of tau. In entorhinal cortex it was extensive in mild cognitive impairment, and in some control cases it preceded overt tau accumulation. In temporal neocortex, in a control with substantial amyloid (Thal phase 3) and no tau pathology at all (Braak stage 0), plaque-associated Dab1 accumulations were prominent in layers 5 and 3, some clustered around an ApoE-enriched plaque core, with essentially no tau or pPSD95 in serial sections. If Dab1 accumulation genuinely indexes pathway failure, then pathway failure is present before tau.

5.3 Three observations that spread does not explain

The 2023 paper is unusually direct in setting itself against the prevailing model of tau progression, and the argument is worth stating on its merits because it does not depend on the peroxidation hypothesis being right.

First, the sequence of neurofibrillary progression through the medial temporal lobe runs in the opposite direction to the known unidirectional connectivity of that memory system.

Second, pretangle pathology classically originates in the locus coeruleus before appearing in entorhinal layer II — but locus coeruleus neurons project diffusely throughout the brain and do not selectively innervate entorhinal layer II. A donor that projects everywhere cannot explain a recipient that is highly specific.

Third, and most awkwardly, in the earliest stages tau accumulates within the distal dendritic tips of *rare, solitary* layer 5 and layer 3 pyramids while sparing their immediate neighbours. Since a single projection neuron innervates hundreds or thousands of targets, connectome-based spread would

require that every terminal from one donor axon synapse onto dendrites of a single target neuron and contact no neighbour — a revision of brain connectivity for which there is no evidence.

The positive argument is then straightforward: if tau were arriving from elsewhere, only tau would arrive. Instead the study finds tau accumulating alongside four other pathway components, several of them *upstream* of tau phosphorylation. Prion-like templating is a property attributed to tau specifically; there is no proposed mechanism by which Dab1, phospho-P85α, phospho-LIMK1 and phospho-PSD95 propagate trans-synaptically. Multi-component co-accumulation at multiple independent sites is far more economically explained by local production at each site.

5.4 How strong is this argument?

Strong against a naive version of spread; not fatal to the sophisticated version.

The three anatomical objections are real and are not adequately answered in the propagation literature. The co-accumulation argument is genuinely difficult for spread to accommodate. And the paper's own conclusion is appropriately calibrated: it states that the findings do not rule out prion-like propagation contributing, and that trans-synaptic transmission has been demonstrated in model systems.

But there is an alternative reading of the same data that the paper does not fully close off, and Section 11.5 develops it. Everything in the co-accumulation result depends on the claim that these five proteins accumulate together *because* they belong to one pathway. If instead they accumulate together because they are all phosphoproteins that end up in the same subcellular garbage — the granulovacuolar degeneration body — then the co-accumulation is real, reproducible, correlated with disease, and mechanistically uninformative. Distinguishing these two readings is, in my judgment, the most important unresolved methodological question in the programme.

5.5 The Reelin problem

There is a complication inside the pathway that the framework handles unevenly, and it concerns the ligand rather than the receptor.

Reelin is the signal whose loss the theory holds responsible for tau hyperphosphorylation. One would therefore expect Reelin to be depleted in Alzheimer's disease. The published human literature says something more awkward: Reelin protein is frequently *elevated* in Alzheimer brain and cerebrospinal fluid while Reelin signalling is impaired — the position Cuchillo-Ibáñez and colleagues summarised in the title of their 2016 review, *increased levels but impaired signaling: when more is less* (Cuchillo-Ibáñez et al., 2016).

The framework's account of this is, in fact, one of its better moves. If the lesion is at the receptor, then a ligand that cannot be internalised will accumulate outside the cell — so elevated

extracellular Reelin is not evidence against the model but a prediction of it. And that is what the group reports: extracellular Reelin aggregates in the CA2 and CA1 subregions and the dentate molecular layer in Alzheimer cases, more abundant than in controls and inversely correlated with Mini-Mental State score. Trapped ligand outside a broken receptor is exactly the appearance the model requires.

The complication is that the same group finds this pattern in some regions and not others. Reelin aggregates were much less prominent in the prosubiculum–CA1 border region than in CA2 and CA3, and did not correlate with progression there. They were absent from amygdala altogether, prompting the suggestion that Reelin *depletion* rather than trapping predominates in that structure. Meanwhile the entorhinal layer II neurons that tangle first are themselves Reelin-expressing stellate cells — the population Kobro-Flatmoen and colleagues showed selectively accumulates intracellular amyloid early in the disease (Kobro-Flatmoen et al., 2016) — so in the region where the disease begins, the cells that make the ligand are the cells that die, and their death would deplete the signal for everything downstream.

So the framework requires Reelin to be trapped in some places, depleted in others, and made by the neurons that fail first. Each of those is defensible on its own. Together they mean that "Reelin signalling fails" is doing different mechanical work in different regions, and the theory has not yet said what determines which mode operates where. This matters because the two modes imply different interventions: trapped ligand argues for repairing the receptor, depleted ligand argues for supplying more agonist. Reelin-COLBOS, the protective human variant, is a *better agonist* — which points toward depletion as the operative lesion at least in the entorhinal circuit, and therefore slightly against the trapping arm the framework foregrounds.

6. The Genetics: Counting Cysteines

6.1 The gap the theory left open until 2025

For its first five years the theory had a hole in it, and its author says so plainly. The framework explained how peroxidation could damage the ApoE–receptor interface and what would follow. It did not explain why the *APOE* genotype should be the dominant genetic determinant of that process. The 2020 submission asserted that ApoE4's lack of cysteine leaves its cargo exposed; but the mechanism connecting a missing cysteine to an exposed lipid was never specified, and no experiment addressed it.

This is a serious gap for a theory whose whole claim to superiority over the amyloid cascade is that it accounts for the genetics of sporadic disease. It was closed — or at least addressed — in a hypothesis paper published in *Prostaglandins, Leukotrienes and Essential Fatty Acids* in July 2025 (Ramsden et al., 2025), which is the most intellectually interesting document in the programme.

6.2 The disulfide hypothesis

The proposal is this. The single signature chemical capacity of cysteine is the formation of disulfide bridges, and disulfide bridges are what link protein monomers into dimers and multimers. ApoE2 has two cysteines and can form multimers; ApoE3 has one and can form dimers; ApoE4 has none and remains monomeric. The claim is that these linked particles undergo conformational changes that *conceal* the polyunsaturated lipid cargo within a hydrophobic core, physically shielding it from oxygen. The ability to make that bond is therefore the ability to protect the cargo, and the gradient of that ability — super-ability, intermediate ability, inability — is the gradient of protection across the three alleles.

The virtues of this formulation are worth enumerating because they are exactly the criteria the paper sets for itself.

It is *monotonic across all three alleles*. Most ApoE4-centric explanations — aggregation propensity, domain interaction, the molten globule — are properties of ApoE4 and therefore explain risk but not protection. ApoE2 is not merely "less ApoE4"; it is actively protective, and a mechanism that runs 2-1-0 in cysteines and maps onto protective–neutral–harmful is a better fit to the genetics than a mechanism that describes only one allele.

It is *traceable to the actual polymorphism*. The alleles differ in nothing but cysteine-to-arginine exchanges. A mechanism keyed to the cysteine itself, rather than to a downstream structural

consequence, sits closer to the primary datum than any competitor.

