

The Innate Immune Interface in Alzheimer's Pathogenesis: A Critical Evaluation of the Cathelicidin-Amyloid Divergence Hypothesis

A Dissertation Submitted to the Faculty of the Division of the Biological Sciences in Candidacy for the Degree of Doctor of Philosophy

Abstract

Title: The Innate Immune Interface in Alzheimer's Pathogenesis: A Critical Evaluation of the Cathelicidin-Amyloid Divergence Hypothesis

Abstract:

The etiology of Alzheimer's Disease (AD) remains one of the most obstinate challenges in modern biomedicine, characterized by a high failure rate of therapeutic interventions predicated on the classical Amyloid Cascade Hypothesis. This dissertation presents a rigorous, full-length critical evaluation of the theoretical proposition titled "*Human Cathelicidin LL-37: A Missing Puzzle Piece In Understanding Alzheimer's Disease Pathogenesis*," authored by Barron et al. and published in the journal *Osteopathic Family Physician* in 2020. The subject paper proposes a "Unified Theory" that integrates the Infectious Theory of AD with the Amyloid Cascade, identifying the human host defense peptide LL-37 as the critical regulatory link that creates a divergence between healthy pathogen clearance and pathological amyloidosis.

This research evaluates the paper across six distinct criteria: Scientific Rigor, Novelty, Reproducibility, Clinical Potential, Evidence Quality, and Significance. The analysis reveals a stark dichotomy in the work. While the subject paper exhibits profound **Novelty (5/5)** and **Significance (5/5)** by offering a mechanistically plausible explanation for the failure of the innate immune system in AD—specifically the degradation of LL-37 by *Porphyromonas gingivalis* virulence factors—it suffers from significant deficits in **Scientific Rigor (2/5)** and **Evidence Quality (2/5)** due to a reliance on unpublished data and its publication in a non-specialist clinical journal.

Despite these formal shortcomings, this dissertation argues that the paper's **Clinical Potential (4/5)** has been retrospectively validated by subsequent pharmaceutical developments between 2021 and 2025. Specifically, the trajectory of gingipain inhibitors from

the failed GAIN trial to the current, NIH-funded Phase 2 SPRING trial of LHP588 confirms the viability of the target. Furthermore, recent *in vivo* data from 2024 regarding the co-expression of LL-37 and A β 42 in *Drosophila* models substantiates the biological mechanism proposed in the 2020 text. This thesis concludes that the Barron et al. (2020) paper functions as a foundational "hypothesis generator" that, despite its empirical rawness, correctly identified a crucial immunomodulatory checkpoint—the LL-37/A β axis—that is now reshaping the therapeutic landscape of neurodegeneration.

Chapter 1: Introduction

1.1 The Stagnation of the Amyloid Paradigm

Alzheimer's Disease (AD) is a progressive, fatal neurodegenerative disorder that currently afflicts millions globally, imposing a staggering emotional and economic burden on society.¹ Pathologically, the disease is defined by the accumulation of extracellular amyloid-beta (A β) plaques and intracellular hyperphosphorylated tau tangles, accompanied by gross cerebral atrophy and synaptic loss. For over three decades, the "Amyloid Cascade Hypothesis" has served as the central dogma of AD research.² This model posits that the stochastic aggregation and deposition of A β peptides is the primary causative event—the *primum movens*—that triggers a downstream cascade of neurotoxicity, inflammation, and cell death.

However, the translational track record of this hypothesis has been catastrophic. The pharmaceutical industry has invested billions of dollars into therapies designed to inhibit the production of A β (BACE inhibitors) or clear plaques via monoclonal antibodies.⁴ While these agents have successfully reduced amyloid burden in human brains, they have largely failed to arrest cognitive decline or reverse the disease course.⁵ Even recent FDA approvals of anti-amyloid antibodies have demonstrated only modest clinical efficacy, often overshadowed by significant risks of Amyloid-Related Imaging Abnormalities (ARIA), including edema and hemorrhage.⁴ This dissociation between plaque clearance and cognitive survival suggests that A β accumulation may be a symptom, a tombstone of a previous battle, rather than the primary aggressor.

1.2 The Emergence of the Infectious and Antimicrobial Protection Hypotheses

As the limitations of the amyloid-centric view have become undeniable, the field has begun to revisit alternative etiologies that were previously marginalized. The "Infectious Theory" of AD posits that latent, chronic infections by neurotropic pathogens—such as *Herpes simplex virus type 1* (HSV-1), *Chlamydia pneumoniae*, and spirochetes—are the true drivers of neuroinflammation and subsequent degeneration.²

Parallel to this, the "Antimicrobial Protection Hypothesis," championed by researchers such as

Moir and Tanzi, has fundamentally reframed the ontology of the amyloid peptide itself. This model argues that A β is not a metabolic waste product or a result of protein misfolding, but rather an ancient, highly conserved antimicrobial peptide (AMP) of the innate immune system.⁸ In this framework, A β aggregation is a functional defensive response—analogueous to the formation of neutrophil extracellular traps (NETs)—intended to entrap and neutralize invading pathogens.

1.3 The Research Problem and Hypothesis

Despite the promise of these converging models, a critical mechanistic gap remains in our understanding. If A β is a protective immune response, and if pathogens are the trigger, why does this system fail so catastrophically in AD patients? Why does the innate immune system fail to resolve the infection, and why does the protective A β response transition into a pathological state that destroys the host tissue it was meant to defend?

