# Disciplinary Silos in AD Research, 1950–2020

## *A Bibliometric and Structural Critique*

How Citation Geography, Funding Allocation, and Training Pathways Delayed the Tripartite Thesis by Seventy Years

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## Abstract

Why did the assembly of a tripartite mechanistic thesis for Alzheimer's disease — combining locus-coeruleus / NAD+ bioenergetic vulnerability (Phase I), microglial and oligodendrocyte homeostatic collapse (Phase II), and perineuronal-net / extracellular-matrix erosion (Phase III) — require seventy years, when each of its components had been independently described in the published literature by the mid-1980s? This paper offers a structural, evidence-based answer. Drawing on the Oskar Fischer Prize entrant corpus (151 independent submissions, 135 audited against a 235-mechanism trilogy registry), the synthesis-report convergence finding (25 of 30 entrants converging on lysosomal/v-ATPase failure from seven distinct upstream triggers), the published trilogy-relevance audit, and a wider survey of the AD bibliometric record, we trace the disciplinary geography of three communities — noradrenergic systems neuroscience, glial / immunological neurobiology, and matrix / critical-period plasticity research — and show that they barely intersected with mainstream AD research from 1950 to 2018. Concurrently, the amyloid-cascade community absorbed disproportionate funding, journal pages, and prestige, generating a citation gravity well that distorted the field's epistemic landscape. Our argument is diagnostic, not accusatory. Citation patterns, NIH funding allocations, journal segmentation, and training-pathway separation are presented as the structural conditions under which a real, multi-stream signal could be detected only by 151 independent investigators working outside the consensus and only later assembled into a coherent thesis. The paper closes with counterfactual analysis (the trilogy was assembleable by 2005 had cross-silo dialogue been institutionalised), an estimate of the cumulative cost of delay (~25 million person-years of dementia), and a structural-reform agenda that the Oskar Fischer Prize itself prefigures. The Collapse Trilogy thesis is rare because the conditions for its assembly are rare. Building those conditions deliberately, this paper argues, is the strongest legacy the Fischer Prize program can leave.

**Keywords:** disciplinary silos, bibliometrics, sociology of science, Alzheimer's disease, amyloid cascade, locus coeruleus, microglia, perineuronal nets, Oskar Fischer Prize, citation analysis, NIH funding, science policy.

# Contents

## Note on Method

This paper is structurally and bibliometrically diagnostic, not historiographic in the narrative sense. The methodology proceeds through four registers. *First*, archival reconstruction of NIH RFA priorities and journal review patterns is taken from publicly accessible sources (NIH RePORTER, journal editorial statements, congressional testimony) and from secondary historical accounts (Lock, 2013; Whitehouse & George, 2008; Whitehouse, 2014). *Second*, the Oskar Fischer Prize entrant corpus is treated as a *natural experiment* in distributed inquiry: 151 independent investigators, working without coordination, generated mechanistic hypotheses for AD between 2022 and 2026. The trilogy-relevance audit (Gustafsson, 2026a) classifies 135 of these against a 235-element registry of canonical mechanisms across the three Collapse Trilogy domains (Phase I bioenergetic, Phase II homeostatic, Phase III synaptic). *Third*, the synthesis report (Gustafsson, 2026b) summarises the qualitative finding that twenty-five of thirty graded entrants converge on a shared downstream node — lysosomal acidification failure / v-ATPase disassembly — from seven distinct upstream triggers. *Fourth*, where appropriate we draw on standard bibliometric methods (Bornmann & Daniel, 2008; Mingers & Leydesdorff, 2015) to characterise community structure and citation flow. We make no claim of new empirical bibliometrics; rather, we treat the Fischer corpus as the load-bearing dataset and the secondary literature as scaffolding.

The argument is offered in a diagnostic register. The aim is not to indict individual scientists, programme officers, or journal editors. The aim is to identify the structural features — funding incentives, journal segmentation, training pathways, citation conventions, peer-review norms — that produced and sustained the silos, and to specify reforms that would not require any individual to behave heroically.

# 1. Introduction: Why a Tripartite Thesis Took Seventy Years

The dominant question in the history of Alzheimer's research — historiographically, scientifically, and socially — is not which hypothesis turned out to be correct. It is why the field's center of gravity remained immovable for so long in the face of accumulating contrary evidence. This paper proposes a structural answer: the field's epistemic geography was not a single landscape but an archipelago. The *Collapse Trilogy* thesis (Gustafsson, 2026c, 2026d, 2026e) — synthesising locus-coeruleus (LC) and NAD+ bioenergetic vulnerability (Phase I), microglial / oligodendrocyte homeostatic collapse (Phase II), and perineuronal-net (PNN) and matrix-metalloproteinase (MMP)-mediated synaptic erosion (Phase III) into a single mechanistic picture — was *constructible* from existing literature by the mid-1980s. It was *not constructed* until 2025.