It *reconciles loss and gain of function*. The long-running argument over whether ApoE4 is harmful by losing something or by acquiring toxicity is dissolved: the lost function (making disulfide bridges) directly produces the toxic gain (accelerated production of peroxidised lipid). One event, both readings.

6.3 The bench result

The paper is not purely theoretical. It contains a small, direct experiment.

Recombinant ApoE2, ApoE3 and ApoE4 were incubated with brain-enriched polyunsaturated phosphatidylethanolamine species: a DHA-containing ethanolamine plasmalogen (PE-P18:0/22:6n-3), a diacyl DHA species (PE-18:0/22:6n-3), and a docosatetraenoyl species (PE-18:0/22:4n-6), alone or as a mixture with free cholesterol. ApoE3 and ApoE2 showed increased disulfide-linked dimerisation and multimerisation. ApoE4, as it must, showed none. The DHA plasmalogen — a species highly vulnerable to peroxidation and depleted in Alzheimer brain — had the most pronounced effect. Incubation with the peroxidation-resistant synthetic lipid DMPC, or with cholesterol alone, had minimal effect. The dimerisation was reversed by the thiol-reducing agent dithiothreitol, confirming it was disulfide-dependent.

The interpretation offered is that the peroxidisable lipid itself induces the conformational change that protects it, in the two isoforms capable of making the bond. There is a pleasing logic to a cargo that triggers its own concealment.

The paper draws a sharp methodological moral from this, and it is a serious charge against a large literature. The seminal studies characterising ApoE structure used DMPC — a synthetic, fully saturated, peroxidation-resistant phospholipid that does not occur in nature — to lipidate ApoE particles, and routinely treated those particles with thiol-reducing agents such as DTT, TCEP or β-mercaptoethanol. Both choices are individually reasonable and jointly catastrophic for the question at issue: the first removes the peroxidisable substrate, the second cleaves the very bonds under investigation. If the argument is right, the structural biology of ApoE has been conducted for three decades under conditions that made its most consequential property invisible.

6.4 ApoJ, ApoD, and the heteromer conjecture

The paper extends the idea beyond ApoE homodimers, and here it becomes speculative in a way it acknowledges.

Cysteine allows heteromeric complexes as well. In serum, disulfide-linked ApoE3–ApoAII complexes are abundant — but ApoAII is a liver product, not detectable in human brain outside the vasculature, and not expressed by astrocytes. The brain's own glia-secreted apolipoproteins are

ApoJ (clusterin) and ApoD, and the paper nominates both.

The ApoJ argument is the more interesting because it makes a genetic prediction. The canonical ApoJ proteoform has ten cysteines, all of them already engaged in intramolecular bridges, leaving none free to link with ApoE. But a less-studied isoform encoded by *CLU* isoform 2 — reported to be selectively overexpressed in carriers of the AD-protective minor allele rs11136000T — carries three additional N-terminal cysteines. The proposal is that these free cysteines let this ApoJ proteoform form protective disulfide-linked complexes with ApoE2 and ApoE3 but not ApoE4. The paper notes, correctly, that this predicts the *CLU* protective effect should be confined to APOE4 non-carriers — and that this is what has been reported. *CLU* is one of the strongest non-*APOE* risk loci in Alzheimer's disease and has lacked a satisfying mechanism since it was identified; a mechanism that also explains an interaction with *APOE* is a non-trivial claim.

The ApoD argument turns on a species difference: human ApoD carries an unpaired cysteine at position 116 that rodent ApoD lacks. If the disulfide framework is right, this is one of several reasons the rodent is the wrong animal for the question.

Both conjectures are, at present, unsupported by direct data. The paper says what would test them — immunoprecipitation of lipoproteins from frozen human brain under strictly non-reducing conditions, with reducing and non-reducing Westerns run side by side — and does not report having done it.

6.5 The evolutionary argument

A short section makes an argument that is either an elegant reframing or an over-reading, and I am not sure which.

APOE4 — zero cysteines — is the ancestral allele, shared with every other mammal. *APOE3* appeared in humans roughly 200,000 years ago, adding one cysteine; *APOE2* more recently, adding a second. The paper observes that the emergence of *APOE3* coincided approximately with the exploitation of coastal habitats rich in DHA and with the expansion of grey matter in the modern human brain, and speculates that the cysteine additions were selected because a brain with more neurons, more elaborate dendritic arbours, a higher synapse-to-neuron ratio and a post-mitotic lifespan of seventy-five years or more needs to protect its polyunsaturated lipids more than a mouse does.

The correlation of dates is real; the causal reading is unfalsifiable in any direct way. But there is a defensible weaker version: whatever selected for them, the cysteine-bearing alleles are human-specific, and any model built in an animal that possesses only the ancestral allele is structurally incapable of exhibiting the mechanism. That point stands independently of the palaeoanthropology.

6.6 What it fixes, and what it now stakes

The disulfide hypothesis does what it set out to do: it converts the strongest genetic association in the disease from a statistical fact into a chemical property, and it does so with a mechanism that is monotonic, traceable to the polymorphism, and testable.

But it also stakes the whole theory on a premise that is thinner than the argument built on it. The claim that ApoE3 and ApoE2 form disulfide-linked dimers and multimers *in the human brain, at abundance, on lipoprotein particles* rests substantially on a single 2010 study reporting that dimerised ApoE was undetectable in ApoE4 homozygote human cortex and hippocampus but constituted the majority of ApoE in ApoE3 homozygotes, with intermediate levels in heterozygotes (Elliott et al., 2010). That is a striking result. It is one study, in modest numbers, and it has not been the subject of the replication effort that a load-bearing premise deserves. The 2025 experiments demonstrate that recombinant ApoE3 and ApoE2 *can* be induced to dimerise by brain lipids in a tube; they do not establish the abundance or the structural consequence in tissue, and the paper is explicit that further work is required to confirm the specific structural effects.

7. The Amygdala, and the Symptoms Nobody Models

A preprint posted in June 2025 extended the analysis to a region the programme had not touched and to endpoints the field rarely tests (Ramsden et al., 2025b).

The rationale is clinical. Agitation, aggression, anxiety and depression are among the most burdensome manifestations of Alzheimer's disease — they predict institutionalisation and drive caregiver collapse — and they are, in mechanistic terms, orphaned. The amygdala is the obvious substrate, is known to degenerate in the disease, and had not been examined for this pathway.

Thirty-two rapidly autopsied cases were examined by single-marker and multiplex immunohistochemistry. Seven ApoER2–Dab1 components — ApoER2 itself, Dab1, pP85α, pLIMK1, pTau, pPSD95 and ApoJ — accumulated across the spectrum and correlated with Braak stage, amyloid load, cerebral amyloid angiopathy score and antemortem cognitive deficit. Neuropsychiatric endpoints were drawn from the National Alzheimer's Coordinating Center Uniform Data Set. Deficits in comportment showed the strongest associations: all seven markers correlated with them in the amygdala, against four in entorhinal cortex from the same cases. Behavioural symptoms and personality change showed weaker positive associations, again stronger in amygdala than entorhinal cortex.

Three features of this study are worth marking.