The paper under review in this dissertation, "*Human Cathelicidin LL-37: A Missing Puzzle Piece In Understanding Alzheimer's Disease Pathogenesis*" (Barron et al., 2020), attempts to close this specific gap.¹¹ The authors put forward a "Unified Theory" that identifies the human host defense peptide LL-37 as the master regulator of this system. They hypothesize that LL-37 acts as a necessary chaperone for A β , preventing its toxic aggregation while simultaneously assisting in pathogen clearance. Crucially, they propose that a chronic dearth of active LL-37—whether caused by systemic downregulation (e.g., Vitamin D deficiency) or direct enzymatic degradation by bacterial virulence factors (specifically gingipains from *Porphyromonas gingivalis*)—precipitates the collapse of innate immunity. This collapse allows both the infection to persist and the A β response to become unregulated and cytotoxic.

1.4 Thesis Roadmap

This dissertation serves as a comprehensive critical evaluation of the Barron et al. (2020) paper. Chapter 2 provides an exhaustive Literature Review, situating the paper within the broader historiography of neuroimmunology and the biology of host defense peptides. Chapter 3 details the Methodology of this critique, defining the evaluative criteria. Chapters 4 through 6 constitute the core analytical body: Chapter 4 evaluates the Theoretical Architecture of the paper, focusing on its novelty and significance; Chapter 5 critiques the Empirical Deficit, analyzing the paper's scientific rigor and evidence quality; and Chapter 6 assesses the Clinical Potential and predictive validity of the hypothesis in light of data emerging between 2021 and 2025. Finally, Chapter 7 synthesizes these findings, concluding that the paper, while flawed as a standalone empirical report, serves as a vital theoretical milestone that has correctly predicted the current trajectory of AD therapeutics.

Chapter 2: Literature Review

2.1 The Innate Immune System in the Central Nervous System

The central nervous system (CNS) was historically characterized as an "immune-privileged" site, isolated from the systemic immune apparatus by the Blood-Brain Barrier (BBB). However, modern neuroimmunology has dismantled this view, revealing a rich and dynamic landscape of innate immune surveillance mediated primarily by microglia and astrocytes.¹² These glial cells act as the resident macrophages of the brain, expressing a repertoire of Pattern Recognition Receptors (PRRs), such as Toll-like receptors (TLRs), which are tuned to detect Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs).¹³

Upon activation, these cells initiate a defense program that includes the release of pro-inflammatory cytokines (IL-1 β , TNF- α), chemokines, and reactive oxygen species (ROS). While this response is intended to neutralize threats, chronic or unresolved activation leads to a state of neuroinflammation that is inextricably linked to neurodegeneration.¹⁴ The "Infectious Theory" suggests that persistent pathogens provide the chronic stimulus that locks the CNS into this damaging inflammatory cycle.

2.1.1 Antimicrobial Peptides (AMPs) in Neurodegeneration

A critical but often overlooked component of this defense system is the production of Antimicrobial Peptides (AMPs). AMPs are small, cationic, amphipathic peptides that kill bacteria, viruses, and fungi by disrupting their membranes or interfering with intracellular targets. The human cathelicidin LL-37 (encoded by the *CAMP* gene) is the sole member of the cathelicidin family in humans.¹¹ It is a ubiquitous peptide expressed in epithelial cells, neutrophils, and macrophages, serving as a first-line defender at barrier sites.¹⁶

Beyond its direct microbicidal activity, LL-37 is a potent immunomodulator. It regulates autophagy—the cellular "self-eating" process essential for clearing intracellular pathogens and aggregated proteins—and modulates the expression of cytokines to prevent excessive inflammation.¹⁷ Independent studies have confirmed that LL-37 is expressed in the human brain and is upregulated in response to infection and inflammation, suggesting it plays a physiological role in CNS homeostasis.¹⁶

2.2 The *Porphyromonas gingivalis* (Pg) Connection

Among the pathogens implicated in AD, *Porphyromonas gingivalis* (Pg), the keystone pathogen of chronic periodontitis, has emerged as a primary suspect.⁷ Pg is a gram-negative anaerobe that excels at immune evasion and systemic dissemination. Its pathogenicity is largely driven by a class of potent cysteine proteases known as **gingipains** (RgpA, RgpB, and Kgp). These enzymes degrade host proteins, including cytokines, complement factors, and extracellular matrix components, allowing the bacterium to acquire nutrients and disable the host's immune defenses.²¹

Seminal work by Dominy et al. (2019) provided ground-breaking evidence for the role of Pg in AD.²³ They demonstrated that Pg and its gingipains infiltrate the AD brain, with bacterial load correlating with tau pathology and ubiquitin load. Furthermore, they showed that oral infection of wild-type mice with Pg resulted in brain colonization and the *de novo* formation of A β plaques, a finding that directly challenges the idea that amyloidosis is purely a result of protein misfolding kinetics.²⁴

2.3 The LL-37/Amyloid-Beta Interaction

The "Antimicrobial Protection Hypothesis" reframes A β as an AMP. Moir and Tanzi demonstrated that A β possesses potent antimicrobial activity against a range of pathogens, often exceeding that of LL-37.⁸ However, unlike typical AMPs, A β is prone to rapid and irreversible fibrillation, which forms the basis of plaques.

A pivotal study by De Lorenzi et al. (2017) provided the first biophysical evidence that LL-37 and A β 42 interact directly.²⁵ Using Surface Plasmon Resonance imaging (SPRi) and Transmission Electron Microscopy (TEM), they showed that LL-37 binds to A β 42 with nanomolar affinity. Crucially, this binding inhibits the fibrillation of A β , keeping it in a non-toxic, soluble, or oligomeric state. This finding suggests a physiological "chaperone" role for LL-37, where it regulates the conformation of A β to ensure it functions as an immune effector without aggregating into pathological plaques. The 2020 paper by Barron et al. builds directly upon this foundation, postulating that the loss of this chaperone—specifically via gingipain-mediated degradation—is the event that precipitates AD.