The temporal gap is striking. By 1985, the laboratory had in hand: *(i)* Mann, Yates, and Marcyniuk's morphometric demonstration that LC neurons are catastrophically depleted in AD (Mann, 1983; Bondareff, Mountjoy, & Roth, 1981); *(ii)* the foundational characterisation of microglia as a CNS-resident immune lineage (del Río-Hortega, 1932; Streit, 1995, drawing on a tradition that long predated his synthesis); *(iii)* Brückner, Celio, and others' description of perineuronal nets surrounding parvalbumin interneurons (Celio, 1986); and *(iv)* the autophagy-lysosomal vacuole accumulation phenotype that Suzuki, Terry, and others had documented in AD ultrastructure since the 1960s (Suzuki & Terry, 1967; later Nixon, 2005). Each of these threads, individually, was a candidate structural hypothesis for AD. None was integrated.

This paper asks a single question: *why?*

The answer, we argue, lies in the disciplinary topography of late-twentieth-century neurodegeneration research. The amyloid-cascade hypothesis (Hardy & Higgins, 1992) acted not merely as a scientific proposition but as an organising attractor — a citation gravity well that pulled funding, prestige, journal pages, and trainees into a single explanatory frame, while the rival communities (LC, glial, matrix) remained loosely coupled enclaves whose members rarely sat on each other's grant panels, rarely co-authored, and rarely cited each other's work. This was not conspiracy; it was the predictable equilibrium of a field whose institutions reward

concentration. The Fischer Prize corpus is a natural experiment that demonstrates the consequence: when 151 independent investigators are given permission to ignore the consensus, they converge on a coherent, multi-stream picture that the consensus framework cannot accommodate.

The paper proceeds as follows. Chapter I establishes the amyloid cascade's hegemony as a structural fact. Chapters II–IV map the three silos that the trilogy thesis spans. Chapter V presents the bibliometric core: the Fischer corpus, its citation overlap (or absence thereof), and its convergence on a shared downstream node from seven distinct upstream triggers. Chapter VI argues that this uncoordinated convergence is the strongest possible evidence that the silos were preventing the recognition of a real signal rather than constructing a false one. Chapter VII estimates the cumulative cost. Chapter VIII proposes structural reforms. Chapter IX generalises beyond AD. The Conclusion situates the Oskar Fischer Prize as one prototype of the institutional forms a post-silo field would require.

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## Chapter I. The Amyloid Cascade as Hegemon

### 1.1 The 1992 Inflection Point

Hardy and Higgins published "Alzheimer's Disease: The Amyloid Cascade Hypothesis" in *Science* in April 1992 (Hardy & Higgins, 1992). The paper was eight hundred words. It proposed, on the strength of familial AD genetics (APP mutations linked to early-onset disease), that amyloid-beta deposition is the proximate cause of AD and that all subsequent pathology — tangles, synapse loss, neurodegeneration, dementia — is downstream. The claim was modest in its empirical content (the data cited would not have supported the strong conclusion); the claim was immodest in its programmatic implications. It offered the field something it badly needed: a single causal mechanism, a single therapeutic target, a single biomarker.

The field accepted the offer. Over the following decade, the Hardy–Higgins paper accumulated citations at a rate that no other AD hypothesis paper has matched (Lock, 2013, pp. 71–78). By 2010 it had become the most-cited single paper in AD research history, with downstream amplification through review articles, textbook chapters, and grant introductions whose obligatory opening sentence — "Alzheimer's disease is characterised by the deposition of amyloid-beta…" — established the

cascade as the field's grammatical default. This was not a neutral choice. It systematically forclosed alternatives by constraining what counted as a legitimate research question.

### 1.2 RFAs and the Funding Capture, 1998–2018

The funding record is the most concrete manifestation of the cascade's hegemony. NIH issued a series of Requests for Applications (RFAs) over twenty years that explicitly named amyloid-related mechanisms — APP processing, gamma-secretase, beta-secretase, immunotherapy targeting Abeta, anti-aggregation small molecules — as priority targets (NIH, 1998; NIH, 2003; NIH, 2008; NIH, 2014; reviewed in Whitehouse, 2014; Lock, 2013). Concurrently, *no* RFA in this twenty-year window named the locus coeruleus, NAD+ metabolism, microglial homeostasis, perineuronal nets, oligodendrocyte myelination, or matrix metalloproteinases as a priority target for AD research. (Several such RFAs existed for *other* disorders — MMPs for stroke, PNNs for amblyopia, microglia for HIV-associated neurocognitive disorder — which is a key part of the silo story we develop in Chapters II–IV.)

The dollar magnitude was substantial. Estimates compiled across NIH RePORTER queries indicate that between 2000 and 2018, amyloid-targeted preclinical and clinical research absorbed an order of magnitude more dedicated funding than any of the alternative mechanism categories (Whitehouse, 2014; Schneider, Mangialasche, Andreasen, et al., 2014). This is consistent with the broader historical record: the cascade's hegemony was not merely intellectual but material.

### 1.3 The "Amyloid Mafia" Critique

The phrase "amyloid mafia" appears in print at least as early as the early 2000s (attributed to Whitehouse and to Castellani; see discussion in Lock, 2013, pp. 134–139). It denotes the phenomenon of a small, tightly cited research community whose members repeatedly serve as journal reviewers, grant reviewers, conference organisers, and editorial board members, with the predictable consequence that submissions challenging the cascade encounter elevated rejection rates and submissions extending it encounter elevated acceptance rates (Whitehouse, 2014; Lock, 2013; Castellani, Lee, Zhu, Perry, & Smith, 2009). The critique is not — in its serious form — a conspiracy theory. It is a description of equilibrium dynamics in a field with concentrated peer-review networks.

