THE CASE FOR THE CASCADE

A Steelman of Amyloid Primacy in Alzheimer's Disease

The Genetic Anchor · The Biomarker Order · The Trials
The Refined Cascade · The Predictive Record

A Position Brief Prepared under the Organic Network Synthesis methodology

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A companion counter-brief to The Unified Architecture of Collapse. This corpus repositions amyloid from initiating cause to one node of a wider architecture; a repositioning is honest only if the case it argues past is first stated at full strength. That is the whole task of this document — and it withholds rebuttal by design.

"A theory has not been answered until it has been answered at its strongest. What follows is the case for amyloid, put as its ablest proponents would put it, and left standing."

— ONS Methodology Working Notes, 2026

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Abstract

This is a brief with an unusual discipline: it argues a position the rest of this corpus does not hold, and it argues it at full strength. The Organic Network Synthesis programme repositions amyloid-β from the initiating cause of Alzheimer's disease to one validated node within a temporal, multi-lane architecture. That repositioning is only honest if the case it argues past is first stated as its ablest proponents would state it — not caricatured, not pre-emptively rebutted, not surrounded by the qualifications that make disagreement easy. Accordingly, this document sets out the strongest case for amyloid primacy: the near-dispositive human genetics in which every Mendelian route to the disease converges on a single molecular readout; the biomarker ordering in which amyloid moves first, prospectively, by a decade and more; the second-generation antibody trials in which removing fibrillar amyloid measurably slows clinical decline, converting amyloid from correlate to cause; the refined cascade that absorbs the burden–dementia gap and the resilience data through the soluble-oligomer and necessary-but-not-sufficient reformulations; and the framework's record of risky predictions that came true. Only the final short section marks where this corpus diverges, and it does so with a pointer rather than a refutation. The purpose is not to convert the reader but to establish the position that any competing theory — including this corpus's own — must beat. Amyloid primacy is that position. This brief is why.

On the Purpose of This Brief

A theory has not been answered until it has been answered at its strongest. The failure mode of every integrative or "beyond-amyloid" programme is to win its argument against a weak version of the cascade — the version in which amyloid is claimed to be sufficient, in which plaque count is claimed to equal dementia, in which the negative trials are treated as a clean refutation — and to mistake that victory for a victory over the real thing. The real amyloid cascade hypothesis, as held by its most careful proponents, makes none of those weak claims, and it is considerably harder to move.

This brief therefore performs a single service. It states the case for amyloid primacy in the voice of its best advocates, without the hedges and asides that the rest of this corpus would ordinarily supply, and it withholds rebuttal until a brief closing section that does no more than name where the corpus parts company and where the fuller counter-argument may be found. Within the numbered sections that follow, there are no concessions to the house view. That is deliberate. A steelman with

an escape hatch in every paragraph is not a steelman.

I. The Genetic Argument — The Load-Bearing Case

The strongest evidence for amyloid causality is not a mechanism, a mouse, or a scan. It is human genetics, and it is close to dispositive. Every known genetic route to Alzheimer's disease converges on a single biochemical outcome — an increase in amyloid-β, and specifically in the aggregation-prone Aβ42 species or the Aβ42/40 ratio — and the direction of the effect never reverses.

Autosomal-dominant familial Alzheimer's disease is caused by mutations in three genes: the amyloid precursor protein (APP) and the presenilins PSEN1 and PSEN2. More than three hundred such mutations are known, and they are not scattered in their effect. The APP mutations cluster precisely at the secretase cleavage sites that generate or shape amyloid-β; the presenilin mutations alter the processivity of γ-secretase so as to raise the proportion of longer, more aggregation-prone Aβ species. Hundreds of independent mutations, in three different genes, discovered in unrelated families across the world, converging on one molecular readout, is not the signature of a coincidence. It is the signature of a causal chain, and it was the original and still the firmest basis of the amyloid cascade hypothesis (Goate et al., 1991; Hardy & Higgins, 1992; Selkoe & Hardy, 2016).

The gene-dosage evidence sharpens the argument to a point. A duplication of the APP locus alone — no altered protein, merely an extra wild-type copy — causes autosomal-dominant early-onset Alzheimer's disease with cerebral amyloid angiopathy (Rovelet-Lecrux et al., 2006). More Aβ, from more gene, produces the disease. The same logic is written across Down syndrome: trisomy 21 carries a third copy of APP, and individuals with Down syndrome develop Alzheimer neuropathology at near-universal rates from the fourth decade of life. The decisive control is the rare partial trisomy that spares the APP locus. Prasher and colleagues reported a woman with partial trisomy 21 in whom APP was present in only two copies; at seventy-eight she had no Alzheimer's disease on neuropsychological, imaging, or neuropathological assessment (Prasher et al., 1998). Trisomy of chromosome 21 does not cause Alzheimer's disease; the extra dose of APP does. It is as close to a natural knockout experiment as human neurology offers.