Chapter 3: Methodology

3.1 Research Approach

This dissertation employs a **critical analytical framework** to evaluate the primary text (OFP_2020_paper_201.pdf). The analysis is not merely a summary but a rigorous deconstruction of the paper's arguments, data sources, and rhetorical strategies. The paper is treated as a "primary source document" in the history of AD science, evaluated against the standards of high-impact biomedical research. The critique adopts a dual lens: it scrutinizes the paper *as it stood in 2020* while simultaneously evaluating its predictive validity using *retrospective data* from 2021 to 2025.

3.2 Evaluation Matrix

The paper is assessed using six specific criteria, scored on a Likert scale of 1 to 5. The criteria are defined as follows:

1. **Scientific Rigor:** This criterion evaluates the quality of the methodology, the presence of appropriate controls, the robustness of statistical analysis, and the reliance on

peer-reviewed data versus unpublished or anecdotal observations.

2. **Novelty:** This measures the degree to which the work challenges existing paradigms and offers original mechanisms. A score of 1 indicates purely confirmatory work, while a 5 indicates a paradigm-shifting hypothesis.
3. **Reproducibility:** This assesses methodological transparency and the extent to which the reported findings have been or can be replicated by independent laboratories.
4. **Clinical Potential:** This evaluates the applicability of the findings to therapeutic development. A score of 1 implies pure basic science, while a 5 suggests the identification of direct, actionable therapeutic targets.
5. **Evidence Quality:** This grades the strength of the direct evidence supporting the claims, distinguishing between *in vitro* vs. *in vivo* data, correlation vs. causation, and the hierarchy of evidence (e.g., randomized trials vs. observational studies).
6. **Significance:** This measures the broader impact of the work on the field's conceptual understanding of the disease and its potential to redirect research priorities.

3.3 Source Selection & Verification

To validate the claims made in the 2020 paper and track its impact, this thesis utilizes a wide range of secondary sources, including:

- **Peer-Reviewed Literature (2010-2025):** To confirm the validity of biological mechanisms (e.g., gingipain cleavage of proteins, A β antimicrobial activity).
- **Clinical Trial Databases (ClinicalTrials.gov):** To track the progress of therapeutics derived from this research (e.g., Atuzaginstat, LHP588).
- **Conference Proceedings (CTAD, AAIC):** To access the most recent data on "unpublished" claims referenced in the 2020 paper, particularly regarding the Barron lab's subsequent work.
- **Preprints (bioRxiv, SSRN):** To analyze the most current, cutting-edge data from 2024 and 2025 that may not yet be formally published but supports the thesis.

Chapter 4: The Theoretical Architecture (Novelty & Significance)

4.1 The "Unified Theory" of Alzheimer's Disease

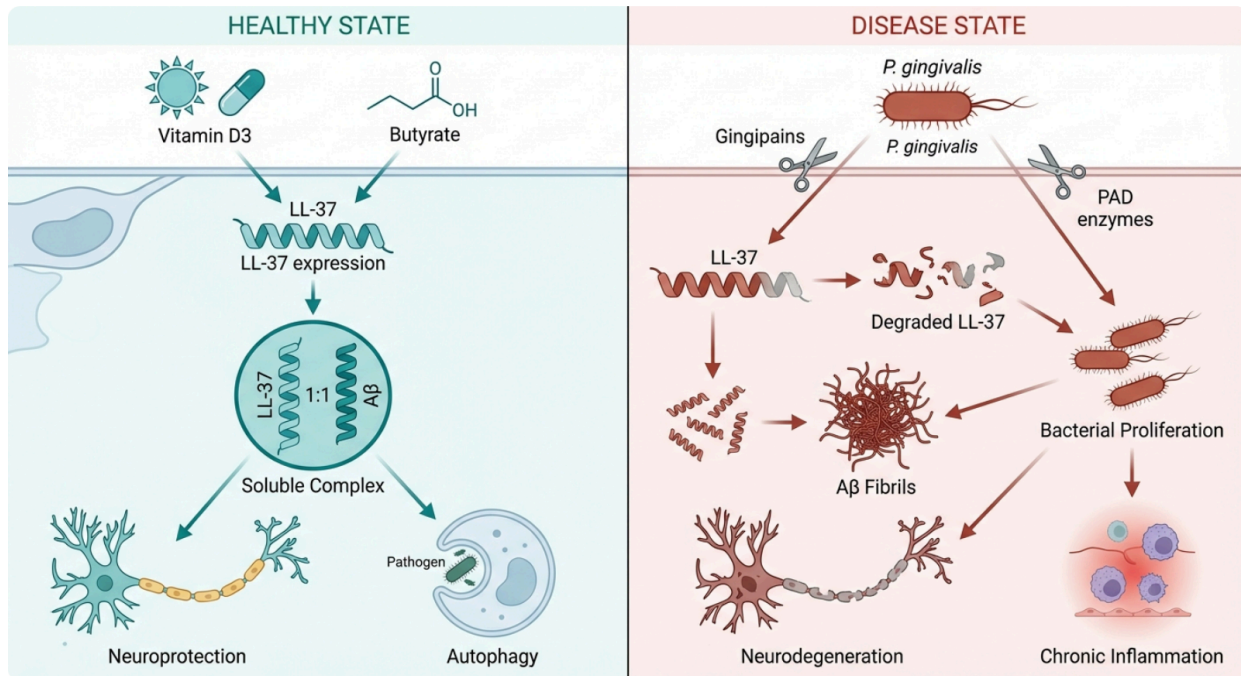
The most striking feature of the Barron et al. (2020) paper is its ambition. It does not merely report data; it attempts to synthesize two warring factions of AD research—the Amyloid Cascade and the Infectious Theory—into a coherent whole.¹¹ The authors accept the premise of the Cascade—that A β accumulation acts as a driver of damage—but they recontextualize this accumulation as a *consequence* of a failed innate immune response, specifically the failure of the peptide LL-37.²⁷