Whitehouse (2014) catalogued instances in which papers challenging the cascade were rejected at high-impact journals and subsequently published in lower-impact venues, with citation trajectories markedly suppressed compared to comparably rigorous cascade-supporting work. Lock (2013) documented analogous patterns in clinical trial design, where mechanistic biomarker selection (CSF Abeta42, amyloid PET) systematically privileged the cascade as the implicit success criterion: a trial that improved cognition without changing the amyloid biomarker would, under the cascade framework, be classified as a failed disease-modifying trial.

### 1.4 The Negative Trial Sequence

The clinical trial record is the field's most unambiguous datum. Over the period 2002–2020, the cascade hypothesis was tested in human patients through a sequence of high-cost, statistically well-powered Phase III trials targeting amyloid-beta directly:

- **Bapineuzumab** (Salloway et al., 2014): no clinical benefit; halted.
- **Solanezumab** (Doody et al., 2014; Honig et al., 2018): no clinical benefit at primary endpoint; halted in mild-to-moderate AD.
- **Crenezumab** (Salloway et al., 2018): no clinical benefit; halted.
- **Gantenerumab** (Bateman et al., 2022 [DIAN-TU]; Ostrowitzki et al., 2022 [GRADUATE]): no clinical benefit at primary endpoint; halted in sporadic AD.
- **Verubecestat, Atabecestat, Lanabecestat** (Egan et al., 2018; Henley et al., 2019): BACE inhibitors halted for futility or worsening of cognition.

In a Popperian framework, this sequence constitutes falsification. A Phase III negative outcome is the most stringent test the medical sciences can apply; six independent failures across mechanistically distinct anti-amyloid strategies, with biomarker engagement confirmed in most cases, should have prompted serious reconsideration. The field's response was, on the whole, to refine the cascade — earlier intervention, different epitopes, plaque-specific targeting — rather than to question its central premise.

### 1.5 The Lecanemab–Donanemab Apotheosis

The 2022–2024 period brought lecanemab (van Dyck et al., 2023) and donanemab (Sims et al., 2023) to FDA approval on the strength of Phase III trials demonstrating biomarker engagement, plaque clearance, and a statistically significant but clinically modest slowing of cognitive decline (Clinical Dementia Rating–Sum of Boxes change of approximately 0.4–0.7 points on an 18-point scale over 18 months). The drugs carry meaningful safety burdens — amyloid-related imaging abnormalities (ARIA) with edema and microhemorrhages, particularly in *APOE4* homozygotes — and the modest efficacy has prompted debate over clinical meaningfulness (Whitehouse, 2024; Walsh et al., 2024).

We do not argue that lecanemab and donanemab are inert. We argue that the field's celebration of these results as the cascade's vindication illustrates the structural problem this paper concerns. A hypothesis that, after thirty years and tens of billions of dollars, yields drugs that produce a 0.4-point change on an 18-point scale is not vindicated; it is, at best, partially correct on a narrow margin. In any other scientific field, this trajectory would have prompted a serious widening of the explanatory aperture decades earlier. That it did not is the question this paper is built around.

# Chapter II. The Noradrenergic Silo

## 2.1 The Locus Coeruleus Research Program, 1950–2010

The locus coeruleus (LC) is a small bilateral nucleus in the dorsal pons containing approximately 50,000 neurons in the human brain, supplying noradrenergic innervation to nearly the entire neocortex, hippocampus, and cerebellum. Its anatomical reach is unique: a single LC neuron can branch to project to thousands of cortical sites (Foote, Bloom, & Aston-Jones, 1983). LC research developed as a distinct subfield from the 1960s onward, anchored by figures including Floyd Bloom, Stephen Foote, Gary Aston-Jones, Susan Sara, and (later) Mara Mather. Their cumulative output by 2010 had established: *(i)* the LC's role in arousal, attention, and memory consolidation; *(ii)* its remarkable selective vulnerability to neurodegeneration; *(iii)* its noradrenergic suppression of microglial and astrocytic inflammation (Feinstein et al., 2002); and *(iv)* the early appearance of phospho-tau in LC neurons in pre-clinical AD.

The most consequential data came from the Mann–Marcyniuk–Bondareff group: by the early 1980s, postmortem stereology had established that LC cell loss in clinical AD was on the order of 40–70%, far exceeding the loss in most cortical regions (Mann, 1983; Bondareff et al., 1981; Iversen, Rossor, Reynolds, et al., 1983). This was widely cited within the noradrenergic and aging communities, but it did not migrate into the mainstream AD literature in any sustained way. The mainstream remained hippocampus-centric, organised around the medial temporal lobe pathology that aligned with the cascade-derived focus on Abeta deposition and tangles in entorhinal and hippocampal neurons.

## 2.2 Braak & Del Tredici 2011: The Paper That Should Have Ended Hippocampus-Centrism

Braak and Del Tredici (2011) published, in *Acta Neuropathologica*, a stereological reanalysis of pre-clinical AD brains demonstrating that the *earliest* identifiable phospho-tau pathology (preceding any cortical involvement) appears in LC neurons. The implication was structural: the disease process begins in the brainstem, ascends through the basal forebrain, and only later involves the medial temporal lobe and neocortex. The hippocampus, on this account, is a midstream target, not the origin.

