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Evaluating the Lipid Peroxidation and ApoER2–Dab1 Disruption Hypothesis in Sporadic Alzheimer's Disease

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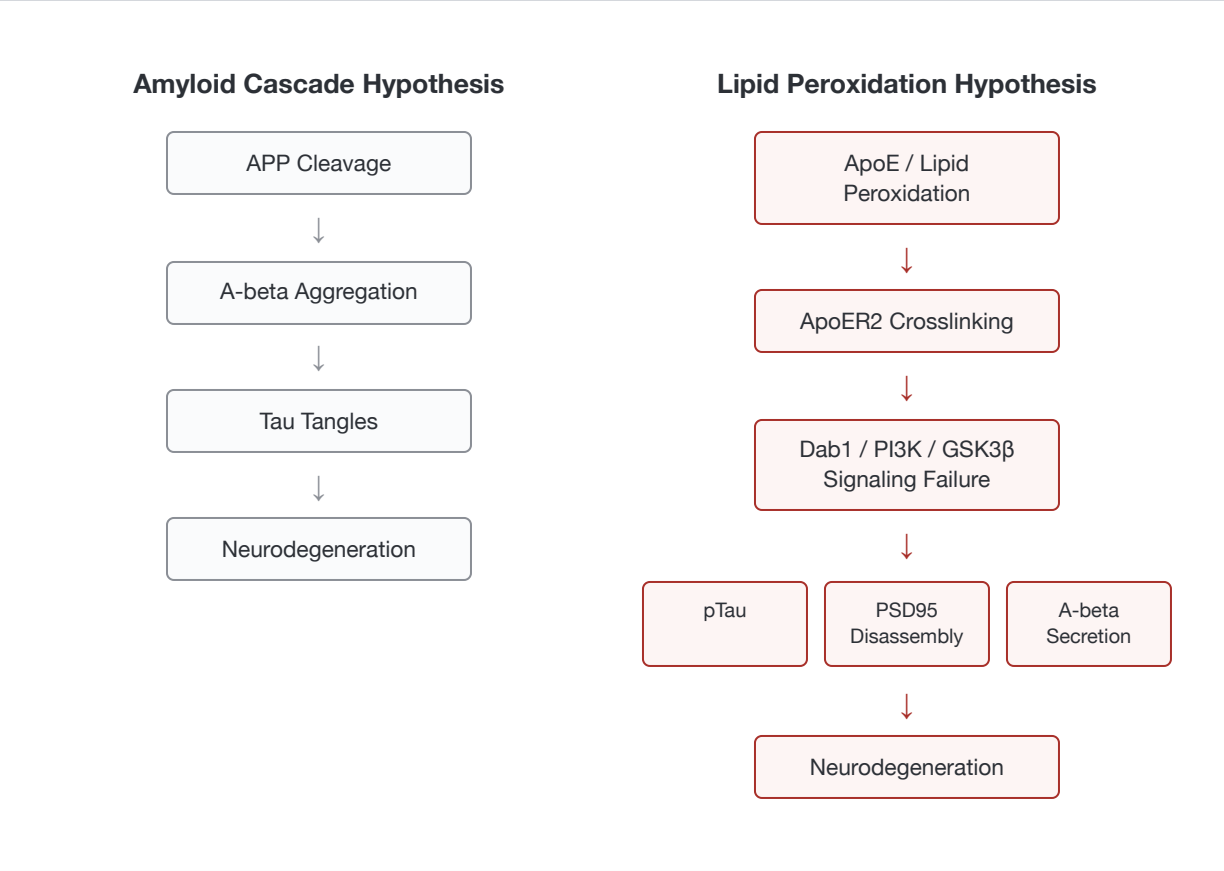
Abstract

Paradigm Shift: Amyloid Cascade vs. Lipid Peroxidation Frameworks



While the traditional Amyloid Cascade posits Aβ accumulation as the primary driver of tauopathy and synaptic loss, the Ramsden hypothesis positions lipid peroxidation and APOE4 structural vulnerabilities as the initiating lesions. In this framework, receptor crosslinking disrupts Dab1 signaling, simultaneously triggering tau hyperphosphorylation, synaptic disassembly, and protective Aβ secretion.