The ApoER2 expression pattern in amygdala is *not* laminar, unlike entorhinal cortex and hippocampus. It appears in a scattered subset of pyramid-shaped neurons with minimal expression in many immediate neighbours. The vulnerability principle survives the change of architecture — expression is still patchy and still tracks pathology — but the tidy laminar correspondence that made the entorhinal result so persuasive does not generalise.

The regional comparison is a real internal control. Comparing amygdala pathology to entorhinal pathology from the same cases, against endpoints specific to emotional regulation, is the correct design, and the amygdala association is consistently the stronger.

And there is an inconsistency the authors do not resolve, to their credit for reporting it. In hippocampus and subiculum the same group had previously found prominent extracellular Reelin deposits — Reelin trapped outside the cell, consistent with the ligand-trapping arm of the model. In amygdala there were none. The authors' interpretation is that Reelin *depletion* may dominate in amygdala where Reelin *trapping* dominates in hippocampus. That may be right, but it means the

mechanism is not identical across regions, and a theory whose principal selling point is that one lesion explains everything has to be careful about acquiring regional sub-mechanisms.

Depression correlated *inversely* with pathway components. The authors flag this as unexpected and suggest apathy as the confound — greater disease severity reducing the affective response to one's own deficits. That is plausible, and it is the sort of thing a cross-sectional postmortem design cannot settle.

8. April 2026: The Theory Acquires a Fluid

8.1 MECP2-pS423

The most recent development, and the reason this is a useful moment to revisit the programme, appeared in *Acta Neuropathologica* in April 2026 (Liu et al., 2026). It is led by Qing-Rong Liu rather than Ramsden, who is senior author, and it moves the work into territory none of the previous papers occupied.

MECP2 is the methyl-CpG-binding protein mutated in Rett syndrome — a global epigenetic repressor. In mice, activity-dependent phosphorylation at Ser421 permits translocation out of the nucleus, relieving repression and activating neurotrophin expression. Mecp2-pS421 rises in the neuronal soma of APP/PS1 mice, and ablating Mecp2 increases GSK3β activity — which is the link to tau, since GSK3β is the kinase at the heart of the ApoER2–Dab1 story. Whether the corresponding human site, Ser423, does anything in Alzheimer's disease was unknown.

The group made an antibody specific to MECP2-pS423 and a quantitative selective-reaction-monitoring assay on LC-MS/MS, and applied both to human brain, cerebrospinal fluid and serum.

8.2 What it shows

In postmortem cortex and hippocampus, MECP2-pS423 rose across the clinicopathological spectrum and correlated with histological progression and cognitive deficit. At the cellular level it colocalised with phosphorylated tau in granulovacuolar degeneration bodies and in neuritic plaques — the same two lesions where the ApoER2–Dab1 components land. Levels rose in cerebrospinal fluid and in serum from patients clinically diagnosed with Alzheimer's disease before death. And a primate-specific, N-terminally truncated MECP2-E3 isoform transcript was increased in the middle temporal gyrus of Alzheimer cases.

8.3 Why this matters more than it looks

Three reasons.

It is a measurement, in blood, derived from a mechanism. The Alzheimer's biomarker field has converged on plasma p-tau217 and related assays, which are superb diagnostics and are agnostic about mechanism — they measure the pathology everyone already agrees on. A

serum marker derived from a specific causal model is a different kind of object: if the model is right, it is a target-engagement readout, and target-engagement readouts are what the programme has conspicuously lacked. The National Institutes of Health has filed a patent application on mechanism-based biomarkers with Ramsden named as an inventor, which is disclosed in the 2023 paper and indicates this was the intended trajectory some time ago.

It supplies a route out of postmortem tissue. Every criticism in Section 11.1 turns on the cross-sectional character of autopsy material. A fluid measurement can be taken twice in the same person. It converts an untestable ordering claim into a testable one.

It nominates a mechanism for a phenomenon the pathway model does not otherwise reach. If MECP2 phosphorylation relieves epigenetic repression, and if MECP2 loss raises GSK3β activity, then the model acquires a transcriptional arm — a way in which the same kinase node changes what the neuron *transcribes*, not merely what it phosphorylates.

8.4 And why it strains the theory

The same result creates two problems.

The first is scope. MECP2-pS423 is not an ApoER2–Dab1 pathway component. Its connection to the framework runs through GSK3β, which is a node shared by dozens of signalling pathways and is among the least specific kinases one could nominate. A theory that began as a claim about a covalent modification at one receptor interface has, over six years, accreted a cytoskeletal arm, a synaptic arm, a lipid-delivery arm, an amyloid arm, a neuropsychiatric arm, and now an epigenetic arm. Each addition is individually reasonable. Cumulatively, the framework's capacity to accommodate new findings is beginning to outrun its capacity to exclude them, and a model that explains everything is on its way to explaining nothing. The paper's own framing — a "promising mechanism-based biomarker and potential therapeutic target" — describes a marker of disease severity as much as a marker of this mechanism.

The second is the granulovacuolar body, and it is the sharper problem. MECP2-pS423 colocalises with tau in granulovacuolar degeneration bodies. So do pP85α, pLIMK1 and pPSD95. So — from a large independent literature — do casein kinase 1δ, phosphorylated PKR, phosphorylated eIF2α, phosphorylated TDP-43, and components of the necrosome. Granulovacuolar bodies are, functionally, a compartment where phosphorylated proteins destined for degradation accumulate when degradation fails. Finding one more phosphoprotein in them is not strong evidence that the protein's pathway is causally upstream. Section 11.5 develops this as the central objection to the programme.

9. The Other Half: A Career Spent Lowering the Substrate

9.1 Where he came from

It would be possible to assess the Alzheimer's work in isolation. It would also be a mistake, because the dietary programme is not a separate career that happens to share an author — it is the source of the theory's central intuition and, potentially, its only near-term intervention.

The intuition is that the peroxidisable lipid load of human tissue is not a fixed biological constant. It is partly a dietary variable, it has changed enormously within living memory, and it can be changed back. Blasbalg and colleagues, with Ramsden as an author, documented the scale of the twentieth-century shift in American intake of omega-6 and omega-3 fatty acids (Blasbalg et al., 2011). The recovered-data re-analyses of the Sydney Diet Heart Study and the Minnesota Coronary Experiment (Ramsden et al., 2013; Ramsden et al., 2016) established that raising linoleic acid intake in the name of cholesterol lowering did not, in those trials, lower mortality. And the mechanistic work established that lowering dietary linoleic acid measurably lowers circulating bioactive oxidised linoleic acid metabolites in humans (Ramsden et al., 2012).

That last result is the crucial one for present purposes, and it is easy to skip past. It establishes that the *substrate for peroxidation is dose-responsive to diet in human beings*. Whatever else is uncertain, this part is not.

9.2 The diet as an instrument

The high-omega-3, low-omega-6 diet — H3-L6 — is a controlled-feeding intervention that has been through methodological development, protocol publication, and multiple randomised trials. In chronic migraine it reduced headache days and improved biochemical endpoints (Ramsden et al., 2021, *BMJ*). In persistent post-traumatic headache among 122 service members it reduced headache days per month by 2.1 and average daily intensity by 0.9 points relative to control, and raised circulating 17-hydroxy-DHA, though it did not significantly improve the Headache Impact Test score (Zamora et al., 2025).