This paper should have reorganised the field. It did not. Citation analysis indicates that, while the paper accumulated respectable citations within the neuropathology and noradrenergic communities, it was rarely cited in cascade-framed reviews and rarely featured in the introductory framing of AD grants over the period 2011–2018. By 2018, a small but growing literature was beginning to cite Braak & Del Tredici 2011 as a foundational citation (Mather & Harley, 2016; Weinshenker, 2018), but the structural reorganisation it implied had not occurred.

The reasons are partly disciplinary. Braak & Del Tredici's argument required familiarity with brainstem neuroanatomy, with the literature on LC vulnerability, and with the staging conventions of the Braak group itself — knowledge largely absent from the training pathways of cascade-framed cortical biologists. The paper was, in a sense, written in a different scientific dialect.

### 2.3 Mather, Sara, Aston-Jones: Citations Out of the Mainstream

Mather and Harley (2016) reviewed the LC's role in cognitive aging, arguing that LC integrity should be considered a primary determinant of resilience to AD. Sara (2009) reviewed the LC's role in memory consolidation, with implications for the noradrenergic deficits in AD. Aston-Jones and Cohen (2005) provided the foundational integration of LC function in attention and adaptive gain. None of these reviews is rare; all are well-cited. The bibliometric anomaly is the citation *direction*: these papers are heavily cited within the systems-neuroscience and cognitive-neuroscience communities and are sparsely cited within mainstream AD review literature.

This is the signature of a silo. The information existed; the channels did not.

### 2.4 NAD+ and the Bioenergetic Stream

A parallel literature on NAD+ metabolism, sirtuins, and CD38 developed within metabolic and aging biology, almost entirely outside AD research. Verdin (2015), Lautrup, Sinclair, Mattson, and Fang (2019), Camacho-Pereira et al. (2016), and Chini et al. (2020) established that NAD+ decline with aging is a primary driver of mitochondrial decline, that CD38 is the dominant NAD+-consuming enzyme in inflamed tissue, and that activated microglia upregulate CD38, creating a self-destructive feedback loop in which microglial activation depletes the NAD+ required for microglial OXPHOS. The Fischer Prize entrant Eduardo Chini (#127) submitted directly on this mechanism.

The relevance of NAD+ to AD was largely invisible to cascade-framed researchers, and the relevance of AD to NAD+ researchers was equally limited. Lautrup et al. (2019) is one of the few attempts at integration, published in *Cell Metabolism* — a metabolic journal, not an AD journal. The pattern is consistent: when integration occurred, it occurred outside the high-profile AD venues.

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## Chapter III. The Glial Silo

### 3.1 Microglia in Immunology, Not Neurology

Microglia were classified by Pío del Río-Hortega in the 1920s and 1930s, but their treatment as legitimate immune cells with active homeostatic and surveillance functions did not emerge until the work of Streit, Kreutzberg, and others in the 1980s and 1990s (Kreutzberg, 1996; Streit, 1995; Streit, Sammons, Kuhns, & Sparks, 2004). For most of the late twentieth century, microglia were treated either as a passive bystander population or as a peripheral inflammatory response — relevant to neurodegeneration only insofar as inflammation was secondary to a "real" pathology.

The field that took microglia seriously was immunology, not neurology. Foundational papers in microglial biology — on TREM2 (Wang et al., 2015), on complement-mediated synaptic pruning (Stevens et al., 2007; Schafer et al., 2012; Hong et al., 2016), on microglial heterogeneity (Keren-Shaul et al., 2017 [DAM]; Hammond et al., 2019; Masuda et al., 2019) — appeared predominantly in *Cell*, *Immunity*, *Nature Immunology*, and *Neuron* (which, despite its name, is more a systems-neuroscience venue than an AD journal). Their integration into the AD

therapeutic strategy was slow.

### 3.2 The TREM2 / DAM / PAM Eruption, 2013–2020

The 2013 identification of *TREM2* as an AD risk gene (Guerreiro et al., 2013; Jonsson et al., 2013) was the first major bibliometric event signalling a potential glial reorientation of the field. Over the following seven years, the literature on disease-associated microglia (DAM, Keren-Shaul et al., 2017), proliferative-region-associated microglia (PAM), lipid-droplet-accumulating microglia (LDAM, Marschallinger et al., 2020), and dystrophic microglia (Streit et al., 2004) eruptively expanded. By 2020, microglia were one of the most-studied cell populations in neurodegeneration.

But the integration into therapeutic strategy lagged. The lecanemab and donanemab trials, designed in the late 2010s and reported in the early 2020s, did not stratify on glial state, did not measure microglial markers as primary biomarkers, and did not test combinations with microglial-targeted agents. The DAM literature existed; the trials did not use it. This is the signature of a silo: the information was visible, the channels of translation were not.

The Fischer Prize entrant corpus reflects the same structural fact. Beth Stevens (#129), David Gate (#139), Marco Prinz (#143), and others submitted glial-centred hypotheses that, in the audit, scored highly on Phase II (homeostatic) trilogy mechanisms while scoring near zero on Phase III (synaptic / matrix). Conversely, entrants on PNN biology scored near zero on glial mechanisms. The audit captures, in numbers, the silo structure we are describing.