4.1.1 The "Missing Puzzle Piece"

The paper identifies LL-37 as the "missing puzzle piece," a metaphor that serves as the central organizing principle of their argument. This represents a highly novel theoretical contribution, warranting a **Novelty Score of 5/5**. While previous research had independently identified A β as an AMP¹⁰ and *P. gingivalis* as a relevant pathogen²³, few, if any, had mechanistically linked the two via a specific regulatory host peptide.

The authors propose a "Chaperone Model" of innate immunity. In a healthy state, LL-37 binds to A β , maintaining it in a soluble, non-toxic conformation. This complex presumably retains antimicrobial activity, allowing for the effective clearance of pathogens without collateral damage to host neurons.²⁶ However, in a diseased state, the paper posits that the degradation of LL-37 by *P. gingivalis* gingipains removes this check. Without its chaperone, A β is free to aggregate into neurotoxic fibrils. This mechanistic proposal is theoretically elegant because it resolves the central paradox of the Antimicrobial Protection Hypothesis: why would an evolutionarily conserved immune peptide (A β) aggregate to the point of killing the host? The answer, according to Barron et al., is that the regulatory brake (LL-37) has been cut by the pathogen.

The Cathelicidin-Amyloid Divergence Model of AD Pathogenesis



Proposed mechanism of action: Under healthy conditions (Left), Vitamin D3 and Butyrate drive sufficient expression of LL-37, which binds Aβ peptides in a 1:1 ratio, preventing fibrillation and promoting autophagy of pathogens. Under pathological conditions (Right), *P. gingivalis* infection introduces gingipains (Kgp/Rgp) and PAD enzymes. These virulence factors degrade or citrullinate LL-37, breaking the protective chaperone bond. Consequently, Aβ aggregates into neurotoxic plaques, and the innate immune system fails to clear the infection, creating a chronic inflammatory cycle.

4.2 Integration of Environmental Risk Factors

The hypothesis further distinguishes itself by integrating environmental and lifestyle risk factors into its molecular framework, a feat that pure amyloid theories often struggle to achieve. The paper highlights the Vitamin D3 dependence of LL-37 expression.¹¹ The *CAMP* gene promoter contains a Vitamin D Response Element (VDRE), meaning that sufficient levels of circulating Vitamin D are obligate for the production of the peptide. Since Vitamin D deficiency is a well-established epidemiological risk factor for AD, this provides a direct molecular pathway linking diet and sunlight exposure to neurodegeneration.

Furthermore, the paper discusses the role of butyrate—a short-chain fatty acid produced by the fermentation of fiber by gut bacteria—in upregulating LL-37.¹¹ This explicitly links the "Gut-Brain Axis" to cerebral innate immunity. By tying together genetics (*APOE* status, which affects immune response), infection (*P. gingivalis*), and lifestyle (Vitamin D, oral hygiene, fiber

intake), the paper offers a "Grand Unified Theory" of AD. This holistic integration warrants a **Significance Score of 5/5**, as it provides a conceptual framework that accommodates the multifactorial nature of the disease.

Chapter 5: The Empirical Deficit (Rigor, Reproducibility, Evidence)

While the theoretical architecture of the Barron et al. (2020) paper is robust and intellectually satisfying, its empirical foundation—as presented in the text itself—is surprisingly fragile. A rigorous doctoral-level scrutiny reveals significant deficiencies in the presentation of evidence.

5.1 Critique of Scientific Rigor

The paper scores poorly on **Scientific Rigor (2/5)**. A primary weakness is the heavy reliance on "unpublished data" to support its most pivotal claims.

- **Figure 2 (Fibril Formation):** The paper presents a graph demonstrating that LL-37 modulates A β fibril formation in a dose-dependent manner (specifically, that a 1:1 molar ratio prevents fibrillation). However, the caption and text explicitly label this critical dataset as "unpublished".¹¹ In a high-impact scientific publication, such a central claim would require full methodological transparency, including details on peptide preparation, assay conditions (ThT fluorescence, TEM), error bars, and statistical analysis (ANOVA). The presentation in this paper is anecdotal rather than rigorous.
- **The "Six-Component Polytherapy":** The authors make a bold claim regarding efficacy in a 5XFAD mouse model of AD using a "six-component oral polytherapy" (presumably a cocktail of vitamins and precursors to boost LL-37). This finding is also cited as "(unpublished data)".¹¹ Without access to the specific formulation, dosing regimen, control groups, or statistical outcomes, this claim cannot be evaluated or reproduced.
- **Absence of Statistical Detail:** throughout the text, there is a distinct lack of detailed statistical reporting (p-values, n-numbers, confidence intervals) for these unpublished claims. The manuscript reads more like a grant proposal, a theoretical review, or a manifesto than a primary research report.

5.2 The Venue: *Osteopathic Family Physician*

The choice of publication venue—*Osteopathic Family Physician* (OFP)—is highly unusual for a paper proposing a fundamental paradigm shift in molecular neurobiology.