The relevance to Alzheimer's disease is that this is a deliverable intervention against the exact variable the theory nominates as pathogenic, held by the same investigator who proposes the theory. Very few theories of Alzheimer's onset are accompanied by a validated human intervention against their own postulated upstream cause.

9.3 The trial that has not been run

And yet no trial of this diet against any cognitive or Alzheimer-biomarker endpoint appears in the published record. The dietary programme's endpoints remain headache, pain, mood and lipid mediators. The Alzheimer's programme's endpoints remain tissue and, now, fluid. The two halves have not been joined.

There are respectable reasons. Prevention trials in cognition require thousands of participants and years of follow-up; controlled feeding at that scale is nearly impossible; and until 2026 the programme had no biomarker with which to run a short mechanistic trial instead of a long clinical one. That last constraint has just been removed, which makes the gap more conspicuous than it was a year ago.

There is also a genuine scientific complication, and it is the sharpest unexamined tension in the whole framework. The H3-L6 diet lowers linoleic acid — an omega-6 with two double bonds — and raises EPA and DHA. DHA has six double bonds and is the single most peroxidisable fatty acid in human biology. On the theory's own logic, raising brain DHA raises the substrate for exactly the reaction the theory says causes the disease. The 2025 disulfide paper supplies a partial answer — DHA-containing plasmalogens are what *induce* the protective disulfide conformational change in ApoE3 and ApoE2 — but that answer only holds for people who have a cysteine to work with. In an *APOE4* homozygote, on this model, DHA is substrate without shield.

The theory therefore contains an unstated and clinically consequential prediction: that the cognitive effect of high-dose DHA supplementation should differ by *APOE* genotype, and could be null or adverse in *APOE4* homozygotes. Section 12.3 takes this up, because there is now a trial that bears on it.

10. The Convergence: What Arrived Without Him

The most important thing that has happened to this theory in the last two years was not done by its author. Between 2022 and 2026, five independent lines of work — genetic, structural, cell-biological and neuropathological — arrived at positions that either corroborate the framework's premises or occupy the same ground from a different direction. This section sets them out, because taken together they change the standing of the theory more than any of its own papers do.

10.1 The genetics came to the pathway

In 2022, Bracher-Smith and colleagues performed a whole-genome analysis restricted to *APOE4* homozygotes in UK Biobank — 5,390 individuals, 288 cases and 5,102 controls — asking what modifies risk within the highest-risk genotype (Bracher-Smith et al., 2022). One novel genome-wide significant locus emerged: *DAB1* (rs112437613, odds ratio 2.28, 95% CI 1.73–3.01, $p = 5.4 \times 10\text{-}9$). Pathway analysis then implicated the *DAB1–RELN* pathway itself, suggesting epistasis between the *APOE* locus and this pathway. No *APOE*-locus SNP was associated with disease within the *ε4ε4* stratum, which is what one would expect once that variable is held constant.

This is an independent, hypothesis-free, human genetic result naming the exact adaptor protein at the centre of the framework, and naming it as an *APOE4*-conditional modifier — which is precisely the interaction structure the theory predicts, since the theory holds that ApoE4 disables the same pathway from the ligand side.

10.2 A protective variant of Reelin

In 2023, Lopera and colleagues reported a member of the Colombian *PSEN1*-E280A kindred who remained cognitively intact far beyond the kindred's median age of onset, developing mild dementia only at 72 (Lopera et al., 2023). He carried a heterozygous variant in *RELN* — H3447R, named COLBOS — described as gain-of-function, with an enhanced ability to activate Dab1 and to reduce tau phosphorylation. His brain carried a very high amyloid burden with strikingly limited entorhinal tau.

Set beside the *APOE3*-Christchurch case reported four years earlier from the same kindred (Arboleda-Velasquez et al., 2019), the pattern is remarkable: the two best-documented instances of human resistance to autosomal-dominant Alzheimer's disease both involve variants in ligands of ApoER2 and VLDLR, and in both the phenotype is amyloid preserved, tau suppressed, cognition spared. This is the strongest human evidence anywhere that the Reelin–ApoE-receptor axis sits

causally upstream of tau — and it arrived from a kindred study with no connection to the peroxidation framework.

10.3 The cell biology came to the lipid — three laboratories, three directions

The decisive development is more recent and more complicated, because it is simultaneously the strongest corroboration the framework has received and a direct challenge to one of its arms.

In January 2025, Guo and colleagues published a large study in *Cell*, from Denali Therapeutics with David Holtzman (Guo et al., 2025). Its findings: impaired LDL-receptor binding by lipidated ApoE2 avoids the receptor-recycling defects seen with lipidated ApoE3 and ApoE4, and decreases uptake of cholesteryl esters. In human neurons, ApoE particles carrying polyunsaturated-fatty-acid cholesteryl esters produced an allelic series — ApoE4 > ApoE3 > ApoE2 — for lipofuscinosis, an age-related lysosomal pathology that *is a product of lipid peroxidation*. Lipofuscin increased lysosomal accumulation of tau fibrils. Injecting PUFA-cholesteryl-ester-loaded ApoE4 particles into the hippocampus of wild-type mice was sufficient to induce lipofuscinosis. And the protective Christchurch mutation also reduced receptor binding and phenocopied ApoE2.

Their conclusion: decreased lipidated-ApoE–receptor interaction lowers Alzheimer risk by reducing the endolysosomal delivery of ApoE and its pathogenic lipids.

Then, in December 2025, Ralhan and colleagues at Alberta published in *Neuron* (Ralhan et al., 2026). Their finding: ApoE2 and ApoE3-Christchurch particles protect neurons from ferroptosis by *extracting oxidised unsaturated lipids* out of the neuron through the ABCA7 transporter, while ApoE4 particles exacerbate the effects of those lipids and produce endolysosomal dysfunction. Reducing the oxidised-lipid burden with ApoE2 or ApoE3Ch particles rescued endolysosomal function and restored neuronal activity defects. ABCA7 is itself one of the best-established non-*APOE* Alzheimer risk genes.

Set the three accounts side by side.

Table 1 — Three accounts of the same lesion.

	Ramsden (2025)	Guo et al. (2025)	Ralhan et al. (2026)
Pathogenic entity	Peroxidised PUFA-phospholipid on the ApoE particle	PUFA-cholesteryl ester delivered into the lysosome	Oxidised unsaturated lipid retained in the neuron
Why E2/E3Ch protect	Disulfide bridges conceal the cargo in transit	Reduced receptor binding: less lipid delivered	Enhanced efflux of oxidised lipid via ABCA7
Direction of traffic	Neither — protection is in transit	Inward delivery is the lesion	Outward export is the protection
Failure compartment	Endosome (receptor cannot release, cannot recycle)	Lysosome (lipofuscinosis)	Endolysosome
Principal evidence	Human postmortem tissue; recombinant protein	Human neurons; mouse; structural	Neurons; ferroptosis assays
Allelic series	E2 > E3 > E4	E2 > E3 > E4	E2, E3Ch > E4

Three laboratories, three methods, three mechanisms — and near-complete agreement on the two things that matter most: the pathogenic entity is peroxidisable polyunsaturated lipid carried by ApoE, and the failure is endolysosomal. Six years ago that premise was heterodox. It is now, on the evidence, close to being the field's working position on what *APOE* actually does.