The protective direction completes the proof. The A673T variant in APP reduces β-secretase cleavage of the precursor by roughly forty percent, and its carriers are protected not only against Alzheimer's disease but against ordinary age-related cognitive decline (Jonsson et al., 2012). This is

the amyloid hypothesis read forwards rather than backwards: every pathogenic APP mutation raises amyloid and causes the disease; this one variant lowers amyloid and prevents it, acting at the very same biochemical step in the opposite direction. If the amyloid hypothesis required a single controlled human experiment, A673T is it. And the common-variant genetics now points the same way: APOE4 homozygosity has been reclassified as a near-Mendelian genetic form of Alzheimer's disease, with virtually complete penetrance of the pathology by age seventy-five and a mechanism substantially routed through impaired amyloid clearance (Fortea et al., 2024).

The ledger below states the pattern that no competing theory has matched: across every genetic route into and out of the disease, the arrow runs one way.

Genetic route	Effect on amyloid-β	Phenotype
APP mutations at secretase sites (Swedish, Arctic, London…)	Aβ production or aggregation	Early-onset autosomal-dominant AD
PSEN1 / PSEN2 mutations (>300 known)	Aβ42/40 ratio	Early-onset AD, near-complete penetrance
APP locus duplication	Aβ (extra wild-type copy)	Early-onset AD with amyloid angiopathy
Trisomy 21 with APP triplicated	Aβ (three copies)	Near-universal AD neuropathology by the 40s
Partial trisomy 21 sparing APP (two copies)	Aβ not elevated	No AD at age 78 (Prasher)
APOE4 homozygosity	Aβ (impaired clearance)	Near-Mendelian AD by age 75 (Fortea)
APP A673T (Icelandic)	β-cleavage ~40%	Protection from AD and from normal decline

There is a reason the field's most senior figures return, whenever the hypothesis is challenged, to this same ground. One may debate the mechanism downstream; one cannot get away from the genetics.

II. Temporal Precedence — Amyloid Moves First

A cause must precede its effect, and amyloid does. The biomarker natural history of Alzheimer's disease, assembled over two decades and formalized in the NIA-AA research framework, describes an ordered sequence in which amyloid markers change first: cerebrospinal-fluid Aβ42 begins its decline, and amyloid positron-emission tomography turns positive, some fifteen to twenty years

before the first cognitive symptom — before tau spreads beyond the medial temporal lobe, before measurable neurodegeneration, before the first complaint of forgetfulness (Jack et al., 2018; Villemagne et al., 2013).

The objection that biomarker ordering in sporadic disease is reconstructed after the fact is answered by autosomal-dominant Alzheimer's disease, where onset can be predicted from the family mutation and the sequence can be timed prospectively against it. In the Dominantly Inherited Alzheimer Network, cerebrospinal-fluid Aβ42 changes are detectable approximately twenty-five years before expected symptom onset, amyloid deposition on PET some fifteen years before, with tau-related and neurodegenerative markers and cognitive decline following in a fixed order thereafter (Bateman et al., 2012). This is not a correlation salvaged after the endpoint is known; it is a prospectively staged sequence in which amyloid is first.

The modern form of the argument is more precise still, and more difficult to answer. It does not claim that amyloid directly produces every downstream lesion. It claims that amyloid is the permissive trigger that licenses the spread of tau. Limbic, medial-temporal tau pathology is common in cognitively normal ageing and is, on its own, relatively inert; what converts it into the neocortically spreading, dementia-producing tauopathy of Alzheimer's disease is the presence of amyloid. In amyloid-negative individuals, tau tends to remain confined; in amyloid-positive individuals, it spreads. On this reading amyloid is not the whole disease, but it is the switch that starts it — and the switch is thrown first.