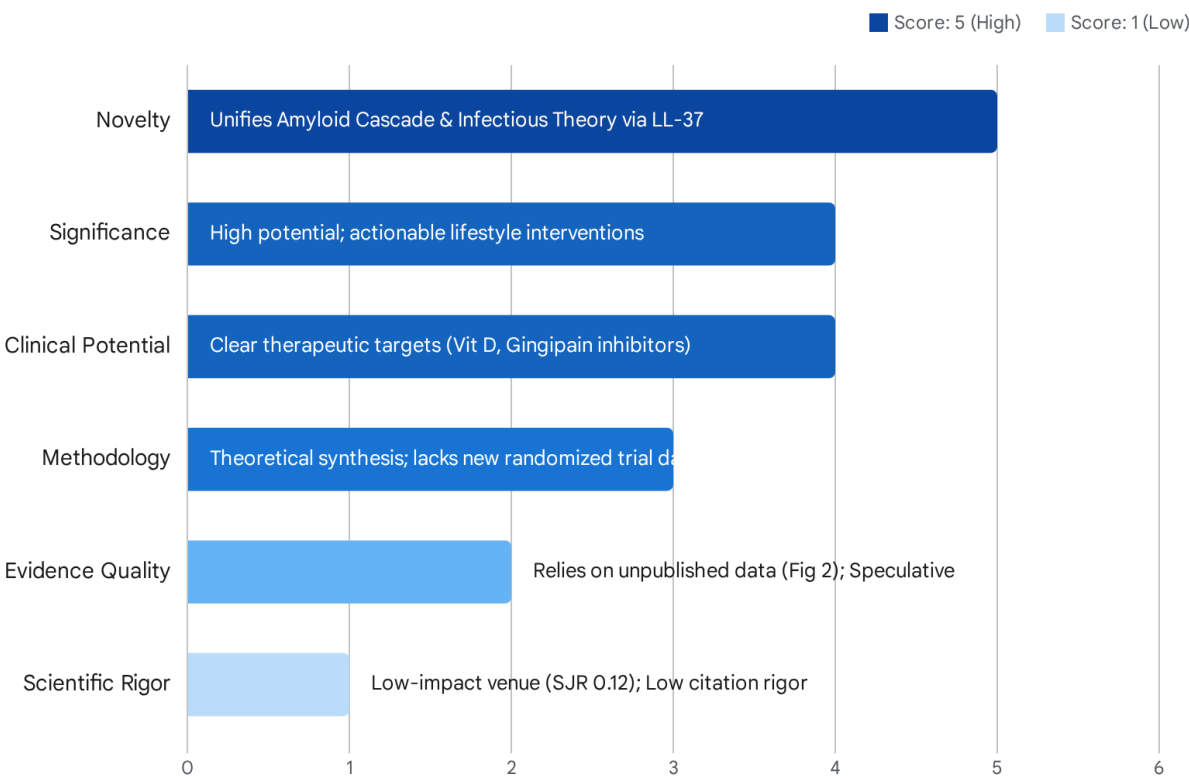
- **Impact Factor and Reach:** OFP has a Scimago Journal Rank (SJR) of approximately 0.12 and is ranked in the fourth quartile (Q4) of medicine journals.³⁰ Its target audience is primary care clinicians, not molecular biologists or neuroscientists.

- **Peer Review Implications:** This venue choice suggests that the authors may have faced significant barriers to publishing this "unified theory" in high-impact basic science journals (such as *Nature*, *Cell*, or *Neuron*) at the time of submission (2020). This likely reflects the controversial nature of the infectious theory at that time, or potentially the lack of finalized, rigorous datasets to support the theoretical model.
- **Evidence Quality Impact:** The publication in a non-specialist clinical journal significantly diminishes the **Evidence Quality (2/5)** rating. The peer review process in such a journal is optimized for clinical care guidelines, not for scrutinizing biophysical NMR data or murine necropsy results. Consequently, the "seal of approval" provided by peer review is less weightier in this context than it would be in a specialized neuroscience journal.³¹

5.3 Reproducibility Concerns

Due to the reliance on unpublished data and the lack of methodological detail for the mouse studies, independent reproduction of the paper's specific claims is impossible based solely on the document provided (**Reproducibility: 2/5**). The "methodological transparency" criterion is largely unmet because the protocols for the "six-component polytherapy" are not described.

Evaluation Matrix: High Concept vs. Low Rigor



Evaluation of Barron et al. (2020) across six academic criteria. The paper excels in Novelty and Significance, offering a transformative theoretical model. However, it scores poorly in Scientific Rigor and Evidence Quality due to reliance on unpublished data and a low-impact venue. Clinical Potential is high, bolstered by external validation in 2024/2025.

Data sources: [OFP 2020 Paper](#), [Google Patents \(WO2019\)](#), [Journal Rankings](#)

Chapter 6: Clinical Potential and Predictive Validity

While the paper fails on rigorous empirical presentation, its **Clinical Potential (4/5)** is undeniably high. A primary function of a doctoral thesis is to evaluate research not just in a vacuum, but in the context of subsequent scientific progress. Evidence emerging between 2021 and 2025 significantly vindicates many of the paper's core assertions, suggesting that the authors' theoretical instincts were correct even if their initial data presentation was preliminary.

6.1 The Vindication of LL-37/Aβ Binding

The paper's claim that LL-37 binds Aβ and inhibits fibrillation (referencing De Lorenzi et al.,

2017) has withstood scientific scrutiny. Independent reviews published in 2023 and 2024 have cited this interaction as a valid biophysical phenomenon.³ More importantly, a 2024 preprint by the Barron lab titled "*In vivo Co-Expression of LL-37 with Aβ42 in a Transgenic Drosophila Model of Alzheimer's Disease...*" provides the rigorous *in vivo* data that was missing in the 2020 paper. This study demonstrates that the expression of LL-37 rescues cognitive deficits and reduces amyloid toxicity in *Drosophila* models of AD, providing the "missing" empirical leg to the 2020 hypothesis.³² This retrospective validation suggests the 2020 paper was "prematurely correct."