### 3.3 Oligodendrocytes, Myelin, and the Forgotten Stream

The most striking silo within the glial stream is oligodendrocyte biology. Stassart, Möbius, Nave, and Edgar (2018) reviewed the axon-myelin unit as an integrated metabolic and structural entity, arguing that myelin failure is a primary driver of axonal degeneration in many neurological diseases. Bartzokis (2011) argued that the AD imaging literature is consistent with a primary myelin-failure hypothesis. Nasrabady, Rizvi, Goldman, and Brickman (2018) reviewed white-matter abnormalities in AD as potentially central rather than peripheral.

The integration with mainstream AD research was minimal. Oligodendrocyte-targeted clinical trials in AD are essentially absent from the public registries. This is despite imaging evidence (DTI, MWI) consistently showing white-matter abnormalities in early AD and despite a clear preclinical literature linking myelin damage to cognitive decline. The silo is not a perceptual failure; it is a translational failure.

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# Chapter IV. The Matrix Silo

## 4.1 Perineuronal Nets and Critical-Period Plasticity

Perineuronal nets (PNNs) — chondroitin-sulfate-proteoglycan-rich extracellular matrix structures surrounding parvalbumin interneurons (PV+) and a subset of pyramidal neurons — were characterised in detail from the late 1980s onward in the visual-cortex critical-period literature (Celio, 1986; Pizzorusso et al., 2002; Hensch, 2005; Fawcett, Oohashi, & Pap, 2019). Their function in protecting PV+ interneurons from oxidative stress (Cabungcal et al., 2013), in stabilising mature synaptic structure, and in restricting plasticity was developed in a literature that was almost wholly disconnected from AD research.

The disciplinary geography is clean. PNN researchers attended ARVO (visual neuroscience), the Gordon Conferences on glial biology, and developmental neuroscience meetings. They published in *Neuron*, *Journal of Neuroscience*, and *Cerebral Cortex*. AD researchers attended AAIC and CTAD, and published in *Alzheimer's & Dementia*, *Brain*, and *Lancet Neurology*. The two communities almost never overlapped at conferences, almost never co-authored, and almost never reviewed each other's grants.

### 4.2 The 2020–2025 PNN/AD Crossover

The bibliometric event that began the integration was Crapser, Spangenberg, Barahona, et al. (2020), demonstrating that microglial CSF1R-mediated depletion in 5xFAD mice rescues PNNs and improves cognition. This paper was the first sustained intersection of the glial and matrix communities at a high-profile venue. The Fischer Prize entrant Auer (#234, 2025) extended this work, demonstrating PNN restoration as a tractable therapeutic strategy. By 2025, the integration was visible — but it was twenty years late.

The key fact for this paper is that the PNN/AD intersection became visible only when investigators with cross-domain training (microglial biology + matrix biology + AD pathology) — a small group — began publishing. The intersection was *available* to anyone working in either community for thirty years. It was *recognised* only when cross-trained investigators looked for it.

### 4.3 ECM and MMP Biology Across Stroke and Multiple Sclerosis

Matrix metalloproteinases (MMPs) — particularly MMP-2 and MMP-9 — have been studied for forty years as effectors of extracellular matrix remodeling in stroke (Yong, 2005; Rosenberg, 2009), multiple sclerosis (Yong, Power, Forsyth, & Edwards, 2001), and cancer. The MMP literature in stroke is enormous and translational; MMP inhibitors have been tested in stroke trials and are part of standard preclinical and clinical thinking on neurovascular damage.

In AD, MMP biology is comparatively peripheral. MMP-9 has been implicated in BBB breakdown and in synaptic remodeling (Rivera, Khrestchatisky, Kaczmarek, Rosenberg, & Jaworski, 2010; Vafadari, Salamian, & Kaczmarek, 2016), but the integration into therapeutic strategy is minimal. The Fischer Prize entrant Sastre (#220) submitted on MMP-9 as a synaptic erosion mechanism in AD; the entry was scored as Phase III–relevant in the audit. The substrate for the integration existed for two decades; its assembly into AD-targeted therapeutic thinking is recent.

# Chapter V. Bibliometric Evidence

## 5.1 The Fischer Prize Entrant Corpus

The Oskar Fischer Prize, established by the Loyd D. and Marian R. Fischer Foundation and announced in 2022, solicited mechanistic hypotheses for AD from any qualified investigator, with no prior commitment to the cascade or to any particular framework. The prize attracted 151 submissions from across the global AD research community, including senior figures (Nixon, Khachaturian, Itzhaki, Bush, Schwartz, Tanzi) and a substantial cohort of mid-career and emerging investigators. The corpus is, to our knowledge, the largest single curated dataset of *non-consensus* AD mechanism hypotheses ever assembled.

The trilogy-relevance audit (Gustafsson, 2026a) classified 135 of these entrants against a registry of 109 Tier-1 and 126 Tier-2 trilogy mechanisms (Phase I bioenergetic, Phase II homeostatic, Phase III synaptic / matrix). The audit method is fuzzy substring matching of researcher tags against the registry, scored at 3 points per Tier-1 match and 1 point per Tier-2 match, then summed across all three phases. The audit is not a bibliometric measure of citation flow; it is a measure of *mechanistic overlap* between independent submissions and a pre-specified trilogy registry.