The amyloid cascade hypothesis has dominated Alzheimer's disease (AD) research for decades, yet anti-amyloid therapies have failed to arrest cognitive decline in sporadic Alzheimer's disease (sAD). This analysis evaluates an alternative framework: that sAD is driven by peroxidation of apolipoprotein E (ApoE) and subsequent disruption of the ApoE receptor 2 (ApoER2) and Disabled homolog-1 (Dab1) signaling pathway.[1] The evaluation examines Ramsden and colleagues' hy-

pothesis in light of historical, genetic, biochemical, and histopathological evidence. We assess the claim that the APOE4 allele's inability to form disulfide bonds leaves its polyunsaturated lipid cargo vulnerable to oxidative damage. Downstream peroxidation generates reactive lipid aldehydes that crosslink ApoE to ApoER2, disrupting endosomal recycling. This blockade starves the Reelin–ApoER2–Dab1 cascade, removing inhibition on GSK3β and LIMK1 kinases, which trigger tau hyperphosphorylation and postsynaptic density protein 95 (PSD95) disruption. We evaluate anatomical specificity via multiplex immunohistochemistry and consider whether this framework better explains the spatial evolution of tauopathy than prion-like spread models. We also reassess amyloid-beta (Aβ) as a possible protective response overwhelmed by chronic oxidative stress.

Introduction

Sporadic Alzheimer's disease accounts for the majority of dementia cases globally. Unlike familial Alzheimer's disease, sAD is not causally linked to explicit genetic mutations in AβPP or presenilin. Despite astronomical investment in anti-amyloid therapeutics, these interventions have frequently failed to halt or slow cognitive decline, and in some trials have correlated with accelerated brain atrophy.[1] This persistent therapeutic impasse highlights gaps in the amyloid cascade model. The APOE ε4 allele is the single strongest genetic risk factor for sAD, yet the precise molecular mechanism linking this allele to disease risk remains unclear. The amyloid model also struggles to explain selective anatomical vulnerability of specific neuronal populations — entorhinal cortex layer II and locus coeruleus — to early neurofibrillary tangle formation, or the marked increase in lipid peroxidation that precedes plaque and tangle deposition.

Ramsden and colleagues (2022–2025) have articulated an alternative framework: the ApoE–ApoER2 peroxidation cascade hypothesis.[8] They propose that peroxidation of polyunsaturated fatty acids transported by ApoE serves as an initiating molecular event in sAD. Reactive lipid aldehydes from this peroxidation crosslink ApoE to ApoER2, trapping ApoE in the extracellular space while disrupting intracellular Reelin–ApoER2–Dab1 signaling. This cascade disruption leads to destabilization of cytoskeletal elements and hyperphosphorylation of tau.[1] This analysis evaluates the theoretical coherence, empirical support, and histopathological validity of this framework.

Part I: Historical Context and Research Methods

ApoE Isoform Structural Variance and Lipid Protection Capacity

ISOFORM	TOTAL CYSTEINES	DISULFIDE BRIDGE FORMATION	LIPID PROTECTION STATUS	AD RISK PROFILE
ApoE2	2	Super-ability (multimers)	Concealed & Protected	Protective
ApoE3	1	Intermediate ability (dimers)	Concealed & Protected	Baseline
ApoE4	0	Inability (monomer only)	Exposed to Peroxidation	Highest Risk

The presence of Cysteine residues in ApoE2 and ApoE3 enables the formation of intermolecular disulfide bridges. These multimeric structures conceal and protect vulnerable PUFA cargo. ApoE4, lacking Cysteine entirely, remains monomeric, leaving its lipid cargo exposed to severe peroxidation.

The Historical Record

Oskar Fischer's 1907 pathological study of 16 cases of senile dementia identified and characterized extracellular neuritic plaques in 12 patients. Fischer recognized these structures as disease-specific morphological substrates, arguing that plaques accounted for the clinical signs of dementia. This contrasted with earlier researchers who viewed plaques as byproducts of aging.

Fischer's contributions were marginalized through academic rivalry with the Munich school, which secured nomenclatural precedence for Alois Alzheimer's case presentation. Fischer's focus on senile dementia and plaques was sidelined in favor of Alzheimer's emphasis on tangles and early-onset cases.

