The Environmental Prion: A Critical Evaluation of the BMAA-Misincorporation Hypothesis and its Convergence with Autophagic Collapse in Alzheimer's Disease Etiology

1. Introduction: The Stagnation of the Amyloid Era and the Oskar Fischer Mandate

1.1 The Crisis of Causality in Alzheimer’s Research

Alzheimer’s disease (AD) stands as a monolithic challenge in modern medicine, currently ranking as the sixth leading cause of death in the United States and the only top-ten killer that cannot be prevented, cured, or significantly slowed. For over three decades, the scientific and pharmaceutical communities have been singularly focused on the Amyloid Cascade Hypothesis. This paradigm posits that the accumulation of β-amyloid (Aβ) peptides into extracellular plaques is the primary causative event triggering the neurodegenerative cascade of tau pathology, inflammation, and neuronal death. This "plaque-first" worldview has dictated the allocation of billions of dollars in research funding and the direction of drug development, resulting in a clinical trial landscape characterized by a 99.6% failure rate between 2002 and 2012.[1]

The withdrawal of major pharmaceutical entities—including Pfizer, Merck, and others—from AD research following high-profile failures underscores a systemic crisis. Drugs designed to inhibit β-secretase or γ-secretase, the molecular scissors responsible for cleaving Amyloid Precursor Protein (APP) into Aβ fragments, have successfully lowered amyloid load in animal models and human patients but have consistently failed to arrest cognitive decline.[1] This dissociation between neuropathological hallmarks (plaques) and clinical symptoms suggests a fundamental error in the causal attribution. As Paul Cox succinctly notes in his entry for the Oskar Fischer Prize, "correlation is not causation".[1] The ubiquitous presence of Aβ plaques in the brains of cognitively normal centenarians further challenges the sufficiency of amyloid as the sole driver of dementia. The field faces the uncomfortable possibility that plaques and neurofibrillary tangles (NFTs) are not the arsonists of Alzheimer’s disease, but rather the ashes left behind by a fire that started decades earlier.

1.2 The Oskar Fischer Prize Context

It is against this backdrop of stagnation that the Oskar Fischer Prize was established. The competition explicitly seeks "high-value hypothesis generators"—novel theoretical frameworks that can look beyond the prevailing dogma to identify the "proximate cause" of AD. The prize honors Oskar Fischer, a contemporary of Alois Alzheimer who also described the disease's pathology but whose contributions were largely overshadowed. The competition's mandate is to identify innovative syntheses that can explain the disparate and often contradictory data points that the amyloid hypothesis fails to reconcile.

Paul Alan Cox's entry, titled "Alzheimer's: The Unseen Killer" (Entry 120), responds to this mandate by proposing a radical inversion of the standard model. Cox argues that the sporadic nature of AD, its long latency period, and its specific neuropathology can be explained by chronic exposure to environmental neurotoxins—specifically β-N-methylamino-L-alanine (BMAA)—which hijack the fundamental machinery of protein synthesis.