III. The Trials — Removing Amyloid Changes the Disease

For thirty years the amyloid hypothesis rested on genetics and biomarkers, and its critics could fairly say that no one had shown the crucial thing: that removing amyloid changes the course of the disease. That objection is no longer available. Two second-generation monoclonal antibodies that clear fibrillar amyloid have now shown, in large, well-powered, placebo-controlled Phase III trials, that clearing it slows clinical decline. Lecanemab reduced decline on the Clinical Dementia Rating–Sum of Boxes by twenty-seven percent over eighteen months (van Dyck et al., 2023); donanemab produced comparable slowing and cleared amyloid to the point that a majority of treated participants reached amyloid-negativity, with a trial design that let those who cleared fastest stop dosing (Sims et al., 2023).

The magnitude of the clinical effect is genuinely modest, and its proponents do not pretend otherwise. But the modesty of the effect is not the point that matters for causality. The point that matters is directional and it is decisive: a molecule that was merely a bystander — a gravestone, an epiphenomenon, a marker thrown off by some other primary process — would not, when removed, alter the trajectory of the disease at all. Amyloid, when removed, does. That single fact converts amyloid from a correlate of Alzheimer's disease into a cause of it, and it is the strongest new evidence the field has produced in a generation. It is reinforced by the internal dose–response: across these programmes, the degree of clinical benefit tracks the degree of amyloid clearance, which is exactly the relationship a causal agent, and not a passive marker, should show.

Read in this light, the long run of earlier "failures" is not a refutation of the hypothesis but a lesson in how to test it. The antibodies that did not clear fibrillar plaque, the trials that dosed too little or intervened too late in the disease, and the strategies aimed at the wrong amyloid species did not disprove amyloid causality; they mis-specified the target, the stage, or the dose. The antibodies that actually remove fibrillar amyloid, given to patients early enough, are the ones that work — which is precisely what a causal hypothesis predicts and a spurious one does not. The decisive experiments are now under way: the secondary-prevention trials in mutation carriers and in amyloid-positive but cognitively unimpaired individuals test the hypothesis in its purest and most demanding form — remove amyloid before symptoms, and see whether the disease is prevented. Whatever they return, they are the right experiment, and the amyloid hypothesis is the only framework that specified them in advance.

IV. The Refined Cascade Absorbs Its Anomalies

The cascade's critics most often attack a version of it that its serious proponents abandoned years ago. The refined hypothesis, as stated in the field's authoritative modern reviews, does not hold that amyloid is sufficient to cause dementia, nor that plaque burden should correlate with cognitive state (Selkoe & Hardy, 2016; Long & Holtzman, 2019). It holds that amyloid — and in particular soluble Aβ oligomers rather than the insoluble plaque — is the necessary initiating trigger, and that tau is the downstream executioner through which the trigger produces neurodegeneration. Stated this way, the hypothesis absorbs the very anomalies that are said to refute it.

The weak correlation between plaque burden and dementia is not an embarrassment to this version; it is a prediction of it. If the toxic species is the soluble oligomer and not the fibrillar deposit, then counting plaques will measure the wrong thing, and the loose coupling between plaque load and cognition is exactly what one should expect. The resilience data — cognitively intact individuals carrying Alzheimer-range amyloid at autopsy — tell the same story. On the

necessary-but-not-sufficient reading, these are people in whom the trigger is present but the downstream cascade has been disarmed: amyloid has accumulated, but tau propagation, synaptic vulnerability, or the inflammatory response has been held in check. Resilience is thus consistent with amyloid primacy, not evidence against it; it locates the modifiers downstream of amyloid without displacing amyloid from the top.

The interdependence of amyloid and tau, far from diluting the hypothesis, gives it a worked-out molecular spine. Reducing endogenous tau protects neurons against amyloid-β toxicity, demonstrating that amyloid exerts its damage through tau rather than around it (Roberson et al., 2007). The synaptotoxic mechanism of soluble oligomers has been resolved in detail — engagement of the cellular prion protein and metabotropic glutamate receptor 5, activation of Fyn kinase, inhibition of long-term potentiation, and loss of dendritic spines. This is not the hand-waving "amyloid begets tangles begets death" of the caricature. It is a specified pathway from an initiating molecule through a downstream effector to synaptic failure, in which each step has been independently demonstrated.

V. The Predictive Record

The final strength of the amyloid cascade is the one philosophers of science weight most heavily: it made risky predictions before the fact, and they came true. It predicted, when the presenilins were merely genetic loci of unknown function, that they would prove central to amyloid production — and presenilin was subsequently identified as the catalytic core of the γ-secretase that generates Aβ. It predicted the biomarker ordering — amyloid first, then tau, then neurodegeneration, then symptoms — years before the longitudinal cohorts and the dominantly-inherited network confirmed that exact sequence. And it predicted, most riskily of all, that lowering fibrillar amyloid in the brain would slow the clinical disease — a prediction that survived a decade of failed attempts and was finally borne out when antibodies capable of clearing plaque were tested at adequate dose and stage.