Fischer was stripped of his academic positions, arrested by the Gestapo, and perished in Theresienstadt in 1942. His historiographical rehabilitation, initiated primarily by Michel Goedert in 2009, is relevant to current discourse: recent multiplex immunohistochemistry shows that neuritic plaques are the locus where peroxidized ApoE, sequestered Reelin, and disrupted ApoER2–Dab1 components co-accumulate.

Early Recognition of Oxidative Stress

Following biochemical sequencing of Aβ and tau in the 1980s, the amyloid cascade hypothesis achieved dominant status. However, dissenting researchers continuously highlighted unexplained phenomena: Markesbery, Butterfield, and colleagues demonstrated in the late 1990s and early 2000s that lipid peroxidation precedes overt plaque and tangle deposition, particularly in patients with amnestic mild cognitive impairment.[1] The human brain is uniquely susceptible to lipid peroxi-

dation due to high oxygen consumption, modest antioxidant defenses, and dense concentrations of polyunsaturated fatty acids (arachidonic acid, docosahexaenoic acid). Peroxidation of these PUFAs generates reactive electrophilic aldehydes: 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA), and acrolein. These aldehydes covalently modify proteins by targeting histidine, lysine, and cysteine residues.

Crucially, Montine et al. (1997) observed that accumulation of 4-HNE adducts in the AD brain correlated with APOE4 inheritance, providing an early bridge between genetic risk and oxidative damage.

Research Methodology

Evaluation of the hypothesis relies on multiplex fluorescence immunohistochemistry (MP-IHC), developed by Maric and colleagues, which permits sequential probing of dozens of biomarkers on a single 6-micron tissue section. Traditional single-marker immunohistochemistry allows visualization of only 3–4 biomarkers, forcing researchers to use serial slices to infer co-localization. MP-IHC overcomes this limitation through iterative rounds of immunostaining, multispectral imaging, computational registration at subpixel resolution, and antibody stripping.

Empirical data assessed here derive from heavily vetted postmortem cohorts (Banner Sun Health Research Institute, University of Auckland, University of Kentucky). Specimens were procured via rapid-autopsy protocols with mean postmortem intervals of approximately 3 hours. Minimal formaldehyde fixation (48 hours) and rapid procurement preserve phosphorylation states of kinases under investigation.

Part II: Molecular Mechanism

ApoE Structure and the Lipid-Protecting Disulfide Bridge Hypothesis

ApoE is the principal lipid transporter in the central nervous system, synthesized primarily by astrocytes. It traffics cholesterol and polyunsaturated phospholipids to neurons for membrane maintenance and dendritic spine remodeling.

Humans possess three major APOE alleles — ε2, ε3, ε4 — differing by one or two amino acids at positions 112 and 158. APOE4 carriers face dose-dependent increased risk of sAD, while APOE2 is considered neuroprotective. The precise mechanistic linkage between these single amino acid substitutions and neurodegenerative risk remained unclear.

In 2025, Ramsden, Cutler, Li, and Keyes proposed a biochemical explanation: the "lipid-protecting disulfide bridge" hypothesis. The amino acid substitutions involve cysteine-arginine exchanges.

ApoE2 contains two cysteines (Cys112, Cys158); ApoE3 contains one (Cys112); ApoE4 contains none, possessing arginines at both positions.

Cysteine's free thiol group enables formation of covalent intermolecular disulfide bridges.[10] Independent research confirms that ApoE2 and ApoE3 form disulfide-linked homodimers, multimers, and heterodimers in cerebrospinal fluid and brain parenchyma. ApoE4, lacking cysteines, cannot form these bridges and exists as a monomer.

Ramsden's hypothesis proposes that disulfide-linked complexes shield polyunsaturated fatty acid cargo within a tightly packed hydrophobic core, protecting reactive carbon-carbon double bonds from reactive oxygen species. ApoE4, unable to dimerize, leaves PUFA cargo structurally exposed. In the aged brain's oxidative environment, this cargo undergoes accelerated peroxidation, decomposing into toxic electrophilic aldehydes (MDA, 4-HNE, acrolein).