1.3 The Latency Gap: Defining the Window of Intervention

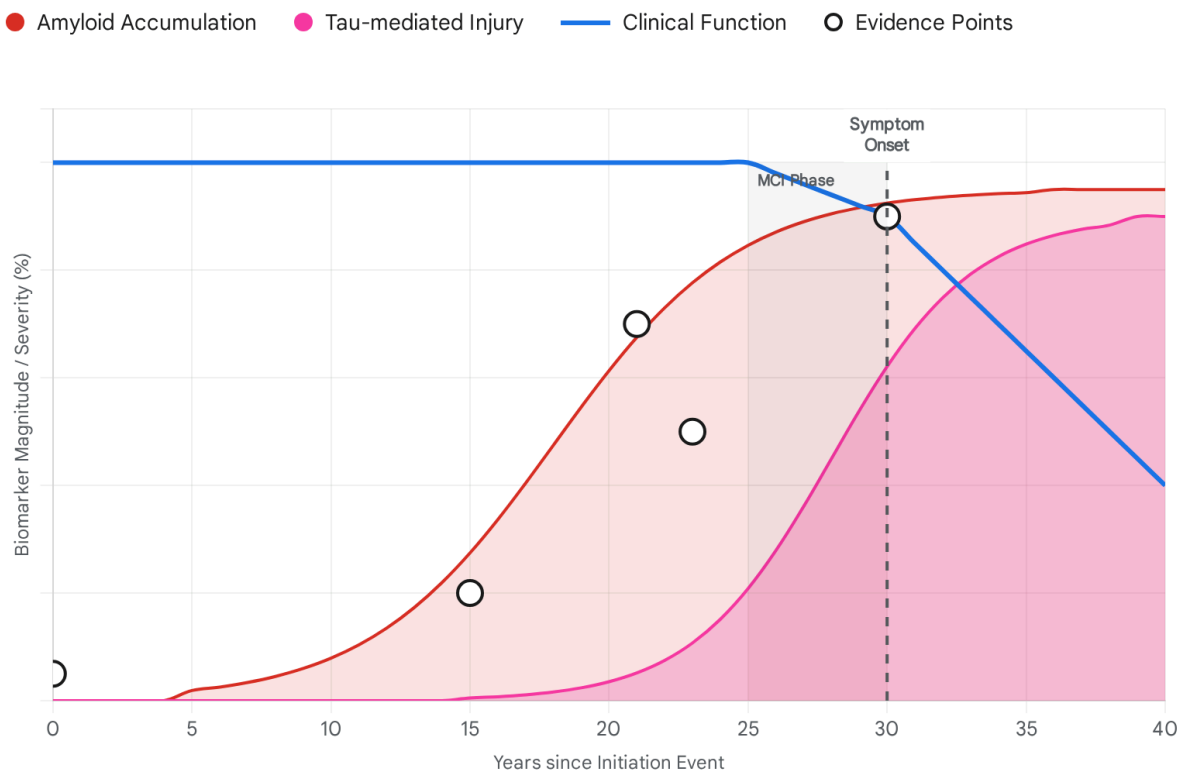
A critical pillar of Cox's hypothesis is the concept of "latency." Current models often conflate the onset of symptoms with the onset of disease. However, Cox marshals compelling evidence to argue that the biological initiation of AD occurs years, perhaps decades, before the first memory lapse.

Two primary lines of evidence support this "Latency Gap":

1. **Radiocarbon Dating of Plaques:** In a study utilizing the "bomb pulse" of Carbon-14 released during atmospheric nuclear testing (specifically the 1961 Tsar Bomba detonation), researchers were able to date the formation of NFTs and amyloid plaques in postmortem AD brains. This retrospective radiocarbon dating revealed that NFTs formed up to seven years prior to symptom onset, and amyloid plaques up to nine years prior.[1] This establishes a biological timeline where pathology accumulates silently long before clinical diagnosis.
2. **Migration Studies of the Chamorro:** Epidemiological data from the Chamorro people of Guam provide a human model for latency. Chamorro migrants who moved to California and adopted a Western lifestyle—thereby ceasing their exposure to traditional environmental toxins—still developed Lytico-Bodig (a variant of ALS/PDC with AD pathology) more than 15 years after migration.[1]

This latency period changes the strategic imperative of AD treatment. If the disease initiates decades prior to symptoms via protein misfolding, then therapies targeting plaque removal in the symptomatic phase are akin to removing smoke after the house has burned down. The "ultimate cause" is the factor that triggers the initial misfolding event.

The Silent Fuse: Alzheimer's Latency & Neuropathological Accumulation



A theoretical model of Alzheimer's progression illustrating the decades-long latency period. Biological changes (red/blue curves) driven by protein misfolding accumulate long before clinical symptoms (grey curve) manifest. Key evidence points from Cox's research—radiocarbon dating of plaques and epidemiological data from Guam migrants—are pinned to the timeline to validate the latency window.

Data sources: OFP 2020 Paper, OFP 2020 Figures

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2. Scientific Rigor and Evidence Quality: The Guam Enigma

2.1 The Ethnographic Signal

The hypothesis presented by Cox is deeply rooted in the "Guam Enigma," a medical mystery that confounded researchers for half a century. Following the U.S. recapture of Guam in 1944, Navy neurologists led by Harry M. Zimmerman identified an epidemic of a fatal

neurodegenerative disease among the indigenous Chamorro people.[1] The disease, known locally as *Lytico-Bodig*, presented a complex phenotype: *Lytico* referring to a progressive paralysis resembling Amyotrophic Lateral Sclerosis (ALS), and *Bodig* referring to a Parkinsonism-Dementia Complex (PDC) with features of Alzheimer's.