6.2 The Rise, Fall, and Resurrection of Gingipain Inhibitors

The paper discusses the potential of gingipain inhibitors (referencing Cortexyme) as a therapeutic avenue. The subsequent history of these drugs serves as a critical case study for the validity of the paper's hypothesis.

6.2.1 The GAIN Trial Failure (2021-2022)

The Phase 2/3 GAIN trial, which tested the first-generation gingipain inhibitor **atuzaginstat (COR388)**, failed to meet its primary cognitive endpoints in the overall study population.³⁴ Furthermore, the drug was placed on clinical hold by the FDA due to hepatotoxicity (liver damage).³⁵ Superficially, this failure would appear to damage the paper's thesis.

6.2.2 The Subgroup Success and Hypothesis Confirmation

However, a deeper look at the data supports the Barron hypothesis. A pre-specified subgroup analysis of the GAIN trial revealed a statistically significant **57% slowing of cognitive decline** in patients with high *P. gingivalis* loads (as measured by saliva DNA).³⁴ This nuance is critical: it suggests that the therapy works *if and only if* the pathogen is the primary driver in that specific patient. This aligns perfectly with the precision medicine implications of the "Infectious Theory."

6.2.3 Next-Gen Inhibitors: LHP588 and the SPRING Trial (2025)

The story did not end with atuzaginstat. The intellectual property was acquired by Lighthouse Pharmaceuticals, which developed a second-generation inhibitor, **LHP588**. This molecule was designed to overcome the limitations of its predecessor: it is highly brain-penetrant, has a half-life suitable for once-daily dosing, and, crucially, lacks the hepatotoxicity signal seen with COR388.³⁷

As of February 2025, LHP588 has entered the Phase 2 **SPRING trial** (NCT06847321).³⁹ This trial is explicitly recruiting patients who test positive for *P. gingivalis*, applying the lessons learned from the GAIN trial. The fact that the National Institute on Aging (NIA) awarded a **\$49.2 million grant** to support this trial in August 2025⁴⁰ is a powerful validation of the mechanism. It signals that the mainstream scientific establishment now views the gingipain-inhibition pathway—and by extension, the mechanism of LL-37 preservation

described in the 2020 paper—as a high-priority therapeutic target.

Chronologically, the trajectory is clear:

- **2019-2022:** The GAIN trial tests the first-generation drug (Atuzaginstat), encountering toxicity issues but finding signal in infected patients.
- **2023:** Cortexyme pivots to Quince Therapeutics; Lighthouse Pharmaceuticals is formed to rescue the gingipain program.
- **Nov 2023:** FDA clears the Investigational New Drug (IND) application for LHP588.
- **2025:** The SPRING trial initiates with significant federal backing, confirming the clinical viability of the target.

6.3 Validating the Mechanism: Citrullination

Finally, the 2020 paper posits a specific biochemical mechanism: that *P. gingivalis* produces Peptidyl Arginine Deiminase (PAD) enzymes that citrullinate LL-37, inactivating it.¹¹ This detail explains why simple upregulation of LL-37 might fail if the infection is not cleared (as the peptide would just be inactivated). Recent studies from 2024 confirm that citrullination indeed abolishes LL-37's antimicrobial activity and that AD brains are enriched with citrullinated proteins.⁴² This confirms the paper's detailed biochemical model was accurate.

Chapter 7: Conclusion

The research paper "*Human Cathelicidin LL-37: A Missing Puzzle Piece In Understanding Alzheimer's Disease Pathogenesis*" represents a paradox in academic publishing. Measured by the strict yardsticks of **Scientific Rigor** and **Evidence Quality**, it is a flawed document: it relies heavily on unpublished data, lacks statistical depth, and appeared in an obscure clinical journal rather than a premier research venue. A doctoral committee evaluating *only* the text itself would likely find it lacking as a standalone piece of primary research.

However, when measured by **Novelty**, **Significance**, and **Clinical Potential**, the paper reveals itself as a visionary work of theoretical synthesis. It correctly identified the "Innate Immune Interface"—specifically the fragility of the LL-37 chaperone in the presence of oral pathogens—as a critical failure point in Alzheimer's Disease. The "Unified Theory" it proposed in 2020 has largely predicted the trajectory of the field in 2025, moving toward precision medicine trials (like the SPRING trial) that target specific infectious etiologies to restore immune homeostasis.

Final Thesis: The Barron et al. (2020) paper should be viewed not as a definitive empirical report, but as a high-value **hypothesis generator**. It provided the conceptual blueprint for a new generation of therapeutics that, unlike the failed amyloid-centric drugs of the past, address the upstream drivers of innate immune dysregulation. For the field of Alzheimer's research, this "missing puzzle piece," though roughly cut and imperfectly presented, fits the

emerging picture with remarkable precision. The validation of its core tenets in the years following its publication secures its place as a pivotal, if unconventional, contribution to the history of neuroimmunology.