Biochemical Crosslinking at the Receptor Interface

Neurons internalize ApoE and lipids primarily via the low-density lipoprotein receptor family, specifically Very-Low-Density Lipoprotein Receptor (VLDLR) and ApoE Receptor 2 (ApoER2). These receptors are positioned at the postsynaptic density and serve dual functions: lipid internalization and transmembrane signaling for Reelin.[1] Reelin is an extracellular glycoprotein secreted by specialized interneurons and projection neurons, essential for synaptic plasticity, dendritic spine formation, and memory consolidation.[1] The interface where both ApoE and Reelin bind to ApoER2 presents biochemical vulnerability. The ligand-binding domains of human ApoER2 are enriched in double-lysine motifs and histidine residues. These differ significantly from rodent models, potentially explaining why transgenic mice often fail to replicate human sAD pathology without artificial overexpression.

Lysine and histidine are primary targets for reactive lipid aldehydes. In vitro analyses show that exposure of ApoE and ApoER2 peptides to these aldehydes generates irreversible lipid-protein adducts.[1] More critically, bifunctional aldehydes act as chemical bridges, forming covalent, acid-stable pyrrole crosslinks between lysine and histidine residues of ApoE and ApoER2.

Intracellular Cascade Disruption

Under normal conditions, the ApoE–ApoER2 complex is rapidly internalized into the early endosome.[1] Within the acidic environment (pH ~6.0), the receptor undergoes conformational change that releases the ligand, and empty ApoER2 recycles back to the cell surface.

Aldehyde-induced pyrrole crosslinks between peroxidized ApoE and ApoER2 are stable in low pH environments. Consequently, the ApoE–ApoER2 complex becomes permanently fused, disrupting the pH-dependent dissociation process. This arrests receptor recycling and traps receptors within enlarged endolysosomal compartments — an established early pathological hallmark of sAD.[1]

With receptors sequestered and the synaptic surface depleted of functional ApoER2, Reelin is blocked from binding. The downstream intracellular cascade collapses.

Kinase Cascade Consequences

Under healthy conditions, Reelin binding to ApoER2 triggers rapid tyrosine phosphorylation of the intracellular adaptor protein Disabled homolog-1 (Dab1) via Src and Fyn kinases.[1] This propagates the signal and simultaneously targets Dab1 for rapid ubiquitination and proteasomal degradation, providing negative feedback.

When peroxidized ApoE crosslinks and occludes ApoER2, Reelin signaling is entirely blocked. Because Dab1 degradation depends on active Reelin signaling, Dab1 aberrantly accumulates within dystrophic neurites. High-resolution MP-IHC studies show massive, globular Dab1 accumulations near neuritic plaques, serving as a biochemical marker of ApoER2 signaling failure.

Phosphorylated Dab1 normally recruits phosphoinositide 3-kinase (PI3K), specifically its regulatory subunit P85α, which activates Protein Kinase B (Akt). This PI3K/Akt pathway inhibits Glycogen Synthase Kinase 3 beta (GSK3β). Concurrently, Reelin–Dab1 signaling activates LIM domain kinase 1 (LIMK1), which phosphorylates cofilin, stabilizing the dendritic actin cytoskeleton and maintaining dendritic spine structure.

The starvation of this pathway removes essential molecular brakes. Failure to activate LIMK1 disrupts cofilin regulation, leading to collapse of dendritic actin cytoskeleton and formation of actin-cofilin rods. Simultaneously, without Akt-mediated inhibition, GSK3β becomes hyperactive, aggressively hyperphosphorylating tau at multiple epitopes (Ser202/Thr205), causing tau detachment from microtubules, microtubule depolymerization, axonal transport failure, and aggregation into neurofibrillary tangles.

Hyperactive GSK3β also phosphorylates postsynaptic density protein 95 (PSD95) at Threonine-19. PSD95 is the master scaffolding protein of the excitatory postsynaptic density, anchoring NMDA and AMPA receptors. Phosphorylation at Thr19 induces disassembly and internalization of excitatory postsynaptic receptor complexes, driving synaptic depression and memory loss.