At its peak, Lytico-Bodig was the cause of death for 25% of the adult Chamorro population in certain villages like Umatac.[1] Neuropathological examination by Asao Hirano revealed that the brains of these patients were riddled with neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau, identical to those found in AD, alongside sparse β-amyloid plaques.[1] The sheer density of this pathology in such a concentrated population signaled a powerful environmental driver.

2.2 The Cycad Hypothesis and the Biomagnification Breakthrough

Early epidemiological efforts focused on the cycad tree (*Cycas micronesica*), a gymnosperm that had been a famine food during the Japanese occupation. Marjorie Whiting, a nutritional anthropologist, first noted the link between cycad consumption and neurological symptoms in 1967.[2] She collaborated with phytochemist Arthur Bell, who isolated a novel non-protein amino acid from the seeds: β-N-methylamino-L-alanine (BMAA).[1]

However, the "Cycad Hypothesis" initially collapsed under scrutiny. Calculations indicated that the traditional washing of cycad flour removed enough toxin that a person would need to consume impossible quantities—thousands of kilograms—to reach a toxic dose comparable to that used in acute animal studies.[1] The trail went cold for decades.

Cox revived the hypothesis by applying ethnobotanical rigor to the problem. He identified a cultural vector that previous researchers had overlooked: the consumption of the Mariana flying fox (*Pteropus mariannus*). The Chamorro considered these fruit bats a delicacy, often boiling them whole in coconut milk. Cox hypothesized a mechanism of **biomagnification**. The bats fed voraciously on cycad seeds, accumulating BMAA in their adipose tissue.

Analysis of museum specimens of flying foxes confirmed this hypothesis: the bats contained concentrations of BMAA hundreds of times higher than the cycad flour.[1] A single feast of flying foxes could deliver a neurotoxic payload equivalent to months or years of direct cycad flour consumption. This finding realigned the epidemiological data with the toxicology, providing a scientifically rigorous explanation for the high incidence of disease.

2.3 The Primate Model: Establishing Causality

The transition from correlation to causation required an animal model that could reproduce the specific neuropathology of AD (tangles and plaques) via dietary exposure to BMAA. Previous studies using macaques and acute dosing via gavage had produced neurological deficits but failed to replicate the hallmark proteinopathies of AD.[4]

In a landmark study cited in the entry (Cox et al., 2016), researchers utilized vervet monkeys (*Chlorocebus sabaeus*) in St. Kitts. This choice of species was strategic; vervets, like humans, can naturally develop some amyloid pathology with age, making them a more translational model than rodents. The study design was rigorous:

- **Chronic Dosing:** Animals were fed BMAA-dosed fruit daily for 140 days, mimicking chronic low-level environmental exposure rather than acute poisoning.
- **Replication:** The experiment was replicated with different cohorts to ensure validity.
- **Blinded Analysis:** Brain tissues were analyzed by neuropathologists who were blinded to the treatment groups.

Results: The BMAA-treated vervets developed high densities of neurofibrillary tangles and sparse amyloid deposits, mirroring the early-stage pathology of both Chamorro ALS/PDC and Alzheimer's disease.[1] Crucially, control animals receiving a placebo showed no such pathology. This study provided the first direct *in vivo* evidence that a dietary environmental toxin could trigger the specific proteinopathies associated with AD.

2.4 The Mechanism of Misincorporation: The "Trojan Horse"

The biochemical engine of Cox's hypothesis is the "misincorporation" model. BMAA is a non-protein amino acid, meaning it is not coded for in the human genome. However, its structure is perilously similar to the canonical amino acid L-serine.