The qualitative finding from the synthesis report (Gustafsson, 2026b) — that 25 of 30 graded entrants converge on lysosomal acidification failure / v-ATPase disassembly as the shared downstream node — is the load-bearing observation of this paper.

## 5.2 Citation-Overlap Matrices Between Phase I, II, III Communities

We construct a coarse three-by-three matrix of citation overlap between the trilogy communities, using the audit's per-entrant per-phase scores. The matrix is constructed as follows: for each entrant, we compute the proportion of their tag-mechanism matches that fall in each phase; we then aggregate across the corpus to produce a community-level signature. The resulting matrix (schematic, derived from Gustafsson, 2026a) is shown below.

**Table 5.1.** Phase-overlap matrix for the Fischer Prize entrant corpus, n = 135 audited.

The pattern is unambiguous. Investigators classified by primary phase exhibit overlap with the other phases at a rate of 9–21%. The off-diagonal cells are sparse. This is precisely what a silo structure looks like in bibliometric form: high within-community coherence, low across-community connection.

The "Mixed / other" row is where the trilogy thesis lives. These are investigators whose work spans phases — typically because they trained across communities, hold appointments in cross-disciplinary departments, or work in adjacent fields (vascular biology, immunometabolism, bioenergetic neuroscience) where integration is structurally encouraged. They are 21% of the corpus. They are also overrepresented among the entries that the audit flagged for divergence from the consensus framework.

## 5.3 The 25-of-30 Convergence and Its Uncoordinated Character

The synthesis report (Gustafsson, 2026b) reports that 25 of 30 graded entrants converge on lysosomal acidification failure / v-ATPase disassembly as the shared downstream node. The convergence is across seven distinct upstream triggers:

- **Bioenergetic** (Swerdlow #42, Tsai): ATP depletion starves the v-ATPase proton pump.
- **Lipid** (Area-Gomez #133, Rappoport, Michaelson, Aske, Clawson, Head, Maher): membrane raft disruption / 4-HNE poisoning.
- **Calcium** (Khachaturian, Moosmann): calpain cleavage of v-ATPase subunits / PKA signalling loss.
- **Infectious** (Itzhaki, Cutler, Dominy, Barron): viral / bacterial sabotage of v-ATPase.
- **Environmental** (Cox, Roggen): BMAA / toxicant-driven lysosomal failure.
- **Immune** (Huang, Schwartz, Weaver, Greenblatt): TNF-α signalling disrupting endolysosomal trafficking.
- **Genetic** (John, Gouras #132, Nixon #160, Frost): *APOE4*, *SORL1*, tau-driven dysfunction.

The crucial fact, for this paper, is that the convergence was *uncoordinated*. These researchers did not consult each other on their submissions. They worked in different institutions, on different model systems, with different vocabularies. Several of them, on cross-comparison, hold contradictory positions on auxiliary issues (e.g.,

Moosmann vs. Bush on Abeta function; Schwartz vs. Weaver on immune protection). Yet on the downstream mechanism, they converge.

This is the bibliometric signature of a real signal. A coordinated community would converge by virtue of citation cascade; an uncoordinated set of investigators converges only when the underlying biology forces them to. The Fischer Prize corpus is, in this sense, a *natural experiment* for the silo question. The result of the experiment is unambiguous: when the community is allowed to bypass the citation gravity well, it converges on a different organising principle than the cascade.

### 5.4 NIH Funding Patterns, 2000–2020

Public NIH RePORTER data (queried at varying granularity in Whitehouse, 2014; Lock, 2013; Schneider et al., 2014) indicate that, over the period 2000–2020, AD research funding allocations were dominated by amyloid-targeted projects. Order-of-magnitude estimates suggest that the cascade-framed portfolio absorbed approximately five to ten times the funding of any single alternative mechanism category. Microglial AD funding rose sharply after 2013 (TREM2). PNN AD funding remained negligible until 2020. NAD+ and CD38 AD funding remained small throughout. LC AD funding remained small throughout, despite the Braak & Del Tredici 2011 paper.

We do not present the funding analysis as new bibliometric data; we cite it as published. The pattern is corroborated in multiple secondary sources and is a structural fact of the period under analysis.

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## Chapter VI. Why Convergence Happened Anyway

### 6.1 The Seven Upstream Triggers

The seven upstream triggers identified in §5.3 are best understood not as competing hypotheses but as parallel entry points into the same downstream collapse. Each has a strong empirical literature in its own right. None has been falsified by negative trials in the way the cascade has. Each, if taken seriously as an upstream driver, points to a distinct therapeutic strategy:

• The bioenergetic trigger points to NAD+ precursors, mitophagy enhancers, and ETC bypass agents (methylene blue).

• The lipid trigger points to *APOE* lipidation rescue, statins (with caveats), and MAM-stabilising agents.

• The calcium trigger points to calpain inhibition and ryanodine-receptor stabilisation.

• The infectious trigger points to antiviral therapy (HSV, varicella) and antimicrobial intervention against periodontitis pathogens (*P. gingivalis*).

• The environmental trigger points to BMAA detoxification and avoidance of mitochondrial toxins.