Position within the HMS+P architecture. The ApoE–ApoER2–Dab1 mechanism described above is, in the language of the cross-axis synthesis (*Templated Misfolding as the Fourth Substrate*, May 2026), the molecular arm of the **lipid availability gate** articulated in HMSP §4.8. The HMSP synthesis identifies brain lipid availability as a cross-cutting gate on the four HMS+P substrates (Homeostatic microglia, Matrix/PNN, Synaptic complement-pruning, and templated Propagation), with APOE genotype as the upstream variable that sets the gate threshold. The Ramsden cascade — APOE4-specific failure of disulfide-bridge protection → PUFA peroxidation → ApoE–ApoER2 pyrrole crosslinking → Dab1/PI3K/GSK3β starvation → tau hyperphosphorylation and PSD95 disassembly — is the most thoroughly characterized molecular instantiation of that gate. The Ramsden hypothesis and the HMS+P gate are not competing accounts; they are, respectively, the molecular-level and substrate-level descriptions of the same upstream variable. The APOE3-Christchurch (R136S) resilience case discussed in HMSP §4.8 is, on this reading, the in-vivo experiment of nature that confirms the Ramsden mechanism: dampening APOE binding to LRP1/LDLR dampens the downstream cascade enough to confer cognitive resilience even against autosomal-dominant disease burden.

Part III: Anatomical Specificity and Disease Evolution

Limitations of the Prion-Like Spread Model

The "prion-like spread" hypothesis argues that pathogenic, misfolded tau originates in a single location and propagates trans-synaptically across connected brain networks. However, this model has logical deficits when mapped against human neuroanatomy:

- Tau pathology reliably spreads from the entorhinal cortex to the CA1 region while sparing the dentate gyrus granule cells for years, despite the dentate gyrus being the massive, direct synaptic target of the entorhinal cortex's perforant pathway.
- Early pTau pathology classically originates in the locus coeruleus before appearing in the entorhinal cortex. Yet locus coeruleus axons project diffusely across virtually the entire neuroaxis; they do not selectively innervate the entorhinal cortex.
- Early pTau pathology frequently isolates in distal dendritic tips of rare, solitary layer III and V neocortical pyramidal neurons, completely sparing immediately adjacent, heavily interconnected neurons — difficult to reconcile with broad synaptic diffusion.

Localized Vulnerability via ApoER2 Expression

The ApoER2–Dab1 disruption hypothesis offers an alternative explanation: tau is locally generated within specific, disparate neurons independently driven into signaling failure.[1] Their vulnerability is determined by: (1) exceptionally high expression of ApoER2, and (2) intense, continuous metabolic demand for lipid-membrane remodeling.[1] Using high-resolution MP-IHC, Ramsden's team mapped ApoER2 expression across 64 rapidly autopsied human brains spanning the spectrum of sAD. ApoER2 is highly expressed in the exact anatomical regions exhibiting earliest pTau pathology:

- Stellate neurons of entorhinal cortex layer II
- ProS-CA1 border region of the hippocampus
- Pontine locus coeruleus and raphe nucleus
- Solitary layer III/V neocortical pyramids

Recent preprints (2024/2025) demonstrate similar ApoER2–Dab1 disruption in the amygdala, correlating with neuropsychiatric manifestations.

REGION	APOER2 EXPRESSION	TAU ONSET	PRION-SPREAD COMPATIBILITY
Locus Coeruleus	Extremely High	Pre-tangle (earliest)	Low (diffuse projections)
ErC Layer II	Extremely High	Braak Stage I	Low (retrograde to flow)
ProS-CA1 Border	High	Braak Stage II	Low (spares adjacent neurons)
Dentate Granule Cells	Low / Moderate	Braak V/VI (late)	Low (direct target, spared early)
Neocortical L3/L5	High (apical tufts)	Braak I/II	Low (spares neighbors)
Neocortical L4	Absent	Spared	High (resistance predicted)

Crucially, MP-IHC shows that pTau does not appear in isolation. In mild cognitive impairment and sAD brains, pTau co-accumulates within ApoER2-expressing neurons alongside undegraded Dab1, phosphorylated P85α, and phospho-LIMK1. This co-accumulation of stalled signaling kinases provides evidence that the Reelin–ApoER2–Dab1 pathway has suffered upstream blockade, triggering local rather than transmitted neurodegeneration.