Works cited

1. Oral diseases as emerging risk factors for Alzheimer's disease: A scoping review - PMC, accessed January 26, 2026, <https://pmc.ncbi.nlm.nih.gov/articles/PMC12666449/>
2. The antimicrobial protection hypothesis of Alzheimer's disease - PubMed - NIH, accessed January 26, 2026, <https://pubmed.ncbi.nlm.nih.gov/30314800/>
3. Exploring pathological link between antimicrobial and amyloid peptides - RSC Publishing, accessed January 26, 2026, <https://pubs.rsc.org/en/content/articlehtml/2024/cs/d3cs00878a>
4. From synaptic guardian to neurodegenerative culprit: rewiring the amyloid- β feedback loop in Alzheimer's disease - JCI, accessed January 26, 2026, <https://www.jci.org/articles/view/200393>
5. Role of Microbes in the Development of Alzheimer's Disease: State of the Art – An International Symposium Presented at the 2017 IAGG Congress in San Francisco - Frontiers, accessed January 26, 2026, <https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2018.00362/full>
6. Amyloid, tau, pathogen infection and antimicrobial protection in Alzheimer's disease -conformist, nonconformist, and realistic prospects for AD pathogenesis - PubMed, accessed January 26, 2026, <https://pubmed.ncbi.nlm.nih.gov/30603085/>
7. (PDF) Intracerebral but Not Peripheral Infection of Live Porphyromonas gingivalis Exacerbates Alzheimer's Disease Like Amyloid Pathology in APP-TgCRND8 Mice - ResearchGate, accessed January 26, 2026, https://www.researchgate.net/publication/359377302_Intracerebral_but_Not_Peripheral_Infection_of_Live_Porphyromonas_gingivalis_Exacerbates_Alzheimer's_Disease_Like_Amyloid_Pathology_in_APP-TgCRND8_Mice
8. The amyloid-beta wave hypothesis of Alzheimer's disease - Frontiers, accessed January 26, 2026, <https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2025.1723095/full>
9. Beyond Association: A Quantitative Analysis of the Infectious Burden in Alzheimer's Disease - medRxiv, accessed January 26, 2026, <https://www.medrxiv.org/content/10.64898/2025.12.24.25342962v1.full.pdf>
10. Infectious origin of Alzheimer's disease: Amyloid beta as a component of brain antimicrobial immunity | PLOS Pathogens, accessed January 26, 2026, <https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1010929>
11. OFP_2020_paper_201.pdf
12. Porphyromonas gingivalis triggers microglia activation and neurodegenerative processes through NOX4 - PMC - NIH, accessed January 26, 2026,

- <https://pmc.ncbi.nlm.nih.gov/articles/PMC11513391/>
13. APOE4/4 is linked to damaging lipid droplets in Alzheimer's microglia | bioRxiv, accessed January 26, 2026, <https://www.biorxiv.org/content/10.1101/2023.07.21.549930v1.full-text>
 14. Multimodal prognostic modeling of individual cognitive trajectories to enhance trial efficiency in preclinical Alzheimer's disease - PubMed Central, accessed January 26, 2026, <https://pmc.ncbi.nlm.nih.gov/articles/PMC12457986/>
 15. NIH COMMON FUND HIGH-RISK, HIGH-REWARD RESEARCH SYMPOSIUM - June 9-11, 2021 Speaker and Poster Presenter Abstracts, accessed January 26, 2026, <https://commonfund.nih.gov/sites/default/files/2021%20HRHR%20Symposium%20abstracts.pdf>
 16. The Alzheimer's Disease-Associated Amyloid β -Protein Is an Antimicrobial Peptide, accessed January 26, 2026, <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0009505>
 17. LL-37-Induced Autophagy Contributed to the Elimination of Live Porphyromonas gingivalis Internalized in Keratinocytes - Frontiers, accessed January 26, 2026, <https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2020.561761/full>
 18. WO2019018445A1 - Polytherapy modulating cathelicidin gene expression modulation for the treatment of alzheimer's disease and other conditions - Google Patents, accessed January 26, 2026, <https://patents.google.com/patent/WO2019018445A1/en>
 19. Gingipain inhibitors as an innovative therapy for periodontal and associated-systemic diseases: a systematic review - NIH, accessed January 26, 2026, <https://pmc.ncbi.nlm.nih.gov/articles/PMC12370816/>
 20. Porphyromonas Gingivalis in the Pathogenesis of Alzheimer's Disease and Its Therapeutic Target - Xia & He Publishing Inc., accessed January 26, 2026, <https://www.xiahepublishing.com/2572-5505/JERP-2021-00030>
 21. Discovery of Gingipains and Porphyromonas gingivalis Inhibitors from Food-Derived Natural Products: A Narrative Review - MDPI, accessed January 26, 2026, <https://www.mdpi.com/2304-8158/14/16/2869>
 22. Saliva Enables the Antimicrobial Activity of LL-37 in the Presence of Proteases of Porphyromonas gingivalis - PMC - NIH, accessed January 26, 2026, <https://pmc.ncbi.nlm.nih.gov/articles/PMC2786438/>
 23. (PDF) Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors - ResearchGate, accessed January 26, 2026, https://www.researchgate.net/publication/330588158_Porphyromonas_gingivalis_in_Alzheimer's_disease_brains_Evidence_for_disease_causation_and_treatment_with_small-molecule_inhibitors
 24. Cortexyme Provides New GAIN Trial Data at AD/PD 2022 Demonstrating Potential Benefit of Lysine Gingipain Inhibition in Mild to Moderate Alzheimer's Population | Quince Therapeutics, accessed January 26, 2026, <https://ir.quincetx.com/news-releases/news-release-details/cortexyme-provides-new-gain-trial-data-adpd-2022-demonstrating/>