The disagreement is about direction, and it is not a small one. Ramsden's model holds that impaired ApoE-receptor-mediated *delivery* of lipid is one of the four arms of the disease. Guo's model holds that reduced delivery is the *mechanism of protection*, and a separate preprint from May 2026 reports engineered LDL-receptor ligand-binding-module peptides designed to competitively *block* ApoE4 endocytosis as a therapeutic strategy. Two programmes are pointing in opposite directions on the same receptor.

To be fair to the framework, this tension is more apparent than it first appears, and the 2025 paper anticipates part of it. On Ramsden's account the poison is the peroxidised particle, and the receptor is the surface it poisons; reducing engagement with a poisoned ligand would be protective on his model too. The two protective *APOE* variants — E2 with its Arg158Cys substitution, and Christchurch with Arg136Ser — are both poor receptor binders, and both are protective; the third protective variant, Reelin-COLBOS, is a *better* receptor activator, and is also protective. The pattern across all three is coherent if one reads ApoE as the ligand you want less of at this receptor and Reelin as the ligand you want more of. That is a defensible position, and it is arguably a cleaner statement of the theory than the "impaired lipid delivery" arm the framework has carried since 2020.

But it is not the position the framework states. The published model still lists impaired lipoprotein internalisation as one of four pathogenic arms. If Guo and Ralhan are right, that arm is not merely wrong but backwards, and the framework would be stronger for dropping it.

10.4 A second laboratory counts the cysteines

In March 2026 — four months ago — Barger and Moerman-Herzog published in *Frontiers in Molecular Neuroscience* a study that reaches the same molecular feature by an entirely different route — a functional assay rather than a structural or neuropathological one — and from a laboratory with no overlap of personnel, institution or method with the Ramsden programme (Barger and Moerman-Herzog, 2026).

Their reasoning: ApoER2 signalling, which uniquely among this receptor family enhances NMDA-receptor activity, depends on the receptor forming dimers or higher-order clusters. The *APOE* alleles differ in the number of cysteines available to form disulfide dimers, and the allele with the highest Alzheimer risk has none. They therefore proposed that lower risk may follow from ApoE's ability to dimerise and thereby promote *receptor* dimerisation and signalling.

They measured NMDA-receptor calcium flux in NTera2-derived neurons exposed to conditioned medium from human astrocytes of differing *APOE* genotype, to recombinant ApoE proteins, to Reelin, to amyloid-β preparations of differing aggregation state, and to secreted APP, with ApoER2 signalling blocked by receptor-associated protein or by siRNA. Reelin, fibrillar amyloid-β, ApoE3 and medium from *APOE* ε*3* astrocytes elevated calcium flux, and the effect required ApoER2. ApoE4 and oligomeric amyloid-β antagonised it. Their conclusion is that the common factor in Alzheimer pathogenesis is antagonism of ApoER2 by agents that cannot promote its dimerisation but competitively inhibit the ligands that can.

Two laboratories, publishing eight months apart, independently identified the cysteine count of ApoE and its capacity to form disulfide bonds as the pivot of *APOE*-related Alzheimer risk, and both routed the consequence through ApoER2. They assign the bond different jobs — Ramsden has it concealing lipid inside the particle; Barger has it clustering the receptor at the membrane — and the two are not mutually exclusive. Independent convergence on an unusual and specific molecular feature is among the more meaningful forms of corroboration available in this field.

It is also worth noting that Barger's functional result puts a number on something Ramsden's tissue work can only infer: ApoE4 does not merely fail to activate ApoER2, it *antagonises* activation. That is the loss-of-signalling premise measured directly, in a cell, with a physiological readout.

10.5 The tissue chemistry came to the raft

In January 2025, Thorwald and colleagues in Caleb Finch's group reported a study of ferroptosis markers in human Alzheimer brain and in ApoE-FAD mice (Thorwald et al., 2025). Alzheimer brains had reduced antioxidant enzymes. Subcellular fractionation showed that oxidative damage was greater, and antioxidant enzyme levels lower, *in lipid rafts* than in non-raft membrane. *APOE ε4* carriers had lower lipid raft yield with greater membrane oxidation. And iron chelation with deferoxamine in the mouse model reduced fibrillar amyloid and lipid peroxidation while raising glutathione-mediated antioxidants.

Two elements of this bear directly on the framework. Lipid peroxidation in Alzheimer brain is not uniformly distributed across the membrane; it is concentrated in the compartment where ApoER2, Dab1, P85α and PSD95 do their signalling — Dab1's phosphotyrosine-binding domain recruits ApoER2–Dab1 complexes to rafts by binding PIP2 and the receptor's cytoplasmic tail simultaneously. And the *APOE4*-associated increase in membrane oxidation, measured directly in human tissue, is the premise the disulfide hypothesis needs.

10.6 What the convergence is worth

A caution is in order. Convergence is not confirmation, and none of these results tests the framework's specific causal claim: that aldehyde-mediated crosslinking of ApoE to ApoER2 is the initiating event. Guo's model runs through cholesteryl esters and the LDL receptor, not phospholipids and ApoER2. Ralhan's runs through ABCA7-mediated efflux. Barger's runs through receptor clustering, not covalent damage. Bracher-Smith's genetics implicates the pathway without saying what disables it.

What the convergence establishes is something more modest and still substantial: the framework's *premises* — that peroxidisable polyunsaturated lipid carried by ApoE is the pathogenic entity, that the *APOE* allelic effect operates through the handling of that lipid, that cysteine and dimerisation are the relevant molecular feature, and that the Reelin–ApoER2–Dab1 axis is causally upstream of tau in humans — have each been independently supported by work that did not set out to support them.

In 2020 those premises were a minority position argued from first principles. In 2026 the argument has moved on from whether ApoE's lipid cargo matters to which direction it is going.

11. Where the Theory Is Weak

11.1 Everything human is cross-sectional

The programme's greatest strength is that its evidence is human brain. Its greatest limitation is the same fact.

Every human study in the series is a cross-section. Cases spanning the clinicopathological spectrum are used to *approximate* a temporal sequence, and the 2023 paper states plainly that such a design cannot establish one. The observation that Dab1 accumulation is extensive in mild cognitive impairment and precedes overt tau in some controls is the strongest ordering evidence available, and it is a comparison between different people, not a sequence within one.

There is no animal work. There is no cell-based test of the central claim. The 2025 hypothesis paper is candid about this, laying out in Sections 3.3 to 3.5 a series of experiments — immunoprecipitation of brain lipoproteins under non-reducing conditions, peroxidation assays comparing ApoE2/E3 multimers with their reduced monomers, treatment of human neurons with peroxidised ApoE4 particles to test for induced tau phosphorylation and amyloid secretion — as things that *should* be done. As of this writing, none is published.

The consequence is that the causal core of the theory has the same status it had in 2020: a chemically demonstrated possibility, an anatomically apt correlation, and no demonstration of occurrence.

11.2 The peroxidation arm has never been closed in a human brain

This deserves separating from the general point because it is the specific missing link.

The framework's initiating event is the covalent joining of ApoE to ApoER2 by a lipid-derived aldehyde. That species has been made in a tube. It has never been found in a person. The 2022 study's human evidence for peroxidised ApoE consists of immunoreactivity with antibodies raised against lipid-aldehyde-modified ApoE — granular structures near plaque cores, partially overlapping native ApoE. Antibody detection of an adducted protein is not identification of a crosslinked heterodimer, and the two claims are not close in strength.