Part IV: Extracellular Consequences and Amyloid-Beta Reappraisal

Extracellular Accumulation and Plaque Formation

MP-IHC imaging of human sAD tissue reveals that ApoER2 ligands — native ApoE, lipid-peroxidation-modified ApoE (HNE-ApoE), ApoJ, and Reelin — accumulate in the extracellular space.[1] Because crosslinked ApoE–ApoER2 complexes cannot be internalized and processed by endolysosomal machinery, these peroxidized toxic lipoproteins build up within the synaptic cleft, forming the dense cores of neuritic plaques identified by Fischer a century ago.

Reconsidering Amyloid-Beta

Rather than acting as the pathological initiator of disease, Aβ secretion may initially serve as a protective physiological response.[1] At physiological (sub-nanomolar) concentrations, Aβ acts as a lipid-soluble antioxidant and transition metal chelator. BACE1, the rate-limiting enzyme in AβPP cleavage producing Aβ, is a stress-response protein upregulated by oxidative stress and lipid peroxidation.[1] Ramsden hypothesizes that as peroxidized ApoE particles accumulate extracellularly due to receptor failure, neurons upregulate BACE1 to secrete Aβ monomers to bind, chelate, and neutralize toxic, oxidized lipid cargo, preparing it for glial clearance.[1] This model explains why ApoE is consistently enriched in the central core of newly formed Aβ plaques, with Aβ forming the surrounding corona.

However, under chronic, unrelenting oxidative assault — exacerbated by absent disulfide-bridge protection in APOE4 carriers — this protective mechanism becomes overwhelmed. High Aβ concentrations overcome solubility limits, oligomerize, form insoluble plaques, trigger microglial and astrocytic inflammatory responses, and transition from neuroprotective antioxidants to neurotoxic aggregates.

Therapeutic Implications

This framework accounts for the failure of billions of dollars invested in clinical trials using monoclonal antibodies to clear Aβ. If Aβ is being secreted to neutralize toxic peroxidized lipids, forcefully removing amyloid without addressing underlying lipid peroxidation strips the brain of its final compensatory antioxidant defense, leaving synapses exposed to unchecked oxidative destruction and potentially accelerating atrophy.

Future therapeutic pipelines should prioritize stabilization of the Reelin–ApoER2–Dab1 signaling axis and mitigation of lipid peroxidation rather than amyloid clearance. Potential interventions include:

- Development of targeted ApoER2 agonists to bypass occluded receptors and restart the Dab1–PI3K survival cascade

- Deployment of lipid-soluble antioxidant scavengers designed to quench reactive aldehydes (4-HNE, acrolein) before irreversible pyrrole crosslinks form
- Advanced gene-editing therapeutics to restore disulfide-bridge functionality in APOE4 carriers

> **Convergence with the HMS+P combinatorial regimen.** The HMS+P synthesis (§5) specifies that no monotherapy targeting any single substrate will produce durable benefit in late-onset disease, and that a substrate-aware combinatorial regimen must include at least one arm operating on the lipid/APOE gate — by isoform-selective APOE modulation, by selective blockade of the propagation-relevant LRP1 interactions while preserving the clearance- and lipid-delivery interactions, or by upstream restoration of astrocyte-derived lipid supply. The three Ramsden-framework interventions enumerated above correspond, in HMS+P language, to direct interventions on the lipid availability gate. They are necessary but, on the HMS+P account, not sufficient: a successful regimen must additionally engage the H substrate (homeostatic microglial restoration), the M substrate (matrix stabilization), the S substrate (complement-pathway restraint), and the P substrate (propagation blockade). The Ramsden framework is therefore a necessary component of an HMS+P-architected regimen rather than an alternative to one.

What This Analysis Cannot Determine

Causal versus correlative relationships: While MP-IHC demonstrates co-accumulation of pathway components, proving that ApoER2 occlusion directly causes (rather than correlates with) downstream kinase activation requires additional evidence. Cross-sectional autopsy data cannot establish directionality of causation without in vivo or experimental validation.