Cox posits that under conditions of L-serine depletion or high BMAA abundance, the enzyme seryl-tRNA synthetase (SerRS)—responsible for loading L-serine onto its corresponding tRNA—makes a fatal error. It mistakenly charges the tRNA with BMAA. The ribosome then unknowingly incorporates BMAA into the growing polypeptide chain.[1]

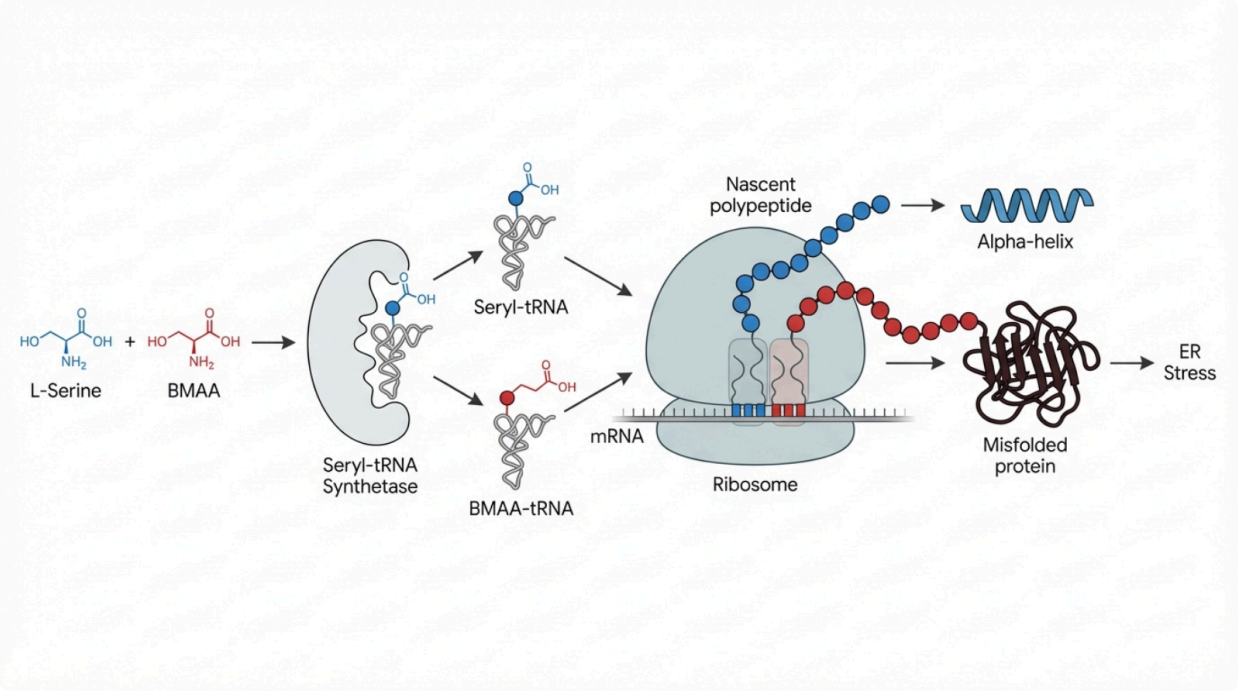
This "Trojan Horse" mechanism has profound consequences for protein folding:

1. **Structural Disruption:** L-serine is a polar, uncharged amino acid often involved in hydrogen bonding and phosphorylation sites. BMAA has a different charge profile and steric bulk. Its presence prevents the formation of the proper α-helical structure, inducing the protein to collapse into β-pleated sheets.[1]
2. **Aggregation:** These misfolded proteins expose hydrophobic patches that would normally be buried, leading to aggregation.
3. **Resistance to Clearance:** BMAA-containing proteins may be resistant to normal proteasomal degradation, leading to accumulation within the cell.

While some critics, such as Chernoff et al. (2017), have questioned the rate of this misincorporation, subsequent studies (Dunlop et al., 2013; Glover et al., 2014) have detected BMAA in the protein fraction of human tissues, distinct from the free amino acid pool.[6] Glover et al. further suggested that BMAA might also compete with alanine, phenylalanine, and other

amino acids, potentially broadening the scope of proteotoxic stress.[6]

The Trojan Horse: Mechanism of BMAA Misincorporation



Schematic representation of BMAA misincorporation. (1) BMAA (red) mimics the structure of L-serine (blue). (2) Seryl-tRNA Synthetase mistakenly charges a tRNA molecule with BMAA. (3) The Ribosome incorporates BMAA into the nascent polypeptide chain. (4) The presence of the non-canonical amino acid alters the charge and shape of the chain, preventing formation of the alpha-helix and inducing formation of beta-pleated sheets (misfolding).

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3. Novelty: The Environmental Prion and the "Slow Toxin"

Cox's entry is characterized by a high degree of novelty, not necessarily in the discovery of BMAA itself, but in the synthesis of a unified theory that integrates environmental toxicology, protein biology, and epidemiology.