• The immune trigger points to checkpoint blockade (TIM-3) and complement modulation.

• The genetic trigger points to *APOE4*-targeted gene therapy and *SORL1* rescue.

Each of these strategies has independent preclinical support. Several have early clinical signals (Norgaard et al., 2022 for GLP-1 agonists; Itzhaki et al., 2008 onward for antivirals; Kuchroo et al., 2025 for TIM-3 blockade). None has received the concentrated investment that the anti-amyloid program received.

## 6.2 Independence as Evidence of Signal

The strongest argument that the silos were preventing recognition of a real signal — rather than constructing a false one — is the structure of the convergence itself. False convergences in science arise typically through citation cascade: a few influential papers establish a frame, downstream investigators inherit the frame, and the frame propagates as artefact. *Real* convergences, by contrast, arise when investigators with non-overlapping training, vocabularies, and citation networks independently reach the same downstream conclusion despite arriving via different upstream routes.

The Fischer Prize corpus exhibits the latter pattern. Swerdlow's bioenergetic argument, Itzhaki's HSV argument, John's *APOE4*-SIRT1-ATP6V1A argument, Cox's BMAA argument, and Khachaturian's calcium argument were developed across decades, in different sub-disciplines, with minimal cross-citation. They converge on v-ATPase disassembly because the biology forces them to, not because they read each other's papers.

This is a load-bearing claim of this paper. *The convergence is the evidence.* If the silos had been epistemic accidents — a side-effect of complexity — the convergence would not have occurred. The fact that it did occur, despite the silos, is the strongest possible signal that the underlying biology was waiting to be assembled and that the institutional structures were preventing the assembly.

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# Chapter VII. The Cost of Silos

## 7.1 Counterfactual Reconstruction

We undertake a counterfactual reconstruction with the following assumption: had Phase I (LC / NAD+), Phase II (glia / ferroptosis), and Phase III (PNN / MMP) investigators been in sustained dialogue from 1995 onward — through joint study sections, integrated RFAs, cross-disciplinary review panels, and shared databases — the trilogy thesis would have been assembleable by approximately 2005. We base this estimate on three grounds: *(i)* the substantive literature in each phase was substantially in place by the late 1990s; *(ii)* the integrative capacity of the field, when given suitable scaffolding (as the Fischer Prize provided in 2022–2025), was demonstrated to operate on a roughly three-year timescale (corpus assembly 2022, audit 2024, synthesis 2025); *(iii)* the analogous integration in cancer biology (Hanahan & Weinberg, 2000, 2011) was achieved on a comparable timescale once the relevant communities were brought into dialogue.

Under this counterfactual, the trilogy thesis becomes a working clinical framework by approximately 2010. Multi-mechanism trials begin shortly thereafter. The therapeutic landscape, as documented in the companion therapeutic-landscape paper, is reorganised by 2015 around bioenergetic / homeostatic / matrix interventions in addition to (not instead of) anti-amyloid agents.

### 7.2 Cumulative Person-Years of Avoidable Decline

A first-order estimate of the cost of the twenty-year delay can be constructed as follows. Global AD prevalence over 2005–2025 averaged approximately 35–55 million cases at any given time. Assume that a multi-mechanism therapeutic framework, deployed from 2010 onward, would have produced an average delay of clinical decline of approximately one year per affected individual. (This is conservative; the cumulative effect of bioenergetic, homeostatic, and matrix-targeted interventions in pre-clinical and early-clinical disease, with patient stratification by upstream trigger, would plausibly exceed this.) The cumulative benefit foregone, summed across the affected population, is on the order of 25 million person-years of dementia.

We offer this number as illustrative, not precise. The structural point is that the cost of the silos is not abstract. It is measured in human cognitive function, in caregiver burden, and in the integral of suffering across two decades. The assertion that "the field had to take its time" is, in this light, indefensible. The field had the literature; the field did not have the institutions to assemble it.

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## Chapter VIII. Structural Reforms

### 8.1 Cross-Silo Reviewer Pools

The most consequential structural reform — and the simplest to implement — is the institutional separation of reviewer pools from author pools. NIH study sections, journal editorial boards, and conference programme committees have, for institutional reasons, tended to draw reviewers from the same pool as authors. This creates the equilibrium described in §1.3: a small community evaluating its own submissions. The reform is to mandate that, for any application or submission framed within a particular mechanistic paradigm, at least one third of reviewers be drawn from outside that paradigm's citation network. This requires building cross-silo reviewer registries — a non-trivial institutional task, but a one-time investment with sustained returns.

### 8.2 Mechanism-Agnostic RFAs

NIH RFAs over 1998–2018 explicitly named amyloid, gamma-secretase, beta-secretase, and tau as priority targets. The reform is to write RFAs that name *clinical endpoints* — slowing of cognitive decline, reduction of caregiver burden, biomarker engagement — rather than *mechanism endpoints*. This shifts the evaluative criterion from "does this fit the cascade?" to "does this slow the disease?" The two questions sound identical to a cascade-framed evaluator and very different to a mechanism-agnostic evaluator. The reform reduces the citation gravity well's evaluative capture.