There is a striking asymmetry here. The programme has invested enormously in multiplex imaging — six iterative staining rounds, sixty-plus markers, subpixel registration, autofluorescence correction — and comparatively little in mass spectrometry of the species its own model nominates as the first event. The group has clear proteomic capability; the 2026 MECP2 paper is built on a

selective-reaction-monitoring LC-MS/MS assay. The tool exists. The experiment has not been reported.

Until it is, the theory's name for itself — a lipid-peroxidation theory — describes the part of it that is least demonstrated in humans. Almost everything the human data actually shows would survive intact if the trigger for ApoER2–Dab1 disruption turned out to be something else entirely: Reelin depletion, amyloid-mediated Reelin sequestration, injury-induced ApoE hypersecretion competing Reelin off the receptor. The 2023 paper lists all three as alternative triggers.

11.3 The dimer premise is thinner than the argument built on it

As noted in Section 6.6, the claim that ApoE3 and ApoE2 exist substantially as disulfide-linked dimers and multimers in human brain rests principally on Elliott et al. (2010). The 2025 experiments show that recombinant ApoE3 and ApoE2 can be driven to dimerise by brain-enriched polyunsaturated phospholipids in vitro, which is a real result and a necessary one, but it does not establish in vivo abundance, and it does not establish that dimerisation produces the conformational concealment the model requires. The paper says as much.

The concealment claim in particular is currently an inference from a chemical capacity, not a structural observation. Nobody has shown that a disulfide-linked ApoE3 dimer buries its polyunsaturated cargo more deeply than an ApoE4 monomer does, nor that the buried cargo peroxidises more slowly. That is a two-experiment question and it sits at the foundation of the genetic arm.

11.4 The antibody problem

Nearly the entire human evidence base is phospho-specific and conformation-specific antibodies applied to formalin-fixed paraffin-embedded tissue. The markers are pP85α-Tyr607, pLIMK1-Thr508, pPSD95-Thr19, pDab1-Tyr220, pTau-Ser202/Thr205, MECP2-pS423, and antibodies raised against lipid-aldehyde-modified ApoE.

The group's validation is better than average — antibodies previously used in human FFPE tissue, negative controls with pre-immune serum and primary omission, positive controls in confirmed cases, RNA–protein co-detection, and automated Western blotting against lysates from cells transfected to overexpress the human targets. This is conscientious.

It does not eliminate the problem, which is that several of these epitopes are unusual, that phospho-epitope preservation in fixed human tissue is notoriously variable, and that no independent laboratory has reproduced the core co-accumulation findings with orthogonal methods. Quantitative phosphoproteomics of microdissected entorhinal layer II across Braak stages would settle in one experiment what a decade of immunostaining cannot.

11.5 The granulovacuolar objection

This is, in my judgment, the strongest single objection to the programme, and it applies to the co-accumulation result on which the four-arm argument depends.

The argument runs: five proteins spanning all four arms of the pathway accumulate together in the same neurons; therefore the pathway is disrupted. But look at where they accumulate. pP85α and pLIMK1 accumulate in "intraneuronal vacuolar structures reminiscent of GVDs." pPSD95 accumulates in vacuolar structures. MECP2-pS423 colocalises with tau in granulovacuolar degeneration bodies. Much of the signal is in one compartment.

Granulovacuolar degeneration bodies are autophagic-lysosomal structures that sequester a long and heterogeneous list of phosphorylated proteins — casein kinase 1δ, phosphorylated PKR, phosphorylated eIF2α, phosphorylated TDP-43, necrosome components — in neurons under proteostatic stress. Their contents index a failure of degradation, not membership of a pathway.

So there are two readings of the same data. On the pathway reading, these five proteins co-accumulate because one upstream lesion disabled the cascade they all belong to. On the compartment reading, they co-accumulate because they are phosphoproteins in neurons whose degradative machinery has failed, and any five phosphoproteins would have done.

The compartment reading also explains the correlations with Braak stage and cognition, since granulovacuolar burden itself tracks both. It would even explain the anatomical specificity, since the vulnerable neurons are the ones that develop granulovacuolar degeneration.

Three things in the data argue against the deflationary reading, and they are worth stating because the objection is not decisive. Dab1 is not a phosphoprotein marker — it is total Dab1 protein, and its accumulation has an independent mechanistic rationale in the proteasomal-degradation literature. Much of the Dab1 and tau signal is in dystrophic dendrites and neuritic plaques, not in granulovacuolar bodies. And the anatomical map of ApoER2 expression is entirely independent of this issue; it would stand even if every co-accumulation result were reinterpreted.

But the objection has not been addressed in print, and the obvious control has not been reported: stain the same sections for phosphoproteins that are *not* in this pathway and are known to enter granulovacuolar bodies, and show that the ApoER2–Dab1 components behave differently. Without that control, the co-accumulation result carries considerably less weight than the papers assign it.

11.6 Delivery and signalling pull in opposite directions

Section 10.3 set this out from the outside; it is worth stating as an internal problem.

The framework asserts two lesions at once: too little ApoE-mediated lipid *delivery* (arm four), and too little Reelin-mediated *signalling* (arms one to three). These imply opposite therapeutic directions at the same receptor. Improving lipid delivery means more ApoE engagement with ApoER2. Restoring Reelin signalling means less ApoE competing for it, since ApoE and Reelin compete for the same receptor — a point the 2023 paper itself makes when nominating injury-induced ApoE hypersecretion as a plausible trigger for pathway disruption.

The human genetics resolves the tension in one direction, and not the framework's. Both protective *APOE* variants bind the receptor poorly. The protective *RELN* variant activates the receptor strongly. The consistent story is: less ApoE at this receptor, more Reelin. Arm four, as stated, sits against that.

11.7 The amyloid-as-antioxidant claim

The least supported element of the 2020 formulation is the proposal that amyloid-β is secreted as a protective antioxidant to neutralise peroxidised ApoE particles, and that plaques and gliosis are initially protective. The supporting evidence assembled in the submission is real but circumstantial: amyloid-β is a lipid-soluble antioxidant and metal chelator at physiological concentration; BACE1 is a stress-response protein; oxidised LDL promotes amyloid oligomerisation in an experimental system. The submission concedes that no evidence links peroxidation of ApoE-enriched lipoproteins to amyloid oligomerisation.

The clinical prediction that followed — that lowering amyloid could be neutral or counterproductive because it removes a protective antioxidant — is the most falsifiable claim the framework has made, and it is under pressure. Lecanemab and donanemab both slowed clinical decline in early Alzheimer's disease (van Dyck et al., 2023; Sims et al., 2023). The effects are small, the harms real, and reasonable people disagree about their clinical meaningfulness; but the direction is positive, not neutral and not adverse. A prediction of "neutral or counterproductive" is not refuted by a small benefit, but it is not vindicated either, and a framework that had predicted the sign correctly would be entitled to more credit than this one can claim.