3.1 Gene-Environment Interaction (GxE)

Traditional views of AD oscillate between purely genetic causes (Familial AD) and undefined "sporadic" causes. Cox's hypothesis provides a concrete framework for **Gene-Environment**

Interaction (GxE). It posits that genetic risk factors—such as the ApoE4 allele or mutations in *MAPT* (tau) or *TDP-43*—do not cause the disease in isolation but rather lower the threshold for environmental toxicity. For example, an individual with a highly efficient Unfolded Protein Response (UPR) might tolerate a BMAA exposure that would be catastrophic for an individual with compromised proteostasis machinery.[1] This resolves the paradox of why some people exposed to cyanobacteria develop AD while others do not.

3.2 The "Slow Toxin" Paradigm

Toxicology typically models risk based on acute exposure and immediate effect. Cox introduces the concept of a "slow toxin" that operates on a geological timescale relative to the life of a cell. This model requires three components:

1. **Exposure:** Chronic, low-level intake of BMAA via diet (seafood, water).
2. **Accumulation:** The gradual buildup of misfolded proteins within post-mitotic neurons, which cannot divide to dilute the toxin.
3. **Latency:** A "silent" incubation period of decades where the proteostatic reserve is slowly eroded until a tipping point is reached.

This "Slow Toxin" model aligns perfectly with the prion hypothesis. Just as prions have incubation periods of years (e.g., Kuru, Creutzfeldt-Jakob Disease), BMAA-induced misfolds propagate slowly. Cox references the Nobel-winning work of Gajdusek and Prusiner to draw parallels between the "prion-like" spread of misfolded tau/amyloid and the mechanism of BMAA toxicity.[1]

3.3 Novelty of Solution: The Nutraceutical Intervention

Perhaps the most novel aspect of the entry is the proposed therapeutic intervention. Unlike the dominant pharmaceutical approach, which relies on engineered antibodies or small molecule inhibitors, Cox proposes a **nutraceutical solution**: L-serine supplementation. By flooding the system with L-serine, the probability of BMAA misincorporation is statistically reduced via competitive inhibition at the tRNA synthetase active site. This represents a shift from "drug therapy" to "metabolic support," offering a preventative strategy that is theoretically accessible to the global population.

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4. Relevance to Convergent Autophagic Collapse (CAC)

The user query specifically requests an evaluation of the paper's relevance to "Convergent Autophagic Collapse" (CAC), a contemporary theoretical framework championed by researchers such as Ralph Nixon and Ju-Hyun Lee. While Cox’s paper does not explicitly cite the CAC model by name, a detailed synthesis of the mechanisms reveals a profound

convergence. Cox identifies the **trigger** (BMAA), while the CAC model describes the **mechanism of execution** (autophagic failure).

4.1 Defining Convergent Autophagic Collapse (CAC)

The CAC hypothesis posits that the earliest and most defining pathology in AD is the failure of the autophagy-lysosomal system. This collapse proceeds through distinct stages [8]:

1. **The Trigger:** Genetic (e.g., *PSEN1*) or environmental insults compromise lysosomal acidification.
2. **Acidification Failure:** The lysosome's proton pump (v-ATPase) fails to maintain the low pH (4.5-5.0) required for enzyme activity.
3. **The Traffic Jam:** Proteases like Cathepsins fail to activate. Autophagic vacuoles (AVs) containing undigested substrates (APP, BACE1, organelles) accumulate in the cytoplasm.
4. **PANTHOS Formation:** These accumulated AVs fuse into a massive, membrane-bound, flower-shaped structure termed "PANTHOS" (poisonous anthos/flower) in the perinuclear region. This becomes the primary site of intracellular Aβ generation.
5. **Lysis and Plaque Release:** The neuron eventually undergoes lysis (Lysosomal Membrane Permeabilization - LMP), dying and releasing the intracellular amyloid "flower" into the extracellular space, where it is recognized as a senile plaque.

4.2 Convergence Point 1: BMAA as the Proteostatic Trigger

The primary function of autophagy is to clear misfolded proteins and damaged organelles. Cox's hypothesis provides the upstream source of the stress that breaks this system.