Initiating event timing: The hypothesis proposes lipid peroxidation as the initiating event, but the analysis relies on postmortem tissue from symptomatic or already-pathological brains. Whether peroxidation actually precedes detectable pathway disruption in living tissue cannot be determined from this data alone.

APOE4-specific vulnerability in homozygotes vs. heterozygotes: The disulfide bridge hypothesis explains why APOE4 lacks protective crosslinking, but the analysis does not fully account for dose-dependent effects or why some APOE4 heterozygotes remain cognitively intact into advanced age.

Role of glial clearance systems: The hypothesis assumes that peroxidized lipids accumulating extracellularly drive the cascade, but the capacity and limitations of astrocytic and microglial clearance of HNE-ApoE and other lipid aldehydes remain incompletely characterized.

Reversibility and therapeutic windows: The hypothesis frames several molecular events as "irreversible" (pyrrole crosslinks, receptor trafficking arrest), but whether these are thermodynamically irreversible or merely require extreme cellular conditions to reverse is not established. The clinical therapeutic window — if interventions target lipid peroxidation before crosslink formation versus after — remains unknown.

Human-specific factors vs. model organism limitations: While the analysis notes that human ApoER2 LA1-2 domains differ from rodents and may explain why transgenic models fail, a direct, mechanistic explanation for species-level differences in disulfide bridge formation and protective capacity is not provided.

Aβ monomer function in vivo: The reappraisal of Aβ as initially protective relies partly on in vitro antioxidant data and BACE1 stress-response upregulation. Whether Aβ monomers at physiological concentrations actually neutralize lipid aldehydes in the synaptic environment, and whether this function is adequate before plaque formation, requires direct evidence.

Alternative mechanisms for selective neuronal vulnerability: While ApoER2 expression correlates with early tau pathology, the analysis does not exclude other factors — such as neuronal morphology, synaptic connectivity density, metabolic state, or protective capacity of local glial environments — as contributors to regional selectivity.

Conclusion

The lipid peroxidation and ApoER2–Dab1 disruption hypothesis integrates historical neuropathology, genetic risk, biochemical mechanisms, and anatomical specificity in a coherent framework. The APOE4 allele's structural inability to form disulfide bridges leaves its lipid cargo exposed to accelerated peroxidation. Reactive lipid aldehydes crosslink ApoE to ApoER2, disrupting receptor recycling and starving the Reelin–Dab1 pathway. This starvation removes inhibition on GSK3β and LIMK1, directly triggering tau hyperphosphorylation and synaptic disassembly in vulnerable neurons.

The hypothesis explains selective anatomical vulnerability through differential ApoER2 expression rather than prion-like spread, and reframes Aβ as a protective response to lipid toxicity that becomes overwhelmed under chronic oxidative stress.

The framework accounts for features the amyloid cascade model failed to explain. However, it remains an integrative hypothesis requiring validation through in vivo studies demonstrating that lipid peroxidation precedes pathway disruption in living tissue, intervention studies showing that targeting peroxidation or receptor function arrests cognitive decline, and mechanistic studies clarifying the full pathway from ApoE crosslinking through kinase activation to synaptic disassembly.

Read alongside the HMS+P cross-axis synthesis, the Ramsden framework occupies a specific and load-bearing position: it is the molecular instantiation of the lipid availability gate (HMSP §4.8) on which the four HMS+P substrates collectively depend. Abandoning the singular focus on amyloid clearance in favor of addressing lipid peroxidation and receptor signaling represents a necessary shift in therapeutic strategy, contingent on further empirical support for the causal claims this framework proposes, and is the gate-arm of a combinatorial regimen that must additionally engage the homeostatic, matrix, synaptic, and propagation substrates.

Works Cited

1. Lipid Peroxidation Induced ApoE Receptor-Ligand Disruption as a Unifying Hypothesis Underlying Sporadic Alzheimer's Disease in Humans. *PMC9268955*, accessed March 30, 2026. *https://pmc.ncbi.nlm.nih.gov/articles/PMC9268955/*

2. 2025 Alzheimer's disease facts and figures. *PMC12040760*, accessed March 30, 2026. *https://pmc.ncbi.nlm.nih.gov/articles/PMC12040760/*

3. Alzheimer's Disease and Frontotemporal Dementia: A Review of Pathophysiology and Therapeutic Approaches. *PMC12087441*, accessed March 30, 2026. *https://pmc.ncbi.nlm.nih.gov/articles/PMC12087441/*

4. Recent Advances in Therapeutics for the Treatment of Alzheimer's Disease. *MDPI 1420-3049/29/21/5131*, accessed March 30, 2026.