The later papers quietly de-emphasise the protective-amyloid claim in favour of a different and better-supported one: that Dab1 serves as an adaptor for both ApoER2 and amyloid precursor protein, that ApoER2–Dab1 signalling regulates APP cleavage in model systems, and that Dab1 accumulating in dystrophic axons around plaques may therefore link pathway disruption to amyloid production. That is a mechanistic claim about where amyloid comes from, not a teleological claim about what it is for, and it is on much firmer ground.

12. Predictions on the Record

A theory's seriousness can be measured by whether it has committed itself in advance to results it does not control. This one has, three times.

12.1 APOE2 gene therapy in APOE4 homozygotes

The 2025 disulfide paper makes an explicit prediction about a trial already running. It holds that delivering *APOE2* should benefit *APOE3* homozygotes, by allowing newly generated ApoE2 to form lipid-protecting disulfide bridges with existing ApoE3. But in *APOE4* homozygotes, who have no cysteine, no ApoE2–ApoE4 complexes can form, and the intervention is predicted to give "only modest or no benefit."

The relevant trial is LX1001, an AAVrh10 gene therapy delivering *APOE2* into the central nervous system — and it is being conducted exclusively in *APOE4* homozygotes. Fifteen participants with mild cognitive impairment or mild-to-moderate dementia were dosed across four ascending cohorts. Interim data reported at the Clinical Trials on Alzheimer's Disease conference in October 2024 showed dose- and time-dependent increases in cerebrospinal-fluid ApoE2, no amyloid-related imaging abnormalities, and reported improvements in tau biomarkers. These results were presented in conference and corporate communications and have not, at the time of writing, appeared in a peer-reviewed publication; they should be weighted accordingly.

This is an uncomfortable early signal for the prediction, and it is worth being precise about why the prediction is vulnerable. ApoE2 has two cysteines. It can form ApoE2–ApoE2 homodimers and multimers regardless of what the host's endogenous ApoE4 is doing. The model's reasoning requires that the therapeutic benefit come from *heteromeric* ApoE2–ApoE4 complexes, which cannot form — but the model's own protective mechanism, concealment of cargo within disulfide-linked particles, should operate on newly generated ApoE2 particles on their own. The prediction may therefore be under-specified rather than wrong. Either way, a Phase 1/2 biomarker signal in fifteen patients settles nothing, and the fuller data will be informative.

12.2 Anti-amyloid therapy

Discussed in Section 11.7. The 2020 prediction of neutral-to-counterproductive effects from amyloid lowering has not been borne out in direction, though the magnitude of benefit is small enough that the framework is not embarrassed by it. Status: not vindicated; not refuted.

12.3 DHA in APOE4 carriers

This is the sharpest prediction implicit in the framework, and the one its author has said least about.

If DHA is the most peroxidisable lipid in the brain, and if the disulfide bridges that conceal it are absent in ApoE4, then raising brain DHA in an *APOE4* homozygote increases substrate without increasing protection. The framework implies a genotype-by-treatment interaction for omega-3 supplementation, with least benefit — possibly harm — in *APOE4* homozygotes.

The relevant trial is PreventE4, which randomised cognitively unimpaired individuals aged 55 to 80 to two grams of DHA daily or placebo for two years, with the explicit aims of testing whether *APOE ε4* carriage impairs brain DHA delivery and whether high-dose DHA affects imaging biomarkers and cognition (Yassine et al., 2023). Only the baseline findings have been published in full (Yassine et al., 2023); the outcome results were first presented at the Clinical Trials on Alzheimer's Disease meeting in October 2024 and are, at the time of writing, known principally from conference reporting. As reported, treatment raised the cerebrospinal-fluid DHA-to-arachidonic-acid ratio, raised brain DHA in *APOE4* carriers, and higher DHA was associated with better cognitive scores. Attrition was substantial — roughly sixty per cent completed, with COVID-era dropout — so the trial is under-powered relative to design.

The earlier and larger question mark comes from Quinn and colleagues' 2010 trial, which found no benefit of DHA supplementation on cognitive decline in established Alzheimer's disease, with epidemiological signals of benefit concentrated in *APOE4* non-carriers (Quinn et al., 2010).

The framework should say something here and does not. The interaction it implies is testable, clinically consequential, and would be an unusually specific prediction to have on the record. Its absence from the published work is the most conspicuous omission in an otherwise unusually explicit programme.

Table 2 — Predictions on the record and their present status.

Prediction	Source	Test now running	Status
APOE2 gene therapy gives little benefit in APOE4 homozygotes	Ramsden et al., 2025	LX1001 Phase 1/2 (n=15, APOE4/4 only)	Early biomarker data run against it; prediction may be under-specified
Amyloid lowering neutral or counterproductive	2020 submission	Lecanemab, donanemab Phase 3	Direction not borne out; magnitude small; neither vindicated nor refuted
Interventions lowering lipoprotein peroxidation give larger benefit in APOE4 carriers	Ramsden et al., 2025	None	Untested
Omega-3 benefit should interact with APOE genotype	Implied, not stated	PreventE4 (n=365, under-powered by attrition)	Framework has not committed; trial reports carrier benefit
Peroxidised ApoE–ApoER2 crosslinks exist in human brain	Ramsden et al., 2022	None published	The decisive open experiment

13. Grading the Evidence

Each claim below is graded on the evidence available as of August 2026. **Established** means demonstrated directly, in human material or by direct experiment, and independently corroborated. **Supported** means demonstrated directly but not independently replicated, or replicated only in model systems. **Inferred** means extrapolated from model systems or from correlational human data. **Assumed** means required by the framework and not demonstrated.

Table 3 — Graded evidence ledger.

Claim	Principal evidence	Grade
Reactive lipid aldehydes adduct ApoE and ApoER2 lysine/histidine motifs and crosslink ligand to receptor	LC-MS, TOF-MS, Western; sequence-specific controls (Ramsden et al., 2022); prior crosslinking of ApoE by peroxidation products (Montine et al., 1996)	Established (in vitro)
Aldehyde crosslinks are acid-resistant at lysosomal pH	Direct pH-reversibility experiments (Ramsden et al., 2022)	Established (in vitro)
ApoER2 expression in human brain maps onto the anatomy of early neurofibrillary vulnerability, and VLDLR and LRP1 do not	*In situ* hybridisation plus IHC across five regions, 64 cases, three brain banks (Ramsden et al., 2023)	Established
Lipid peroxidation is increased early in Alzheimer's disease	Longstanding independent literature (Markesbery et al., 2005); raft-localised oxidation with APOE4 effect (Thorwald et al., 2025)	Established
The APOE allelic effect operates through handling of peroxidisable polyunsaturated lipid	Three independent laboratories, three methods, same allelic series (Ramsden et al., 2025; Guo et al., 2025; Ralhan et al., 2026)	Established
Multiple ApoER2–Dab1 components co-accumulate in the same neurons and neurites across affected regions	Multiplex IHC, 64 + 32 cases; correlations with Braak stage, amyloid load, MMSE (Ramsden et al., 2023, 2025b)	Supported
Dab1 accumulation indexes local failure of Reelin–ApoER2 signalling	Rodent and cell evidence for Reelin-induced proteasomal Dab1 degradation (Bock et al., 2004), applied to human tissue	Inferred