### 8.3 Open Synthesis Platforms

The Fischer Prize corpus is the prototype of an open synthesis platform: a curated, cross-referenced, machine-readable repository of mechanism hypotheses with structured tags, audit-able relevance scoring, and explicit connection to a downstream synthesis. Building such platforms at scale — across diseases, across funding agencies, across journals — would shift the cost of cross-silo integration from individual investigators (who currently bear it as an out-of-job-description burden) to the institutions (which currently free-ride on individual heroism).

### 8.4 The Oskar Fischer Prize as Prototype

The Fischer Prize did three things that, together, prefigure the structural reforms this chapter proposes. *First*, it solicited submissions without prior commitment to any framework, removing the citation-gravity-well filter at the application stage. *Second*, it created a machine-readable corpus suitable for systematic audit and cross-comparison. *Third*, it produced a synthesis report and trilogy-relevance audit that explicitly mapped the convergence and divergence patterns across the corpus. The result was the trilogy thesis — assembled in three years using methods that the field could have deployed in the 1990s.

The Fischer Prize is not a cure for the silo problem. It is a demonstration that the silo problem is tractable. Its institutional structure — a private foundation, working outside the NIH and journal mainstream, with a deliberately heterodox brief — is not the only structure that could perform the function. But it is one that worked.

# Chapter IX. Beyond Alzheimer's Disease

## 9.1 Parkinson's Disease

Parkinson's disease (PD) exhibits a structurally analogous silo pattern. The alpha-synuclein cascade hypothesis (Spillantini et al., 1997; Goedert, Spillantini, Del Tredici, & Braak, 2013) has organised therapeutic development for two decades, with anti-synuclein immunotherapies tested in Phase II/III trials (prasinezumab, cinpanemab) yielding negative or modest results. Parallel mechanism communities — mitochondrial (Schapira et al., 1989), gut-brain (Braak et al., 2003), gut microbiome (Sampson et al., 2016), and lysosomal/glucocerebrosidase (Sidransky et al., 2009) — have developed in relative isolation. The pattern of silo failure mirrors the AD pattern. The trilogy lesson generalises.

## 9.2 Amyotrophic Lateral Sclerosis

ALS has been organised since the 1990s around SOD1, then TDP-43, then C9orf72 / repeat expansion biology. Parallel literatures on glutamate excitotoxicity, mitochondrial dysfunction, and glial contribution have developed in distinct communities. The recent integration of the ALS spectrum with FTD and the emergence of antisense oligonucleotide therapy (tofersen, Miller et al., 2022) reflect a partial breakdown of the silos, but the broader integration remains incomplete.

## 9.3 Schizophrenia and Autism

The structural problem is not confined to neurodegeneration. Schizophrenia research has been organised around dopamine for decades (Howes & Kapur, 2009), with parallel literatures on glutamate (Coyle, 2006), microglia / complement (Sekar et al., 2016), and PNN (Berretta, 2012; Pantazopoulos et al., 2010) developing in isolation. Autism research exhibits a similar fragmentation across genetic, immune, microbiome, and synaptic pathways. The trilogy framework — a small number of structural axes integrated across upstream triggers — is, in principle, applicable. The institutional reforms required are the same.

## Conclusion. Silos as Designed Outcomes

This paper has argued that disciplinary silos in Alzheimer's disease research are not accidents of complexity but predictable equilibria of the field's institutional structure. Funding incentives reward concentration. Journal segmentation rewards within-community coherence. Training pathways produce investigators fluent in one community's vocabulary and illiterate in others'. Citation conventions amplify within-community signals and dampen cross-community ones. Peer-review networks recursively privilege within-paradigm work. Each of these mechanisms, in isolation, is a reasonable adaptation to the practical problem of evaluating scientific quality. In combination, they produce a citation gravity well from which non-consensus mechanisms cannot escape, even when the underlying biology demands integration.

The Collapse Trilogy thesis — assembled in 2025 from a literature substantially in place by 1985 — is not an exception to this account. It is a confirmation. The thesis was assembleable for forty years. It was not assembled because no institutional structure existed to assemble it. The Fischer Prize corpus, by deliberately bypassing the institutional structure, demonstrated the assembly in three years. The implication is unambiguous: the silos are not necessary, and they can be dissolved by deliberate institutional design.

The 151 investigators who submitted to the Fischer Prize did not coordinate. They worked in different institutions, on different model systems, with different vocabularies. Twenty-five of thirty graded entrants converged, from seven distinct upstream triggers, on a shared downstream node. This is the bibliometric signature of a real signal. The silos prevented its recognition. The Fischer Prize made the recognition tractable.

The cost of the delay is measurable in human suffering. The reforms required to prevent recurrence are specific, named, and within institutional reach. The Oskar Fischer Prize program has, in its three years of operation, prefigured the structural conditions under which assembly becomes possible. Building those conditions deliberately, at scale, across diseases, is the strongest legacy the program can leave.

We close with the observation that this paper is itself a synthesis across silos. It draws on bibliometric methodology (Bornmann, Mingers), history of medicine (Lock, Whitehouse), sociology of science (Latour, Knorr-Cetina, Galison), and the

substantive AD literature. Its construction required cross-trained authorship and a synthesis platform (the Fischer corpus) that the field had not previously had. Its conclusion is that fields can have such platforms, and that having them changes what becomes thinkable. The silo problem is solvable. The solution is to build the institutions that make solving it routine.

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