5. Global Diseases Deserve Global Solutions: Alzheimer's Disease. *MDPI 2035-8377/17/6/92*, accessed March 30, 2026.

6. Ferroptosis and Alzheimer's disease: a new insight into neurodegeneration. *Frontiers in Immunology*, 10.3389/fimmu.2026.1767/full, accessed March 30, 2026.

7. Lipid-protecting disulfide bridges are the missing molecular link between ApoE4 and sporadic Alzheimer's disease in humans. *bioRxiv 2025.01.17.633633v1*, accessed March 30, 2026.

8. Ramsden et al. Lipid-protecting disulfide bridges hypothesis. *PMC11761642*, accessed March 30, 2026.

9. HYPOTHESIS: Lipid-protecting disulfide bridges are the missing molecular link between ApoE4 and sporadic Alzheimer's disease in humans. *PubMed 40209641*, accessed March 30, 2026.

10. THE ROLE OF MICROGLIAL-TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS 2 (TREM2) IN NEURONAL HOMEOSTASIS AND TAU PATHOGENESIS. *IU Indianapolis ScholarWorks*, accessed March 30, 2026.

11. Prague: What Say You, Alois — Should It Be "Alzheimer-Fischer" Disease? *ALZFORUM*, accessed March 30, 2026.

12. Oskar Fischer and the study of dementia. *PMC2668940*, accessed March 30, 2026.

13. Alzheimer's Disease: The Challenge of the Second Century. *PMC3130546*, accessed March 30, 2026.

14. Neuroscience in Nazi Europe Part III: Victims of the Third Reich. *Cambridge University Press / AOP volume 68D, 745132DCB804BDEA5517217355*, accessed March 30, 2026.

15. Gustav Oppenheim (1882–1937) and the Discovery of Cerebral Amyloid Angiopathy. *ResearchGate 380583696*, accessed March 30, 2026.

16. ApoER2–Dab1 disruption as the origin of pTau-associated neurodegeneration in sporadic Alzheimer's disease. *PMC10720169*, accessed March 30, 2026.

17. Assessment of Lipid Peroxidation in Alzheimer's Disease Differential Diagnosis and Prognosis. *MDPI 2076-3921/11/3/551*, accessed March 30, 2026.

18. Evidence for ApoE receptor 2-Disabled homolog-1 pathway disruption in the amygdala in sporadic Alzheimer's disease. *medRxiv 2025.06.13.25329511v1.full-text*, accessed March 30, 2026.

19. Apolipoprotein E imbalance in the cerebrospinal fluid of Alzheimer's disease patients. *PMC9628034*, accessed March 30, 2026.

20. Apolipoprotein-E forms dimers in human frontal cortex and hippocampus. *ResearchGate 41507312*, accessed March 30, 2026.

21. The Lipocalin Apolipoprotein D Functional Portrait: A Systematic Review. *Frontiers in Physiology*, 10.3389/fphys.2021.738991/full, accessed March 30, 2026.

22. Reelin Signaling by the Prime Neurogenic Niche of the Adult Brain. *MDPI 2571-6980/6/4/43*, accessed March 30, 2026.

23. Modeling the β-secretase cleavage site and humanizing amyloid-beta precursor protein in rat and mouse to study Alzheimer's disease. *PMC7574558*, accessed March 30, 2026.

24. Targeting Brain ApoE Receptors for the Treatment of Alzheimer's Disease. *BrightFocus*, accessed March 30, 2026.

25. *Templated Misfolding as the Fourth Substrate: HMS Becomes HMS+P* — Cross-axis synthesis whitepaper, AdultCognitiveDisease.com, May 2026. §4.8 (Lipid Availability and the APOE Modifier) provides the substrate-level frame within which the present molecular analysis is positioned.