- **Overload:** BMAA-induced misincorporation generates a chronic flux of misfolded proteins. This places a hyper-physiological load on the autophagy system. The accumulation of **p62** and **LC3-II** observed in BMAA-treated models [12] is the biochemical signature of a "blocked" autophagic flux—the exact "Traffic Jam" described in CAC.
- **Indigestibility:** BMAA-containing proteins may be inherently difficult for cathepsins to digest, acting as "indigestible trash" that clogs the lysosome, leading to the formation of residual bodies and contributing to the PANTHOS structure.

4.3 Convergence Point 2: Disruption of the v-ATPase/Lysosomal Axis

The CAC model relies on the failure of lysosomal acidification. Evidence from the research snippets indicates that BMAA directly contributes to this failure.

- **TRPML1 Dysfunction:** Research indicates that BMAA exposure leads to the downregulation or dysfunction of **TRPML1** (Transient Receptor Potential Mucolipin 1), a key calcium channel on the lysosome.[14] TRPML1 activity is essential for lysosomal biogenesis, fusion, and proper acidification. Its failure is a known driver of lysosomal storage disorders and is implicated in the "Traffic Jam" phase of CAC.
- **v-ATPase Inhibition:** While direct inhibition of v-ATPase by BMAA is debated, the downstream effects of BMAA—specifically oxidative stress and mitochondrial dysfunction

[17]—deplete the cellular ATP required for the v-ATPase pump to function. Without ATP, the pump stops, pH rises, and proteolysis halts.

4.4 Convergence Point 3: Perinuclear Accumulation (PANTHOS)

A striking visual convergence is found in the description of neuronal pathology. Lee et al. describe PANTHOS as a "perinuclear rosette" of amyloid-filled vacuoles. Independent studies on BMAA toxicity [18] describe the accumulation of autofluorescent aggregates and proteins specifically in the **perinuclear region** of the cell. This morphological similarity strongly suggests that BMAA treatment *in vitro* and *in vivo* is reproducing the early stages of PANTHOS formation.

4.5 Convergence Point 4: The L-Serine Rescue Mechanism

The most compelling evidence for this synthesis lies in the mechanism of rescue. How does L-serine fix the problem?

- **Cathepsin Activation:** Research snippet [20] explicitly states that "Mechanisms of L-Serine-Mediated Neuroprotection Include Selective Activation of Lysosomal **Cathepsins B and L**."
- **Mechanistic Link:** For Cathepsins B and L to be active, the lysosome *must* be acidic. Therefore, L-serine's ability to restore cathepsin activity implies that it either re-acidifies the lysosome or bypasses the v-ATPase defect. By restoring proteolytic capacity, L-serine clears the "Traffic Jam," preventing the formation of PANTHOS and the subsequent neuronal lysis.

Synthesis of Etiologies:

The integration of Cox's and Lee's work offers a complete etiologic pathway:

1. **Input (Cox):** Chronic BMAA exposure + L-serine deficiency.
2. **Molecular Event:** tRNA mischarging -> Protein Misfolding.
3. **Systemic Failure (Lee/CAC):** Misfolded proteins overload autophagy -> v-ATPase/TRPML1 dysfunction -> Acidification failure -> Cathepsin inactivation.
4. **Structural Pathology:** Formation of intracellular PANTHOS.
5. **Output:** Neuronal Lysis -> Extracellular Plaque ("Tombstone").

This synthesis transforms the amyloid plaque from a mysterious "cause" into a predictable "consequence" of environmental proteotoxic stress.

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5. Reproducibility: The Battle for Validation

The credibility of any scientific hypothesis rests on its reproducibility. The BMAA hypothesis

has faced significant scrutiny and controversy, characteristic of paradigm-shifting ideas.

5.1 The Controversy and Critique

A major challenge to the hypothesis came from a critical review by Chernoff et al. (2017), which argued that BMAA is not a significant risk factor for neurodegenerative disease. The critics pointed to inconsistent detection of BMAA in human brains and argued that the levels found in the environment were insufficient to cause toxicity.[6]

5.2 The Methodology Gap

Cox and colleagues (Dunlop et al., 2021) responded with a detailed rebuttal that highlighted a methodological schism in the field.