Claim	Principal evidence	Grade
The Reelin–ApoER2–Dab1 axis is causally upstream of tau phosphorylation in humans	RELN-COLBOS resistance case (Lopera et al., 2023); DAB1 locus in APOE4 homozygotes (Bracher-Smith et al., 2022); rodent mechanism (Hiesberger et al., 1999)	Supported
ApoE cysteine content and disulfide-linked dimerisation are the pivot of APOE-related risk	Recombinant dimerisation experiments (Ramsden et al., 2025); independent functional convergence (Barger and Moerman-Herzog, 2026); human brain dimer distribution (Elliott et al., 2010)	Supported
Disulfide-linked ApoE dimers/multimers conceal cargo and slow its peroxidation	No direct structural or kinetic demonstration	Assumed
Disulfide-linked ApoE–ApoJ$_2$ and ApoE–ApoD heteromers exist in human brain	Proposed; experiment specified but not reported	Assumed
Peroxidised ApoE–ApoER2 crosslinked complexes are present in human brain at pathogenic abundance	Antibody immunoreactivity only; no mass-spectrometric identification	Assumed
ApoER2–Dab1 disruption precedes and causes tau pathology rather than accompanying it	Cross-sectional ordering only; Dab1 preceding tau in some cases	Inferred
pTau is locally produced at each site rather than propagated	Multi-component co-accumulation; three anatomical arguments against connectome spread (Ramsden et al., 2023)	Supported
Amyloid-β is secreted as a protective antioxidant against peroxidised ApoE	Circumstantial; contrary direction of anti-amyloid trial results	Assumed
Dietary lipid composition modifies the substrate for peroxidation in humans	Randomised controlled feeding trials with biochemical endpoints (Ramsden et al., 2012, 2021; Zamora et al., 2025)	Established
Dietary modification of that substrate alters cognitive or Alzheimer-biomarker outcomes	No trial	Untested

14. What Would Settle It: Six Experiments

The framework is unusually amenable to decisive tests, because its central claim is about a chemical species that either exists in human tissue or does not.

1. Find the crosslink. Immunoprecipitate ApoE from frozen human brain — Alzheimer cases and controls, stratified by *APOE* genotype — under strictly non-reducing conditions, and interrogate the pulled-down material by mass spectrometry for covalent ApoE–ApoER2 species and for aldehyde adducts on the receptor-binding motif. This is the experiment the theory has needed since 2020 and the one whose absence most limits it. A positive result would move the initiating event from Assumed to Established in a single paper. A well-powered negative result would confine the framework to being a theory of ApoER2–Dab1 disruption with an unknown trigger — which would still be a substantial theory, but a different one.

2. Show the concealment. Generate ApoE2, ApoE3 and ApoE4 lipoparticles with brain-enriched polyunsaturated phospholipids under non-reducing conditions; subject them to controlled oxidative stress; quantify peroxidation products. Then repeat with the ApoE2 and ApoE3 particles reduced to monomers. The model predicts a gradient E2 < E3 < E4 that collapses on reduction. This is a two-condition experiment and it is the foundation of the entire genetic arm.

3. Run the granulovacuolar control. On the same sections already stained, add phosphoproteins known to enter granulovacuolar bodies and having no relation to this pathway — casein kinase 1δ, phospho-eIF2α, phospho-PKR. If the ApoER2–Dab1 components are quantitatively and spatially distinguishable from them, the co-accumulation argument is secured. If they are not, the four-arm result requires substantial reinterpretation.

4. Test recycling with peroxidised ligand. Repeat the endosomal-acidification rescue of ApoER2 recycling using ApoE4 particles that have been peroxidised, against non-peroxidised controls. The conformational account predicts rescue in both; the covalent account predicts failure of rescue in the peroxidised condition. One experiment, two theories, opposite predictions.

5. Take the marker forward in living people. With MECP2-pS423 measurable in serum, test whether it rises before tau positron-emission tomography converts, whether it differs by *APOE* genotype, and whether it responds to any intervention that alters lipid peroxidation. Any of these converts a cross-sectional programme into a longitudinal one.

6. Join the two halves of the career. Run the H3-L6 diet, or another intervention that demonstrably lowers lipoprotein peroxidation, in a mechanistic trial stratified by *APOE* genotype,

with the fluid marker as primary endpoint. This is now feasible in a way it was not before April 2026, it is far smaller than a prevention trial, and it would test both the framework's therapeutic prediction and the unstated DHA interaction at once.

15. What This Is a Theory Of

It is tempting to file this work under "the lipid peroxidation hypothesis of Alzheimer's disease" and leave it there. That would be a mistake, because the label names the part of the theory that is least demonstrated in humans and misses what the programme has actually established.

Strip away the trigger, and what remains is an argument about an interface.

The claim is that the human brain has a molecular junction where an unusual number of things meet: a lipoprotein carrying the most oxidisable cargo in the body; a receptor whose binding chemistry is lysine chemistry, which is precisely the chemistry that products of lipid oxidation destroy; a second ligand, Reelin, competing for the same site and carrying a signal that suppresses tau phosphorylation, stabilises actin, and holds the postsynaptic density together; and an adaptor, Dab1, that is consumed by successful signalling and therefore accumulates when signalling fails. This junction is not everywhere. It is concentrated, in the human brain, in entorhinal layer II, in the prosubiculum–CA1 border, in scattered deep pyramids, and in the locus coeruleus. Which is to say: it is concentrated exactly where the disease starts.

That is the finding. Whatever breaks the junction — aldehyde crosslinking, Reelin depletion, amyloid sequestering Reelin, ApoE hypersecretion after injury outcompeting it — the consequences run the same way, because the four arms hang from one receptor. The framework is best read not as a theory of lipid peroxidation but as a theory of *where the human brain is thin*: a claim that Alzheimer's disease is what happens when one particular receptor–ligand interface, unusually loaded and unusually distributed, stops working.

Read that way, three things about the programme make more sense.

It explains why the anatomical result is stronger than the chemical one. The map does not depend on knowing what breaks the junction. It only depends on the junction being there, and it is.

It explains why the convergence described in Section 10 is meaningful even though nobody else is testing the crosslink. Guo, Ralhan and Barger disagree with Ramsden about the direction of lipid traffic and about the job the disulfide bond does. All four agree that what matters about *APOE* is what it does with oxidisable lipid at a receptor. That is the shared claim, and it is his earliest one.

And it explains the theory's peculiar therapeutic silence. A theory of an interface does not hand you a drug. It hands you a list of ways an interface can fail and a demand that you find out which one is happening. That is why six years of work have produced a biomarker and no compound, and why the programme's most valuable near-term output may be an assay rather than a therapy.

There is a last observation worth making, about what kind of scientific object this is.

Almost every major theory of Alzheimer's disease was built in a mouse. This one was built in human tissue, from cases autopsied within three hours of death, and has never been taken into an animal — partly by choice, partly because the animal available carries only the ancestral, cysteine-free allele and therefore cannot exhibit the mechanism at issue. That decision has cost the programme the causal demonstration it needs. It has also given it something the mouse-built theories do not have: everything it claims about the human brain, it has actually seen in one.

The bond ApoE4 cannot make is a small thing — one sulfur atom, absent at position 112, and another at 158. Whether the absence of that bond is the beginning of Alzheimer's disease is not yet known. But the question is now a chemical question with a chemical answer, asked of human tissue, and it is answerable. That is more than most theories in this field can say.

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