A hypothesis that accommodates existing data after the fact is cheap; a hypothesis that says in advance what will be found, and is then found to be right across genetics, biomarkers, and therapeutics, has earned its standing. Whatever its remaining difficulties, the amyloid cascade is not a dogma that survived on inertia. It is a theory that repeatedly stuck its neck out and was repeatedly vindicated, and it remains the only framework in the field with a track record of that kind.

VI. Where This Brief Stops

The foregoing is the case for amyloid primacy stated at its strongest, and it is strong. It is the position any rival account of Alzheimer's disease must beat, and it will not be beaten by rhetoric, by pointing at the modest trial effect sizes, or by treating the plaque as a gravestone. It will be beaten, if at all, only by a framework that accepts every fact above and shows that a different variable does more explanatory work.

This corpus attempts exactly that, and it is worth naming, without arguing here, the three places where it parts company. First, on temporal precedence: the corpus reads the neuropathology of Braak and Del Tredici as placing the earliest detectable lesion not in cortical amyloid but in subcortical, tau-associated pretangle change in the locus coeruleus decades earlier — a first that is upstream of the amyloid-first the biomarkers record. Second, on the trials: it reads a twenty-seven-percent slowing, after amyloid is cleared, as the signature of a necessary node rather than the whole engine — the seventy-three percent of decline that persists being the space the corpus's other lanes are meant to fill. Third, on resilience: it reads the preserved cognition of high-amyloid brains as evidence that the proximate control of dementia lies downstream, in the inhibitory matrix and the microglial state, which become the corpus's chosen targets. Those arguments are developed at length in *The Temporal Architecture of Collapse* and *The Unified Architecture of Collapse*, and they are not rehearsed here.

They are not rehearsed here because the task of this brief was the harder and rarer one. It is easy to state one's own view and gesture at the opposition; it is difficult to put the opposition's case so well that a proponent would sign it, and then to stop. That is what has been attempted. Whatever this corpus concludes about amyloid, it cannot now be said to have argued against a straw man — because the strongest form of the position it argues past is written here, in full, and left standing.

References

Bateman, R. J., Xiong, C., Benzinger, T. L. S., et al. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *New England Journal of Medicine*, 367(9), 795–804. https://doi.org/10.1056/NEJMoa1202753

Fortea, J., Pegueroles, J., Alcolea, D., et al. (2024). APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. *Nature Medicine*, 30(5), 1284–1291. https://doi.org/10.1038/s41591-024-02931-w

Goate, A., Chartier-Harlin, M. C., Mullan, M., et al. (1991). Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*, 349(6311), 704–706. https://doi.org/10.1038/349704a0

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science*, 256(5054), 184–185.

Jack, C. R., Jr., Bennett, D. A., Blennow, K., et al. (2018). NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, 14(4), 535–562.

Jonsson, T., Atwal, J. K., Steinberg, S., et al. (2012). A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature*, 488(7409), 96–99.

Long, J. M., & Holtzman, D. M. (2019). Alzheimer disease: an update on pathobiology and treatment strategies. *Cell*, 179(2), 312–339. https://doi.org/10.1016/j.cell.2019.09.001

Prasher, V. P., Farrer, M. J., Kessling, A. M., et al. (1998). Molecular mapping of Alzheimer-type dementia in Down's syndrome. *Annals of Neurology*, 43(3), 380–383. https://doi.org/10.1002/ana.410430316

Roberson, E. D., Scearce-Levie, K., Palop, J. J., et al. (2007). Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. *Science*, 316(5825), 750–754. https://doi.org/10.1126/science.1141736

Rovelet-Lecrux, A., Hannequin, D., Raux, G., et al. (2006). APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nature Genetics*, 38(1), 24–26. https://doi.org/10.1038/ng1718

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, 8(6), 595–608. https://doi.org/10.15252/emmm.201606210

Sims, J. R., Zimmer, J. A., Evans, C. D., et al. (2023). Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*, 330(6), 512–527. https://doi.org/10.1001/jama.2023.13239

van Dyck, C. H., Swanson, C. J., Aisen, P., et al. (2023). Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*, 388(1), 9–21. https://doi.org/10.1056/NEJMoa2212948

Villemagne, V. L., Burnham, S., Bourgeat, P., et al. (2013). Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurology*, 12(4), 357–367.