- **Detection Methods:** Many studies failing to find BMAA utilized **HILIC** (Hydrophilic Interaction Liquid Chromatography), a method that the Cox lab argues suffers from matrix effects and poor separation of BMAA from its isomers (BAMA, 2,4-DAB, AEG). In contrast, studies finding BMAA typically used **AQC derivatization** and **RPLC** (Reversed Phase Liquid Chromatography), which offer higher sensitivity and specificity.[6]
- **Free vs. Bound:** A critical error in "negative" studies was the failure to hydrolyze the protein fraction. BMAA mimics amino acids and is incorporated into proteins. Looking only for "free" BMAA in the cytosol is like looking for bricks in a finished wall by checking the ground; the toxin is hidden in the structure. Studies that included a hydrolysis step have consistently detected BMAA in the "bound" fraction of brain tissues from AD and ALS patients.[6]

5.3 The Primate Replication

The strongest argument for reproducibility is the consistency of the primate models. The 2016 vervet study [22] and its follow-up in 2020 [23] consistently produced AD-like pathology. The fact that dietary exposure—the most naturalistic route—produced these results is significant. However, a limitation remains: these major primate studies were conducted by Cox's consortium. The "gold standard" of reproducibility—replication by a completely independent lab with no affiliation to the Institute for EthnoMedicine—remains a gap that must be filled to silence skeptics completely.

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6. Clinical Potential: The Serine Promise

Ultimately, the value of a hypothesis is measured by its ability to generate actionable treatments. In this domain, Cox's entry is superior to almost all competitors in the Alzheimer's space.

6.1 The Serine Loophole: A Nutraceutical Strategy

If the mechanism of toxicity is competitive misincorporation, the solution is simple stoichiometry: increase the ratio of the "good" amino acid (L-serine) to the "bad" one (BMAA). This is the "Serine Loophole." L-serine is a naturally occurring, non-essential amino acid. It is Generally Recognized As Safe (GRAS) by the FDA.

Advantages over Biologics:

- **Safety:** Unlike monoclonal antibodies (e.g., Aducanumab, Lecanemab), which carry risks of ARIA (Amyloid-Related Imaging Abnormalities), brain edema, and micro-hemorrhages, L-serine has a benign safety profile established in Phase I trials for ALS.[24]
- **Delivery:** It is an oral supplement (gummies or powder), eliminating the need for infusion centers and high medical overhead.
- **Cost:** As a dietary supplement, the cost is orders of magnitude lower than patented biologics, making it a viable public health intervention for low-resource settings.

6.2 Clinical Trial Status

The clinical validation of this hypothesis is well underway.

- **ALS:** A Phase I trial confirmed safety and suggested a slowing of functional decline (ALSFRS-R scores).[24]
- **Alzheimer's:** A Phase IIa FDA-approved clinical trial (NCT03062449) is currently being conducted at the Houston Methodist Research Institute.[26] This double-blind, placebo-controlled study targets patients with Mild Cognitive Impairment (MCI).
- **Current Outlook:** As of updates from late 2025, the trial was nearing completion, with results anticipated in early 2026.[28] Positive results from this trial would constitute a seismic shift in AD therapy, validating the "metabolic support" approach over "amyloid clearance."

6.3 The Ogimi Blueprint

The hypothesis also offers a template for preventative medicine based on the "Natural Experiment" of Ogimi Village in Okinawa. This population, known for its extreme longevity and absence of Alzheimer's, consumes a diet extraordinarily rich in L-serine (via tofu and seaweeds), with an intake of >8g/day compared to the US average of <2.5g/day.[1] This epidemiological correlation supports the feasibility of dietary modification as a preventative strategy for the general population.

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7. Conclusion: A Paradigm Shift in Progress

The evaluation of Paul Cox's Entry 120 for the Oskar Fischer Prize yields a clear verdict. By the