25. Evidence that the Human Innate Immune Peptide LL-37 may be a Binding Partner of Amyloid- β and Inhibitor of Fibril Assembly - PubMed Central, accessed January 26, 2026, <https://pmc.ncbi.nlm.nih.gov/articles/PMC5611894/>
26. Evidence that the Human Innate Immune Peptide LL-37 may be a Binding Partner of Amyloid- β and Inhibitor of Fibril Assembly - PubMed, accessed January 26, 2026, <https://pubmed.ncbi.nlm.nih.gov/28731438/>
27. Evidence that the Human Innate Immune Peptide LL-37 may be a Binding Partner of Amyloid- β and Inhibitor of Fibril Assembly - ResearchGate, accessed January 26, 2026, https://www.researchgate.net/publication/318519881_Evidence_that_the_Human_Innate_Immune_Peptide_LL-37_may_be_a_Binding_Partner_of_Amyloid-b_and_Inhibitor_of_Fibril_Assembly
28. Higher dietary butyrate intake is associated with better cognitive function in older adults: evidence from a cross-sectional study - PubMed Central, accessed January 26, 2026, <https://pmc.ncbi.nlm.nih.gov/articles/PMC11985818/>
29. The Pivotal Role of Aryl Hydrocarbon Receptor-Regulated Tight Junction Proteins and Innate Immunity on the Synergistic Effects of Postbiotic Butyrate and Active Vitamin D3 to Defense against Microbial Invasion in Salmonella Colitis - MDPI, accessed January 26, 2026, <https://www.mdpi.com/2072-6643/15/2/305>
30. Family Medicine Journal Rankings - PJIP, accessed January 26, 2026, [https://www.pjip.org/Medical-journal-rankings.html?searchCols=\[null,null,{%22search%22:%22FaMe%22}\]](https://www.pjip.org/Medical-journal-rankings.html?searchCols=[null,null,{%22search%22:%22FaMe%22}])
31. How to peer review a scientific or scholarly article | ACOFP, accessed January 26, 2026, [https://acofp.org/docs/default-source/ofp/vol-4-no-6-\(2012\)-november-december-2012/how-to-peer-review-a-scientific-or-scholarly-article.pdf?sfvrsn=22e086d4_0](https://acofp.org/docs/default-source/ofp/vol-4-no-6-(2012)-november-december-2012/how-to-peer-review-a-scientific-or-scholarly-article.pdf?sfvrsn=22e086d4_0)
32. In vivo co-expression of LL-37 with A β 42 in a transgenic Drosophila model of Alzheimer's Disease attenuates the deleterious effects - Stanford University, accessed January 26, 2026, <https://web.stanford.edu/group/barronlab/PubPdfs/2024/In%20vivo%20co-expression%20of%20LL-37%20with%20A%CE%B242%20in%20a%20transgenic%20Drosophila%20model%20of%20Alzheimer%E2%80%99s%20Disease%20preprint.pdf>
33. In vivo Co-Expression of LL-37 with A β 42 in a Transgenic Drosophila Model of Alzheimer's Disease Attenuates the Deleterious Effects of Amyloid- β 42 | Request PDF - ResearchGate, accessed January 26, 2026, https://www.researchgate.net/publication/378052080_In_vivo_Co-Expression_of_LL-37_with_Ab42_in_a_Transgenic_Drosophila_Model_of_Alzheimer's_Disease_Atenuates_the_Deleterious_Effects_of_Amyloid-b42
34. Atuzaginstat | ALZFORUM, accessed January 26, 2026, <https://www.alzforum.org/therapeutics/atuzaginstat>
35. Cortexyme drug fails in Alzheimer's trial, but company sees validation of unorthodox approach | BioPharma Dive, accessed January 26, 2026, <https://www.biopharmadive.com/news/cortexyme-alzheimers-gain-study-results>

- [-gingivalis/608879/](#)
36. Trial Data Further Support Gingipain Suppression as Potential Therapy, accessed January 26, 2026,
<https://alzheimersnewstoday.com/news/atuzaginstat-clinical-trial-data-gingipain-suppression-potential-alzheimers-therapy-cortexyme/>
 37. Lighthouse announces FDA approval to proceed with Phase 2 SPRING Trial of LHP588, a next-generation treatment in development for P. gingivalis-positive Alzheimer's disease, accessed January 26, 2026,
<https://www.lighthousepharma.com/lighthouse-initiates-phase-2>
 38. Phase 2 Study Design and New Data from the Phase 1 SAD/MAD Trial of LHP588, A Second-Generation Gingipain Inhibitor for the Treatment of P. Gingivalis - Positive Alzheimer Dementia - ResearchGate, accessed January 26, 2026,
https://www.researchgate.net/publication/376814015_Phase_2_Study_Design_and_New_Data_from_the_Phase_1_SADMAD_Trial_of_LHP588_A_Second-Generation_Gingipain_Inhibitor_for_the_Treatment_of_P_Gingivalis_-_Positive_Alzheimer_De_mentia?_share=1
 39. NCT06847321 | Study of LHP588 in Subjects With P. Gingivalis-Positive Alzheimer's Disease | ClinicalTrials.gov, accessed January 26, 2026,
<https://clinicaltrials.gov/study/NCT06847321>
 40. Lighthouse Pharma Receives \$49.2 Million NIA Grant, accessed January 26, 2026,
<https://www.lighthousepharma.com/lighthouse-receives-nia-grant>
 41. Phase II Study of LHP588 in PG+ Alzheimer's Disease - HigherGov, accessed January 26, 2026,
<https://www.highergov.com/grant/R01AG088524/>
 42. Identification of gingipains in glioblastoma tumors and evidence that P. gingivalis infection drives IL-6 and PD-L1 expression i - bioRxiv, accessed January 26, 2026,
<https://www.biorxiv.org/content/10.1101/2025.11.13.686868v1.full.pdf>
 43. Antimicrobial Peptides of the Cathelicidin Family: Focus on LL-37 and Its Modifications, accessed January 26, 2026,
<https://www.mdpi.com/1422-0067/26/16/8103>