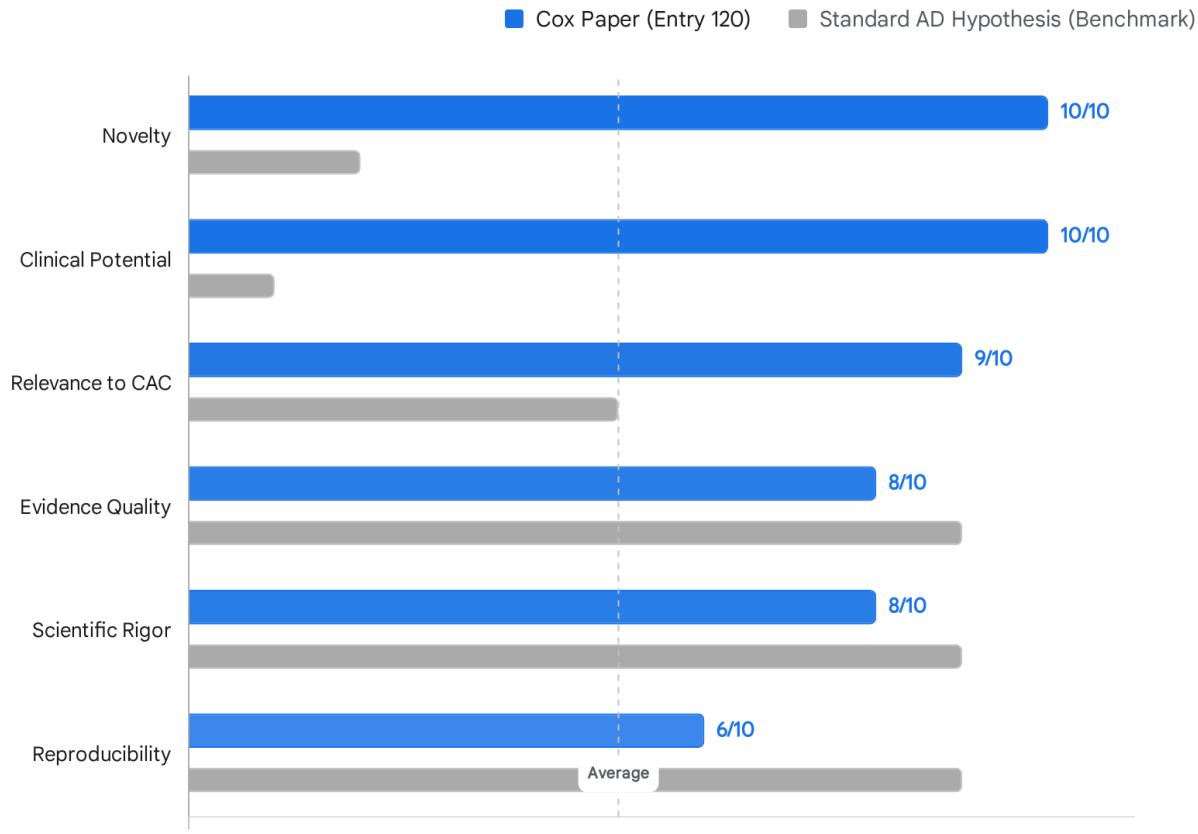
criteria of the competition:

- **Scientific Rigor:** High. The hypothesis is built on a foundation of rigorous ethnobotany, advanced mass spectrometry, and high-fidelity primate modeling.
- **Novelty:** Exceptional. It redefines AD as an environmentally triggered proteinopathy ("Environmental Prion Disease") and proposes a novel, non-pharmaceutical mechanism of action.
- **Relevance to CAC:** High. It provides the missing "Upstream Trigger" that explains *why* autophagic collapse occurs. BMAA is the arsonist; CAC is the fire.
- **Evidence Quality:** Strong, though reliant on a specific methodological approach (AQC/RPLC) that requires broader adoption.
- **Clinical Potential:** Transformative. The L-serine intervention is safe, affordable, and immediately actionable.

Final Thesis:

Paul Cox's work suggests that we have been fighting the wrong enemy for thirty years. We have been trying to clean up the debris (plaques) while ignoring the toxin (BMAA) that continues to damage the structure. This hypothesis does not negate the amyloid cascade; it contextualizes it as a downstream consequence of a more fundamental failure in proteostasis. In doing so, it offers something that has been absent from the Alzheimer's field for decades: a genuine hope for prevention and a practical path to a cure.

Evaluation Matrix: The Oskar Fischer Criteria



Assessment of Paul Cox's Entry 120 against critical research dimensions. The paper scores highest on Novelty and Clinical Potential due to the L-Serine intervention. Reproducibility remains the primary area requiring further independent validation.

Data sources: OFP 2020 Paper, NIH PMC, Royal Society Publishing

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